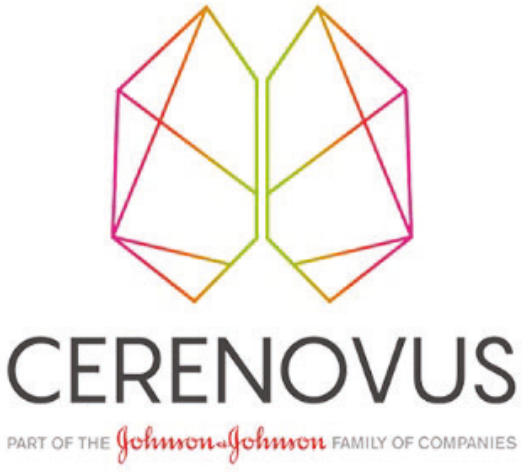

Statistical Analysis Plan (SAP)

Post Marketing **S**tudy of **P**atients to **E**valuate NIMBUS **R**evascularization Effectiveness with Challenging **O**cclusions

Protocol Number: CNV_2018_01

Protocol Version: Version 2

SAP Revision: 1
SAP Revision Date: 25/JAN/2022

Post Marketing **S**tudy of **P**atients to **E**valuate NIMBUS **R**evascularization Effectiveness with Challenging **O**cclusions

Protocol Number: CNV_2018_01

Protocol Version: 2

The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:

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[redacted]

(Print) (Sign) Date

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Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
Version 1	25JAN2022	First edition.

Table of Contents

1 Study Design

This is a prospective, multi-center, single-arm, observational post market study that will consecutively enroll up to 50 subjects treated with NIMBUS at approximately 10 sites in Europe. This study will evaluate NIMBUS, post one or two unsuccessful passes of another Mechanical Thrombectomy device, in the treatment of acute ischemic stroke. Data will be collected at baseline (prior to thrombectomy), during the procedure, and post-procedure. Clinical follow up with subjects will occur over 3 months; at 24 hours and 90 days post procedure.

2 Treatment Assignment

This is a single arm study; all enrolled subjects will be treated with NIMBUS.

3 Interval Windows

Study reports will be summarized by analysis visit as defined in the protocol:

- 24 Hours post-procedure (±8 hours)
- 90-day follow-up (±14 days)

The study schedule is to be adhered to as closely as possible for all subjects. Measurements outside the interval windows will be treated as missing. In the case of repeated measurements taken at the same visit, the most recent non-missing measurement will be used unless specified otherwise.

4 Levels of Significance

No hypothesis tests are planned in the study. All confidence intervals will be reported at a two-sided 95% confidence level. These confidence intervals will not be used for statistical inferences, but for clinical reference purpose and are intended to convey precision in the estimates.

5 Analysis Sets

The following analysis sets are defined in the study:

- **Modified Intent-to-Treat (mITT) Analysis Set**

The mITT Analysis Set consists of all subjects who are enrolled into the study, and who have attempted at least one pass with the NIMBUS device (which includes deployment and retrieval with the NIMBUS device).

A subject is considered enrolled in this study after the physician confirms the subject meets all eligibility criteria, and the subject is consented.

- **mRS Analysis Set**

The mRS Analysis Set consists of all mITT subjects who meet the study criteria as defined in protocol section 9.5.

6 Sample Size Justification

There is no hypothesis test for this post-market study, approximately 50 treated subjects are deemed sufficient to evaluate the performance of NIMBUS.

Approximately 50 subjects will be consecutively enrolled using commercially available Mechanical Thrombectomy devices during the preceding one or two passes. With an enrolled sample size of up to 50 and an attrition rate of no more than 10%, the precision (margin of error) for the primary endpoint is anticipated to be around 10.1% based on 2-sided 95% confidence intervals, where the primary endpoint rate is estimated to be 86%.

$$Margin\ of\ error \approx 1.96 \times SE$$

$$= 1.96 \times \sqrt{\frac{p(1-p)}{n}} = 1.96 \times \sqrt{\frac{0.86 \times (1-0.86)}{45}} = 10.1\%$$

where SE denotes the standard error and p denotes the proportion of subjects who achieve the primary endpoint.

7 Analyses to be Conducted

7.1 General Conventions

Descriptive summary statistics will be presented for all endpoints. The number and percentage of subjects will be summarized for categorical variables. Unless specified otherwise, percentages will be based on subjects with non-missing values. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum. All statistical analyses will be performed using SAS® Studio, Version 9.4 or later.

1. Baseline

Unless specified otherwise, the last non-missing measurement collected during the baseline visit is considered as the baseline measurement (prior to the start of the index procedure).

- The pre-stroke mRS score will be considered as the baseline mRS score.
- The highest (worst) NIHSS score will be considered as the baseline NIHSS score should a subject have more than one non-missing NIHSS score at baseline.

2. Stroke onset date and time

Pre-stroke events are defined as those events that happened prior to the stroke onset date and time.

- For witnessed stroke, the stroke onset date and time as reported from the case report form (CRF) will be used;
- For un-witnessed stroke, the date and time when the patient was last seen well from the CRF will be used.

3. Study Day

Unless specified otherwise, study day will be calculated as the difference between the assessment date and index procedure date, i.e., assessment date – index procedure date, and the date of index procedure is considered as Day 0.

7.2 Disposition of Study Subjects

The number and percentage of subjects in each analysis set will be provided, together with a summary of number of subjects who completed or discontinued the study with associated reasons.

Enrollment by site will be summarized for all consented subjects and each analysis set as well.

7.3 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be summarized for each analysis population, including but are not limited to the following:

- Demographics and baseline characteristics
- Medical history
- Baseline stroke characteristics
- Baseline mRS, NIHSS scores

7.4 Procedural Characteristics

Procedural characteristics and procedure per pass data will be summarized descriptively for each analysis set for the passes Nimbus was used in addition to all procedure passes. Data are including but are not limited to the following:

- Type of mechanical thrombectomy device used
- Type of catheter applied overall and at per pass level, e.g., balloon guide catheter, intermediate catheter, microcatheter etc.
- Clot retrieval per pass
- mTICI scores at the end of procedure and after each pass

7.5 Primary and Secondary Endpoint Analyses

mTICI scores and embolization to a new territory (ENT) will be summarized using the assessments from the independent core lab. Unless instructed otherwise, missing values will be excluded from the analysis. Exact CIs will be conducted around the percentage, unless instructed otherwise.

All-cause mortality and mRS ≤ 2 at 90 days will be analyzed using mITT and mRS analysis sets, all other endpoints will be analyzed using the mITT analysis set.

7.5.1 Primary Endpoint Analysis

- **Successful Revascularization (mTICI ≥ 2b) with NIMBUS as determined by an Independent Core Lab.**

The primary endpoint is successful revascularization after the final pass of NIMBUS, where the successful revascularization is defined as an mTICI score of 2b or greater.

The number and percentage of subjects with a procedural mTICI score ≥ 2b following the final pass of NIMBUS will be summarized, excluding mTICI scores from other devices applied after the final pass with NIMBUS.

Subjects with a missing mTICI score (from the imaging core lab) for the final pass using Nimbus, will be imputed with the final (end of procedure) mTICI score from the imaging core lab if the final pass using Nimbus is the last procedural pass, there were no post mechanical thrombectomy interventions and no intra-arterial thrombolytic agent performed after the final Nimbus pass.

7.5.2 Secondary Endpoint Analyses

1. **Successful Procedural Revascularization (final mTICI ≥ 2b)**

The number and percentage of subjects with a final (end of procedure) mTICI score ≥ 2b will be summarized.

Subjects with a missing mTICI score (from the imaging core lab) at the end of procedure will be imputed with the non-missing mTICI score from the last procedural pass (e.g., pass 1 to 10) from the imaging core lab if there were no post mechanical thrombectomy interventions and no intra-arterial thrombolytic agent performed after the final procedural pass.

2. **Excellent Procedural Revascularization (final mTICI ≥ 2c)**

The number and percentage of subjects with a final (end of procedure) mTICI score ≥ 2c will be summarized.

Subjects with a missing mTICI score (from the imaging core lab) at the end of procedure will be imputed with the non-missing mTICI score from the last procedural pass (e.g., pass 1 to 10) from the imaging core lab if there were no post mechanical thrombectomy interventions and no intra-arterial thrombolytic agent performed after the final procedural pass.

3. **First Pass Revascularization using NIMBUS (mTICI ≥ 2b)**

The number and percentage of subjects with an mTICI score ≥ 2b following the first pass of NIMBUS will be summarized. Subjects with a missing mTICI score (from the imaging core lab) for the first pass using Nimbus, will be imputed with the final (end of procedure) mTICI score from the imaging core lab if the first pass using Nimbus is the last procedural pass, there were no post mechanical thrombectomy interventions and no intra-arterial thrombolytic agent were performed after the first Nimbus pass.

4. **Occurrence of Embolization to a New Territory (ENT)**

The number and percentage of subjects with ENT following the final pass of NIMBUS will be summarized.

5. **Symptomatic Intracerebral Hemorrhage (sICH) at 24 hours specified according to the Heidelberg Bleeding Classification (HBC).**

sICH is defined as a new intracranial hemorrhage as detected by brain imaging, measured at 24 hours post-procedure. The number and percentage of subjects with sICH up to 24 hours post-procedure as assessed by HBC will be summarized.

6. **90 Day All-Cause Mortality.**

Kaplan-Meier analysis (product limit estimates) will be used to estimate all-cause mortality rate using mITT analysis set. All-cause mortality is defined as the event; and the date of mortality is considered as the date of event. Subjects without events will be censored at the date of last contact (e.g. date of study completion or early discontinuation). Deaths beyond 90 days will be listed.

Kaplan-Meier event (failure) rate and associated two-sided 95% CIs using log-log transformation will be reported, the estimate of standard error will be computed using Greenwood's formula.

In addition to the primary analysis using the mITT Analysis Set, the same analysis will be repeated using the mRS analysis set.

7. **Modified Rankin Scale (mRS) ≤ 2 at 90 days.**

The number and percentage of subjects with mRS scores ≤ 2 at 90 days (76 days or above) will be summarized using the mRS analysis set. Subjects with missing mRS scores due to all-cause mortality are considered to have an mRS score of 6 in the analysis. Subjects with missing data due to reasons other than all-cause mortality will be excluded from analysis. Subjects with mRS scores outside or didn't reach the 90-day window, due to reasons other than mortality, will be listed together with their mTICI scores at end of procedure and after final pass of NIMBUS.

In addition to the primary analysis using the mRS analysis set, the same analysis will be repeated using the mITT analysis set.

7.5.3 Ancillary Endpoint Analysis

Ancillary endpoints will be analyzed using the mITT analysis set.

- **Clot Analysis**

  Histopathologic analysis of clot collected

Subjects with any clot composition data (e.g., red blood cells, fibrin measurements) from at least one pass will be included into the clot analyses. Study passes without clots retrieved will be excluded from analyses. Missing data of clot dimension or composition from the central clot are anticipated to be very small. Missing data on clot composition or dimension will be excluded from analysis, should there be any.

Composition of clot components to be evaluated includes RBC, WBC, fibrin, collagen, platelets and Von Willebrand Factor (vWF), as evaluated from the Central Lab, will be summarized per pass and overall. The clot weight (mg) and area (mm^2) will also be summarized per pass and overall in same way.

The total area (across all passes with clots extracted and clot composition measured from central lab) will be calculated to sum up the area from all individual pass with clots. The total weight (across all passes) will be calculated in the same fashion as the total area.

The total amount of RBC (across all passes, %) in terms of area (A) =

$$RBC_{pass\ 1}(\%) \times \frac{A_{pass\ 1}}{Total\ A} + RBC_{pass\ 2}(\%) \times \frac{A_{pass\ 2}}{Total\ A} +, \ldots, + RBC_{pass\ n}(\%) \times \frac{A_{pass\ n}}{Total\ A}$$

The total amount of RBC (%) in terms of weight (W) =

$$RBC_{pass\ 1}(\%) \times \frac{W_{pass\ 1}}{Total\ W} + RBC_{pass\ 2}(\%) \times \frac{W_{pass\ 2}}{Total\ W} +, \ldots, + RBC_{pass\ n}(\%) \times \frac{W_{pass\ n}}{Total\ W}$$

Where $RBC_{pass\ i}$ is the individual pass with RBC measurement; and n is the total number of passes with areas for that subject.

Other clot composition data (e.g., fibrin, white blood cells etc.) will be calculated in the same fashion as RBC, in terms of clot area and weight separately. All clot composition will be summarized per pass and overall across all passes. Additional analyses on clots may be performed as appropriate for exploratory purpose.

- **Hospitalization Analyses**

Medical resource utilization and health economics related data will be summarized.

Hospitalization data will be summarized for alive subjects. Unscheduled hospitalizations post index procedure are considered as re-hospitalizations. The number of subjects who died during the index procedure or re-hospitalizations will be summarized separately.

Subjects with missing admission or discharge date for whom the calculation of length of stay cannot be performed will be excluded from calculation, e.g., withdrawal from study prior to discharge. However they will still be counted towards the number of index procedure hospitalizations and re-hospitalizations, as applicable.

1. **Hospitalization length of stay for index procedure and unscheduled re-hospitalizations**

Summary statistics will include the total length of stay, length of stay in intensive care unit (ICU) and length of stay in medical/surgical floor or routine care, per the following formula:

- Length of stay (days) = date of discharge – date of admission + 1
- Total length of stay (days) = length of stay in ICU (days) + length of stay at medical/surgical floor or routine care.

Discharge location will be summarized for subjects who were discharged alive following index procedure.

2. Healthcare resource utilization for index procedure, post-procedure and re-hospitalizations for unscheduled events.

The number and percentages of subjects with at least one re-hospitalization, the number of re-hospitalizations (including hospitalizations without discharge due to reasons such as death or early withdrawal), and the mean and maximum length of stay will be summarized, where the maximum length of stay is taken to be the maximum stay, in number of days, across all re-hospitalizations at the subject level.

7.6 Analyses of Adverse Events (AEs)

The number of events, the number and percentage of subjects with at least one event will be summarized by body system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), overall and by following categories.

- All AEs
- Serious AE (SAEs)
- Device and/or procedure related AEs (composite)
- Device related AEs
- Procedure related AEs
- Unanticipated serious adverse device effects (USADEs)

7.7 Handling of Missing Data

Missing data for the primary analysis of mRS ≤ 2 at 90 days (section 7.5.2) will not be imputed. The imputation of missing mRS scores at 90 days for sensitivity analysis is detailed in section 7.8.

There are no other missing data imputation planned in the study.

7.8 Sensitivity Analysis

- mRS ≤ 2 at 90 days

Due to reasons other than all-cause mortality, missing mRS scores at 90 days (76 days or above) will be imputed using the last non-missing post-procedure mRS score (e.g., mRS score from discharge or any unscheduled visits) if available. If such

subjects have no post-procedure mRS scores, they will be excluded from sensitivity analysis.

The mRS ≤ 2 at 90 days will also be analyzed by the window of ±14 days using observed data (without last observation carry forward imputation).

7.9 Subgroup Analysis

The primary endpoint will be analyzed by subgroups with clinically meaningful risk factors using the mITT analysis set. Additional subgroup analyses may be performed as applicable. Descriptive statistics (continuous summary measure for the mTICI score) for each subgroup will be presented when there is a minimum of 10 subjects in all subgroup levels, CIs will not be provided due to limited sample size.

- Clot composition: Tough clot vs. Other clot
- Nimbus first use: Procedural Pass 2 vs. Procedural Pass 3
- Vascular location:
- Balloon guide catether (BGC) usage: BGC used vs. BGC not used

  Subjects who used BGC are defined as those who used BGC at least once during procedure; otherwise subjects will be classified as no use of BGC throughout the procedure.
- Use of BGC and/or IC: BGC with IC, BGC without IC vs. no BGC

  BGC with IC – subjects who used BGC and IC at least once during procedure;

  BGC without IC – subjects who used BGC at least once, but none with IC during procedure;

  No BGC – subjects who didn't use of BGC throughout the procedure.

7.10 Additional Analyses

Unless specified otherwise, the following events will be analyzed using the mITT Analysis Set.

- Device deficiency

Subjects with at least one device deficiency data from CRF will be listed.

- Protocol deviations

The number of deviations, the number and percentages of subjects with any protocol deviation will be summarized overall and by deviation category.

- NIH Stroke Scale (NIHSS) total score

The NIHSS total score and change from baseline will be summarized at the scheduled visits with observed data.

- mTICI scores

All mTICI scores will be summarized by pass and at the end of study procedure using the assessments from the core lab.

- First pass effect using NIMBUS

To investigate the first pass effect using NIMBUS, the number and percentage of subjects by mTICI score(including combinations of mTICI ≥ 2b, mTICI ≥ 2c) following the first pass of NIMBUS will be summarized using the assessments from the core lab.

A shift table of mTICI scores from pre-first NIMBUS pass to post-final NIMBUS pass will be summarized, excluding the end of procedure mTICI scores.

Similarly, a shift table of mTICI scores before and after the first NIMBUS pass will be summarized as well.

7.11 Changes from the Planned Analyses

- Analysis window mRS ≤ 2 at 90-day

Due to the potential impact of Covid-19, it is expected that there may be more late 90-day mRS assessments compared to the SAP-defined 90-day window of ±14 than anticipated. In order to minimize the impact of out of 90-day window assessments, analyses on mRS endpoint will include all available assessments on or after 76 days. Analyses using the 90-day window of ±14 days will be considered part of the sensitivity analyses (section 7.8).

Other study endpoints at 90 days (e.g., all-cause mortality at 90 days) are not impacted by the 90-day window as other endpoints are not restricted by the compliance of the 90-day visit.

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