1 TITLE PAGE

Statistical Analysis Plan

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Principal Investigator/s	Dr. Angel Chamorro	
Institution	Medical Statistics Core Facility IDIBAPS - Hospital Clínic de Barcelona	
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2 SIGNATURES' PAGE

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4 STUDY PERSONNEL

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5 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
eTICI	expanded Treatment In Cerebral Infarction scale
FAS	Full Analysis Set
HR	Hazard Ratio
IER	Infarct Expansion Ratio
ICE	Intercurrent event
ICH	Intra-cerebral Haemorrhage
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IQR	Interquartile range
ITT	Intention-to-treat
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
RD	Risk Difference
RR	Risk 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

6 CHANGES IN REVISION 2 FROM PREVIOUS VERSION (REVISION 1)

This new SAP Final version revision 2, dated 09-Dec-2020, overrides previous Final version revision 1, dated 03-Dec-2019. The current version clarifies that the main analysis for the primary endpoint will be based on the Risk Difference (RD) scale rather than the Risk Ratio (RR). This is consistent with the definition of the primary endpoint based on proportions ("the **proportion** of patients with mRS 0 to 1 at 90 days") and the analysis will also be consistent with the sample size calculations where a **21% benefit** was expected. This is more considered as a clarification rather a major change since the scale of differences was also predefined; however, it was unclear in some parts of the previous SAP which one, RD or RR, should be considered as primary.

There is also a change in a secondary outcome as per protocol version 3.1.

Please refer to section 13 for comments to changes implemented in the previous version (rev1)

SAP: Final rev1, Date: 03-Dec-2019 Protocol: 3.0, 20-Nov-2019	SAP: Final rev2, Date: 09-Dec-2020 Protocol: 3.1 04-Dec-2020	Justification
	In signature page and study personnel (sections 2 & 4.2) Signature of the statistical programmer, Ms. Georgina Casanovas is included	To include the task of the statistical programmer
9.3 JUSTIFICATION OF SAMPLE SIZE A sample size of 100 patients per treatment arm in a 1:1 allocation will have at least 80% statistical power for the primary outcome (mRS with 0-1 score values) assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm **(odds ratio (OR) of 2.33**) for a 5% two-sided type I error. **This sample size will also guarantee the study power for that relative treatment benefit even if the success rate in the control group rises up to ≈56%.** Study losses are not taken into account as all randomized patients exposed to the IMP will be included in the analysis. The number of randomised patients not exposed to the IMP is expected to be negligible.	A sample size of 100 patients per treatment arm in a 1:1 allocation will have at least 80% statistical power for the primary outcome (mRS with 0-1 score values) assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm ~~**(odds ratio (OR) of 2.33)**~~ for a 5% two-sided type I error. ~~**This sample size will also guarantee the study power for that relative treatment benefit even if the success rate in the control group rises up to ≈56% for a odds ratio (OR) of 2.33**~~. Study losses are not taken into account as all randomized patients exposed to the IMP will be included in the analysis. The number of randomised patients not exposed to the IMP is expected to be negligible.	The scale benefit for primary endpoint was intended to be shown in a difference of proportion (Risk Difference -RD-) scale and the role of the odds ratio was misleading with regards of this intention.
10.2 Study Estimand and Handling of Missing Data 4. Population-level summary**: Estimation of the Rate Ratio (RR) f**or 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).	4. Population-level summary: Estimation of the **adjusted Risk Difference (RD)** for the PEP will be used as the population-level summary. The l~~**og**~~**-binomial model** adjusted by the randomisation stratum previous alteplase use will be used for the inferential analysis (p-value, RD and 95% Confidence Intervals). Sensitivity analysis: • Adjusted Risk Ratio (RR) will be calculated from the log-binomial regression models as an additional sensitivity measure.	The population-level summary was not in concordance with the aim of the scale of RD, as proposed in sample size justification (section 9.3) and other sections of the protocol: 9.3 Justification of sample size: "*…assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm…*" 10.6.2.1 Primary endpoint: "*The main efficacy variable, excellent outcome, the p**roportion** of patients with a mRS 0 to 1 at 90 days will be estimated using a binomial regression model including the stratification variables, except centre*" 10.6.4.1 "*The primary analysis will be based on the primary efficacy variable, the **proportion** of patients with excellent outcome*" Clarification on the covariates to be used RR used as an additional sensitivity analysis for the primary endpoint (PEP)
Primary, secondary and tertiary endpoints in separate 3rd level section	Inclusion of section 10.4.1 Efficacy endpoints Primary, secondary and tertiary endpoints in 4th level section nested in 10.4.1	To further distinguish between efficacy and safety endpoints Primary, secondary and tertiary endpoints now are subsections of 10.4.1
Safety endpoints	**Primary** safety endpoints	"Primary" has been added to safety endpoint to identify the highly ranked safety end points
10.6.2.1 Primary endpoint The main efficacy variable, excellent outcome, the proportion of patients with a mRS 0 to 1 at 90 days 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].	The main efficacy variable, excellent outcome, the proportion of patients with a mRS 0 to 1 at 90 days will be estimated using a binomial regression model including the stratification variables, except centre **(i.e. using only the previous alteplase use**). **As an additional sensitivity analysis, Risk Ratios (RR**) will be also calculated setting the link 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].	Clarification on the covariates to be used Binomial regression maintained as principal RR as additional sensitivity analysis using log-binomial regression
10.6.2.2 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.	Binary efficacy outcomes will be analysed as described for the primary endpoint (adjusted RD). Safety efficacy endpoints (such as mortality at 90 days and sICH rates at 24 hours) will be analysed using the Fisher exact's test.	To distinguish the analysis of efficacy and safety binary endpoints. Binary efficacy endpoints to be analysed via binomial regression but for safety ones the standard Fisher exact's test will be used.

10.6.2.4.1 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 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 **(i.e. using only the previous alteplase use).**	Clarification on the covariates to be used
10.6.2.4.2 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.	**10.6.2.4.2 Median difference estimation** When applicable, the median difference (95%CI) will calculated using the Hodges-Lehmann estimator (i.e. median of all cross differences between treatments based on the Mann-Whitney distribution) 32,33,34.	The quantile regression is not much used in clinical trials while the Hodges-Lehmann estimator has been widely used. The analysis is changed, and the references updated accordingly.
10.6.2.5 Others … Group comparisons will be conducted using the stratified the log-rank test and, hazard ratios -HR- (95%CI) were taken from the Cox model35, in both cases using the randomisation strata, except centre.	Group comparisons will be conducted using the stratified the log-rank test and, hazard ratios -HR- (95%CI) were taken from the Cox model35, in both cases using the randomisation strata, except centre **(i.e. using only the previous alteplase use).**	Clarification on the covariates to be used
10.6.4.1 Primary efficacy analysis The primary analysis will be based on the primary efficacy variable, the proportion of patients with excellent outcome (mRS 0 to 1). This analysis will be performed by a **log-**binomial regression model specified in section 10.6.2.1 using the imputed data according to the detail given in section 10.2 on the mFAS population set (see section 10.1). Supplementary and Sensitivity analyses are described in section 10.2.1 which will be supportive to the primary analysis.	The primary analysis will be based on the primary efficacy variable, the proportion of patients with excellent outcome (mRS 0 to 1). This analysis will be performed by a ~~log~~ binomial regression model specified in section 10.6.2.1 using the imputed data according to the detail given in section 10.2 on the mFAS population set (see section 10.1). **The estimation of the adjusted Risk Difference (RD) for the primary efficacy variable will be used as the population-level summary for the main analysis.** Supplementary and Sensitivity analyses are described in section 10.2.1 which will be supportive to the primary analysis. **The binomial model adjusted by the randomisation stratum previous alteplase use will be used for the inferential analysis (p-value, RD and 95% Confidence Intervals). Adjusted Risk Ratio (RR) will be calculated from the log-binomial regression models as an additional sensitivity measure**.	The proportions are estimated via binomial and not log-binomial regression. The analysis is clarified to avoid misunderstandings and consistently updated in all sections The methodology for the primary analysis is now clearly described
10.6.4.2 Secondary analysis … The shift analysis of the modified Rankin Scale (mRS) will be analysed using the proportional odds model described in section 10.6.2.	The shift analysis of the modified Rankin Scale (mRS) will be analysed using the proportional odds model **and the parametric van Elteren test, as** described in section 10.6.2.	The van Elteren use was predefined in section 10.6.2 as a sensitivity method, now it is also included here for consistency
10.8 Subgroup analyses …. 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.**	The same ~~log~~ binomial regression model as per the main analysis**, but without the stratum previous alteplase use covariate**, will be used to explore the treatment and the treatment-by-subgroup interaction effects. ~~**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.**~~	Proportions and RD are estimated from the binomial, not the log-binomial, model For consistency the analysis will be the same than for the primary endpoint Adjustment by prior alteplase use cannot be implemented to the subgroup of alteplase use (yes/no). For consistency, it is clarified that analyses of subgroups will not be adjusted. This is a exploratory analysis in a phase 2b trial, therefore the interaction test will be used for informative purposes but not for any decision
10.4.1.2 Secondary endpoints …. 5. Proportion of patients with angiographic improvement on the expanded Thrombolysis in Cerebral Infarction (eTICI) scale. In the eTICI metrics, eTICI grade 0 is equivalent to 0% filling of the downstream territory; eTICI 1 reflects thrombus reduction without any reperfusion of distal arteries; eTICI 2a is reperfusion in 1–49% of the territory; eTICI 2b50 is 50–66% reperfusion; eTICI 2b67 is 67–89% reperfusion; eTICI 2c is 90–99% reperfusion; and eTICI 3 is complete or 100% reperfusion. The final angiography was scored as "improved", "worsened" or "unchanged" with regard to the baseline angiography.	5. Proportion of patients with angiographic changes on the eTICI score. To that aim, all the baseline angiographies will be scored at the core lab by central and blinded reviewers using the eTICI and classified as eTICI2b50, eTICI2b67, eTICI2c, and eTICI3. The post treatment angiographies will be scored using the eTICI and classified as "improved", "worsened" or "unchanged" with regard to the baseline eTICI score.	**Secondary Outcome changed as per protocol version 3.1** This affects to the assessment of angiographies rather than to the statistical analysis but due to its relevance is included in the SAP.

7 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 ICHE91 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 System6 (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.

8 STUDY OBJECTIVES

The study objective is to evaluate whether rt-PA is safe and efficient as an add-on to mechanical thrombectomy in patients with acute ischemic stroke and complete or near-complete recanalization of a proximal vessel occlusion and successful brain reperfusion on cerebral angiogram (corresponding to mTICI score 2b/3)

9 TRIAL CHARACTERISTICS

9.1 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.

9.2 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.

9.3 JUSTIFICATION OF SAMPLE SIZE

A sample size of 100 patients per treatment arm in a 1:1 allocation will have at least 80% statistical power for the primary outcome (mRS with 0-1 score values) assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm for a 5% two-sided type I error. Study losses are not taken into account as all randomized patients exposed to the IMP will be included in the analysis. The number of randomised patients not exposed to the IMP is expected to be negligible.

9.4 STATISTICAL INTERIM ANALYSIS AND MULTIPLICITY ADJUSTMENTS

The analysis will follow the principles specified in the ICHE9[1] 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.

10 STATISTICAL ANALYSIS

10.1 Analysis Populations

There will the following analysis populations for this study:

1) Full Analysis Set (FAS): All patients who are randomized into the study regardless of any treatment of protocol violation, fully in accordance with the intention-to-treat (ITT) principle.
2) 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.
3) 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.
4) The Safety population (SP) is defined as all randomized participants who received the investigational drug (any of the two-arms 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 11).

10.2 Study Estimand and Handling of Missing Data

The handling of missing data will follow the principles specified in the ICH-E9[1] and the CPMP/EWP/1776/99 Rev1. Guideline on Missing Data in confirmatory trials Guidelines[14].

10.2.1 Primary endpoint

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 for the primary endpoint:

1. Population: Patients with symptomatic large vessel occlusion (LVO) in the anterior circulation treated with MT resulting in a mTICI score 2b/3 on cerebral angiography. See protocol section 3.2 for further details.
2. Primary endpoint (PEP): The proportion of patients with mRS 0 to 1 at 90 days (see section 10.6.4.1)
3. Intercurrent events: In principle, the primary estimand will be based on the *treatment policy* strategy for handling intercurrent events. Patient outcomes will be gathered regardless of any protocol violation and imputations rules will be applied only when all efforts to retrieve the outcomes have failed.

   The relevant intercurrent events (ICEs) 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. The number of patients excluded for these reasons are expected to be negligible and completely independent to IMP efficacy or safety issues. For the FAS population the *treatment policy* strategy will be used.

   b. Treatment discontinuation: *treatment policy* strategy, i.e., the efficacy observed assessment will be used regardless of this intercurrent event. If the endpoint is not available, then the strategies described in point d) will be implemented.

c. Death: it is included in category 6 of mRS according to the original scale, therefore it will be counted as failure for the PEP.

d. Other reasons for not assessing the PEP. A flexible mixture combination of *composite* and *hypothetical* strategies will be implemented:

   i. Missing data due to treatment related reasons (i.e. due to efficacy or safety issues) or with relation unknown or unclear: the PEP will be handled using the "*Composite*" strategy (failure).

   ii. Missing data due to univocally identified non-treatment related reasons:

   - If the rate of patients fulfilling this criterion is >10%, then multiple imputation techniques with implemented using the observed rate of improvement in the control arm. No differential rates between treatment groups are expected. This rule would avoid an artefactual relevant increase in the rate of failure (>10%), not expected when extrapolating to the target population.
   - If the rate of patients fulfilling this criterion is ≤10%, then missingness will be imputed to failure (as described in *d.i*).

e. Rescue medication and other reasons for study discontinuation. No rescue medication/strategies are considered for the current treatment strategy.

Missing data for the PEP will be classified according to this plan during the Data Blind Review. Changes from the above-described plan to adapt to new/unexpected ICEs during the blinded review are permitted but they should be traced and justified in the statistical report.

4. Population-level summary: Estimation of the adjusted Risk Difference (RD) for the PEP will be used as the population-level summary. The binomial model adjusted by the randomisation stratum previous alteplase use will be used for the inferential analysis (p-value, RD and 95% Confidence Intervals).

A number of supplementary and sensitivity analyses are proposed:

- Adjusted Risk Ratio (RR) will be calculated from the log-binomial regression models as an additional sensitivity measure.
- A responder analysis imputing to failure regardless the reason for missingness
- Analysis using multiple imputation with the observed rates in the placebo group in all cases
- Analysis using the above-described strategies with the FAS and the PP populations

10.2.2 Other endpoints

Overall, missing efficacy data will be considered as potentially related lack of efficacy irrespectively to the reason for missingness. Therefore, missing data for mRS, Barthel, NIHSS scales will be imputed using a bad percentile of the scale (90% for mRS, 10% for Barthel and NIHSS) rounded to the nearest integer.

With regards to the longitudinal 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.

10.3 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 10.1.

10.4 Endpoints Definition

10.4.1 Efficacy endpoints

10.4.1.1 Primary endpoint

1. The primary outcome will be the **proportion** of patients with *excellent outcome* (mRS 0-1) at day 90.

10.4.1.2 Secondary endpoints

1. 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).
2. Infarct Expansion Ratio on DWI-MRI (continuous variable), at 48h (+/- 24h) of stroke
3. Proportion of patients with/without infarct expansion (dichotomous variable)
4. Infarction Volume on DWI-MRI, at 48h (+/- 24h) of stroke onset
5. Proportion of patients with angiographic changes on the eTICI score. To that aim, all the baseline angiographies will be scored at the core lab by central and blinded reviewers using the eTICI and classified as eTICI2b50, eTICI2b67, eTICI2c, and eTICI3. The post treatment angiographies will be scored using the eTICI and classified as “improved”, “worsened” or “unchanged” with regard to the baseline eTICI score.

10.4.1.3 Tertiary endpoints

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

10.4.2 Primary safety endpoints

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

10.5 Variables

10.5.1 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 IVr-TPA
- Stroke etiology

10.5.2 Efficacy variables

The efficacy variables are listed below:

- mRS 0-1 (excellent outcome) at day 90
- TICI
- NIHSS score
- mRS, and mRS 0-2
- 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.
- Arteriography: vessels occluded (including location and laterality), cervical carotid occlusions and grade, complications, vasospasm, emboli to the new and same territory.

10.5.3 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

10.6 Statistical Methods

10.6.1 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.

10.6.2 Inferential Analysis

All statistical tests will be applied with 0.05 two-sided significance level. Please refer to section 9.4 for details on the handling of multiplicity.

10.6.2.1 Primary endpoint

The main efficacy variable, *excellent outcome*, the proportion of patients with a mRS 0 to 1 at 90 days will be estimated using a binomial regression model including the stratification variables, except centre (i.e. using only the previous alteplase use). As an additional sensitivity analysis, Risk Ratios (RR) will be also calculated setting the link 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].

10.6.2.2 Binary outcomes

Binary efficacy outcomes will be analysed as described for the primary endpoint (adjusted RD).

Safety efficacy endpoints (such as mortality at 90 days and sICH rates at 24 hours) will be analysed using the Fisher exact's test.

10.6.2.3 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. A common 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 $\alpha = .05$ (two-sided 95% confidence intervals).

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

10.6.2.4 Ordinal outcomes and non-gaussian continuous variables

10.6.2.4.1 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 (i.e. using only the previous alteplase use). 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.

10.6.2.4.2 Median difference estimation

When applicable, the median difference (95%CI) will calculated using the Hodges-Lehmann estimator (i.e. median of all cross differences between treatments based on the Mann-Whitney distribution) [32,33,34].

10.6.2.5 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 (i.e. using only the previous alteplase use).

10.6.3 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 10.5.1.

No inferential analysis will be performed for the baseline comparability.

10.6.4 Efficacy variables

10.6.4.1 Primary efficacy analysis

The primary analysis will be based on the primary efficacy variable, the proportion of patients with *excellent outcome* (mRS 0 to 1). This analysis will be performed by a binomial regression model specified in section 10.6.2.1 using the imputed data according to the detail given in section 10.2 on the mFAS population set (see section 10.1). The estimation of the adjusted Risk Difference (RD) for the primary efficacy variable will be used as the population-level summary for the main analysis.

Supplementary and Sensitivity analyses are described in section 10.2.1 which will be supportive to the primary analysis. The binomial model adjusted by the randomisation stratum previous alteplase use will be used for the inferential analysis (p-value, RD and 95% Confidence Intervals). Adjusted Risk Ratio (RR) will be calculated from the log-binomial regression models as an additional sensitivity measure.

10.6.4.2 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 10.6.2.

The shift analysis of the modified Rankin Scale (mRS) will be analysed using the proportional odds model and the parametric van Elteren test, as described in section 10.6.2.

The analysis of binary efficacy and safety (mortality at 90 days and sICH rates at 24 hours) outcomes will be based on the same strategy as per the primary efficacy variable (see section 10.6.2.1). The analysis of longitudinal continuous variables, the shift analysis, and the estimation for ordinal outcomes, when

applicable, is described in sections 10.6.2.3, 10.6.2.4.1 and **¡Error! No se encuentra el origen de la r eferencia.**, respectively.

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 10.6.2 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.

10.6.4.3 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 ordinal and as a categorical).

10.6.5 Safety outcomes

The statistical analysis will consider listings and descriptive statistics (continuous or categorical as appropriate, see section 10.6.1). The continuous safety variables will be described with the absolute values and with the absolute difference from baseline (when applicable) without any imputation.

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 the Safety set.

10.6.5.1 Laboratory parameters

Laboratory parameters (haematology and biochemistry) will be described and listed by visit and treatment group, no inferential analysis will be conducted.

10.6.5.2 Vital signs

Vital signs will be described and listing by visit and treatment group. No inferential analysis will be conducted.

10.6.5.3 Adverse events

Inferential tests (see section 10.6.2) 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.

10.6.5.4 Concomitant medication

The number and percentage of patients with at least one concomitant medication will be described and listed by treatment arm. No inferential analysis will be conducted

The complete information about concomitant medication will be listed.

10.6.5.5 Compliance with the study medication

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

10.6.5.6 Final evaluation

Final evaluation and drop-outs reasons will be described including the timing (visit), and treatment arm. The final evaluation and the drop-outs reasons will also be studied for all population sets.

10.7 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.

10.8 Subgroup analyses

The following 4 subgroups are declared of special interest and they will be investigated for proportion of patients with *excellent outcome* (mRS 0 or 1 at day 90):

1. IV Alteplase in admission (Yes versus No)
2. MT started within 7.3h of symptoms onset versus MT started between 7.4h and 24h.
3. Admission serum glucose concentration ≤100 mg/dl versus >100 mg/dl.
4. Males versus females.
5. Baseline angiographic score eTICI2b50/2b67 brain reperfusion versus baseline angiographic score eTICI2c/3 brain reperfusion.

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 binomial regression model as per the main analysis, but without the stratum previous alteplase use covariate, will be used to explore the treatment and the treatment-by-subgroup interaction effects.

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

10.9 Computation of Derived Variables

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

10.10 Additional statistical analyses

Not applicable.

11 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.

During the DBR, missing data and intercurrent events will be classified according to the plan described in section 10.2. Changes from that plan to adapt to new/unexpected ICEs during the blinded review are permitted but they should be traced and justified in the statistical report.

12 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.

13 CHANGES IN SAP REVISION 1 FROM PREVIOUS VERSION

This new SAP Final version review 1 dated 03-Dec-2019 overrides previous version dated 15-Jul-2019. The current version has adapted the population and primary endpoint to the new protocol version 3.0 dated 20-Nov-2019. The following table reflects only the main changes which affected the specification given in the previous version. Please refer to the updated protocol version 3.0 (20-Nov-2019) for further details on other issues.

Protocol 2.0, 08-Mar-2019	Protocol 3.0, 20-Nov-2019
Protocol Version 2.0: March 08, 2019	 3.0: November 28, 2019
Study Objective The study objective is to evaluate whether rt-PA is safe and efficient as an add-on to mechanical thrombectomy in patients with acute ischemic stroke and complete or near-complete recanalization of a proximal vessel occlusion **but partial** brain reperfusion on cerebral angiogram (corresponding to mTICI score 2b)	 The study objective is to evaluate whether rt-PA is safe and efficient as an add-on to mechanical thrombectomy in patients with acute ischemic stroke and complete or near-complete recanalization of a proximal vessel occlusion **and successful** brain reperfusion on cerebral angiogram (corresponding to mTICI score 2b**/3**)
Subject Population Patients with symptomatic large vessel occlusion (LVO) in the anterior circulation treated with MT resulting in a mTICI score 2b on cerebral angiography	 Patients with symptomatic large vessel occlusion (LVO) in the anterior circulation treated with MT resulting in a mTICI score 2b**/3** on cerebral angiography
Enrolment Patients will be enrolled in the angiosuit by interventionalists or neurologists once a mTICI 2b is confirmed on cerebral angiography. 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	 Patients will be enrolled in the angiosuit by interventionalists or neurologists once a mTICI 2b/3 is confirmed on cerebral angiography. A sample size of 100 patients per treatment arm in a 1:1 allocation will have at least ***80%*** statistical power for the **primary outcome (mRS with 0-1 score values) assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm (odds ratio (OR) of 2.33) for a 5% two-sided type I error. This sample size will also guarantee the study power for that relative treatment benefit even if the success rate in the control group rises up to ≈56%. No study losses are accounted for since all randomised patients will be included in the analysis.**
3.5.1 Primary outcome **Deleted**: ~~Proportion of patients with an improved mTICI score ten (10) minutes after the end of the experimental study treatment.~~	**New**: **Proportion of patients with a mRS 0 to 1 at 90 days**
3.5.2 Secondary Outcomes **Deleted**: ~~Proportion of patients with a mRS 0 to 1 at 90 days~~	**New:** Proportion of patients with angiographic improvement on the Arterial Occlusive Lesion (AOL) scale. AOL describes arterial patency at the site of occlusion based on the degree of luminal opening (none, partial, or complete) with further qualification based simply on the presence (grades 2 or 3) or absence (grades 0 or 1) of any downstream flow.
3.5.4 Pre-specified subgroup analysis … 5. Baseline angiographic score **>90<100%** brain reperfusion (**rTICI2c**) versus baseline angiographic score **≥50<91%** brain reperfusion	 5. Baseline angiographic score **mTICI2b** brain reperfusion versus baseline angiographic score **eTICI2c/3** brain reperfusion according to the local interventionalists
3.6.2 Sample size calculation 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**	 A sample size of 100 patients per treatment arm in a 1:1 allocation will have at least **80%** statistical power for the primary outcome (**mRS with 0-1 score values) assuming a rate of 40% in the control arm and a 21% benefit in the experimental arm (odds ratio (OR) of 2.33)** for a 5% two-sided type I error. **This sample size will also guarantee the study power for that relative treatment benefit even if the success rate in the control group rises up to ≈56%. No study losses are**

secondary outcomes with at least 90 valid patients per arm, as shown in the table below:

accounted for since all randomised patients will be included in the analysis.

3.6.6.1 Primary endpoint

		Control	Experimental	OR / $P_{(Noether)}$	Differences: % or Median	Power[3]
Primary Outcome						
Proportion of patients with a mTICI improvement	%	5%	60%	OR: 0.04	% 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	% diff: 23%	88%
Proportion of patients with no infarct expansion	%|	45%	66%	OR: 0.42	% diff: 21%	81%

OR: Odds 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[57]
2: Estimated the work of the MR Stroke Collaborative Group 2006[54]
3: Sample sizes estimated using nQuery v7.0 software[55], relying on Noether[56] for the Wilcoxon-Mann-Whitney approach for ordinal and non-parametric continuous data, and on Machin & Cambell[57] and Fleis[58] for binary endpoints

The proportion of patients with **an improved mTICI score ten (10) minutes after the end of study treatment** will be estimated using a log-binomial regression model including the stratification variables, except centre. In the unexpected event that the model does not fit, the Poisson regression model with long-link and robust variance estimator will be used instead[59,60,61,62,63]

The proportion of patients with **a mRS 0 to 1 at 90 days** will be estimated using a log-binomial regression model including the stratification variables, except centre. In the unexpected event that the model does not fit, the Poisson regression model with long-link and robust variance estimator will be used instead[59,60,61,62,63]

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