Statistical Analysis Plan (SAP)

Prospective Evaluation to Characterize the Real-World PerFormance of the EMBOVACTM Aspiration Catheter for Neurothrombectomy: A Post-Market Clinical Follow-up Trial

Protocol Version: 1.0

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Prospective Evaluation to Characterize the Real-World PerFormance of the EMBOVACTM Aspiration Catheter for Neurothrombectomy: A Post-Market Clinical Follow-up Trial

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Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
1.0	20JAN2022	First edition.

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1 Study Design

This is a prospective, multi-center, single-arm, post-market clinical follow-up study that will enroll approximately 100 subjects at approximately 10 sites primarily in Europe, with clot collection for follow-on histopathological analysis. Subjects will be included in the study for a period of 3 months after the procedure, including follow up visits at 24 hours, 7 days (or discharge) and 90 days after the procedure.

2 Treatment Assignment

This is a single arm study and all enrolled subjects are intended to be treated with the study device, the EMBOVAC Aspiration Catheter.

3 Interval Windows

Study reports will be summarized using analysis visits as defined below.

- 24 Hours post-procedure (-12 to +48 hours)
- 7-Day/Discharge (-1 to +7 days)
- 90-day follow-up (±15 days)

The study schedule is to be adhered to as closely as possible for all subjects. Data will be summarized by scheduled visit. Measurements outside the analysis windows will be considered as missing in the analysis. In the case of repeated measurements taken at the same visit, the most recent measurement with non-missing values 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 will consist of enrolled subjects who have received treatment (at least one pass; a pass being defined as use of aspiration followed by evaluation of revascularization with angiography) with the study device.

  A subject is considered enrolled in this study once the physician confirms subject meets all eligibility criteria and the subject signs the informed consent.

  The mITT analysis set will be used to analyze effectiveness endpoints.

- **Safety Analysis Set**

The safety analysis set will consist of all enrolled subjects in whom the treatment was attempted, defined by the advancement of the EMBOVAC Aspiration Catheter inside of the subject.

The safety analysis set will be used to analyze safety endpoints.

6 Sample Size Justification

There is no statistical power calculation and no hypothesis tests for this post-market study. 100 subjects are deemed sufficient to characterize the performance of EMBOVAC Aspiration Catheter.

Approximately 100 subjects will be enrolled. With an enrolled sample size of 100 and an attrition rate of no more than 5%, the precision (margin of error) for the primary endpoint is anticipated to be around 8.0% based on 2-sided 95% confidence intervals, where the primary endpoint rate is estimated to be 80%.

$$Margin\ of\ error \approx 1.96 \times SE = 1.96 \times \sqrt{\frac{p(1-p)}{n}} = 1.96 \times \sqrt{\frac{0.8 \times (1-0.8)}{95}} = 8.0\%$$

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.

- 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.

- Study Day

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

- Stroke onset date and time

Stroke onset date and time is defined as follows:

  - 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 subject was last seen well from CRF will be used.

7.2 Disposition of Study Subjects

The number and percentage of subjects in each analysis set will be provided, together with the summary of subjects who early terminated from the study with associated reasons.

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

7.3 Demographic and Baseline Characteristics

All demographic profiles and baseline characteristics will be summarized descriptively for each analysis set as applicable, including but are not limited to:

- Demographics and baseline characteristics, including age at consent (years), sex, height (cm), weight (kg), body mass index (kg/m^2), systolic/diastolic blood pressure (mmHg), ethnicity, race, etc.
- Medical history
- Baseline stroke characteristics, including time to puncture since stroke onset (mins); use of intravenous tissue plasminogen activator (IV-tPA, yes or no), NIHSS score, pre-stroke mRS score (by category of 0, 1, …, 5), etc.

7.4 Procedural Characteristics

Procedural characteristics will be summarized descriptively for each analysis set by pass and overall.

7.5 Primary and Secondary Endpoints

Modified Thrombolysis in Cerebrovascular Infarction (mTICI) scores will be summarized using the assessments from the independent core lab. Missing mTICI scores will be excluded from the analysis.

7.5.1 Primary Endpoint

- **Successful revascularization (final mTICI ≥ 2b), as determined by Core Lab**

  The number and percentage of subjects achieving a final mTICI score ≥ 2b will be summarized using mITT analysis set. A two-sided 95% CI using the normal approximation method will be constructed around the percentage.

7.5.2 Secondary Endpoints

Secondary effectiveness endpoints will be analyzed in the mITT analysis set and secondary safety endpoints will be analyzed in the safety analysis set. Two-sided 95% CIs using binomial exact method will be constructed if required by the endpoint. Missing data will be excluded from the analysis unless instructed otherwise.

7.5.2.1 Secondary Effectiveness Endpoints

- **Successful Revascularization (final mTICI ≥ 2b) without rescue therapy, as determined by Core Lab**

  The number and percentage of subjects achieving a final mTICI score ≥ 2b without rescue therapy will be summarized with CIs. Subjects who received rescue will be considered as failures and included into the denominator of the rate.

- **Complete revascularization (final mTICI ≥ 2c), as determined by Core Lab**

  The number and percentage of subjects achieving a final mTICI score ≥ 2c will be summarized with CIs.

- **First Pass Effect (mTICI ≥ 2c without rescue), as determined by Core Lab**

  The number and percentage of subjects with an mTICI score ≥2c after first pass with the EMBOVAC Aspiration Catheter without rescue therapy will be summarized with CIs. Subjects who received rescue during the first pass will be considered as failures and included into the denominator of the rate.

  Subjects with a missing mTICI score at pass one from the imaging core lab, will be imputed with the final (end of procedure) mTICI score from the imaging core lab if the total number of passes equal to one and no post mechanical thrombectomy interventions and no intra-arterial thrombolytic agent were performed post first pass one.

- **Modified First Pass Effect (mTICI ≥ 2b), as determined by Core Lab**

  The number and percentage of subjects with an mTICI score of ≥2b after first pass with the EMBOVAC Aspiration Catheter, regardless of rescue therapy, will be summarized with CIs.

- Subjects with a missing mTICI score at pass one from the imaging core lab, will be imputed with the final (end of procedure) mTICI score from the imaging core lab if

the total number of passes equal to one and no post mechanical thrombectomy interventions and no intra-arterial thrombolytic agent were performed post first pass.

- **Time to recanalization (Time from arterial puncture to complete recanalization mTICI ≥ 2b), as determined by Core Lab**

  The procedure time, in minutes, from arterial puncture to complete recanalization (achievement of the first mTICI score ≥2b) will be summarized. If a subject was not able to achieve an mTICI score of 2b or greater, the time from arterial puncture to visualization of the final angiogram will be used. Time of arterial puncture, visualization of final angiogram, imaging time per pass will all be based on site reported data; mTICI reading will be based on the core lab.

- **Modified Rankin Scale (mRS) 0-2 at 90 days**

  The number and percentage of subjects achieving mRS 0-2 at 90 days (75 days or above) will be summarized with CIs. 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 mRS scores due to reasons other than all-cause mortality will be excluded. 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.

7.5.2.2 Secondary Safety Endpoints

Device-related SAEs and all-cause mortality, Kaplan-Meier analysis (using product limit estimates) will be applied. Kaplan-Meier event rate and its associated two-sided 95% CIs using log-log transformation will be reported, the estimate of standard error will be computed using Greenwood's formula.

- **Devices related serious adverse events (SAEs) within 90 days of follow up as determined by an independent Clinical Events Committee**

  Kaplan-Meier analysis will be performed to analyze the device related SAE rate within 90 days. Device related SAEs are considered as events; where the event date is the date of first event. Subjects without events will be censored at the date of last contact. The event rate at 90 days with associated 95% CIs will be provided. Device related SAEs beyond 90 days will be listed.

- **sICH at 24h post procedure specified according to the Heidelberg Bleeding Classification (HBC) as determined by an independent Clinical Events Committee**

  sICH at 24 hours post procedure as specified by HBC will be assessed. The number and percentage of subjects with events will be summarized with CIs.

- **NIHSS at 24h post procedure**

  The observed NIHSS total score at 24 hours post-procedure and changes from the baseline score will be summarized.

- **90 Day All-Cause Mortality**

  Kaplan-Meier analysis will be performed to analyze all-cause mortality within 90 days. All-cause mortality is considered as the event; where the event date is the date of mortality. Subjects without events will be censored at the date of last contact. The event rate at 90 days with associated 95% CIs will be provided. Deaths beyond the 90 days will be listed.

7.6 Health Economic Endpoints

Hospitalization data will be analyzed for live subjects in the mITT population.

Unscheduled hospitalizations post index procedure are considered as re-hospitalizations. The number of hospitalized 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 (LOS) cannot be performed will be excluded from calculation, e.g., withdrawal from study prior to discharge etc. However, they will still be counted towards the number of index procedure hospitalizations and re-hospitalizations, as applicable.

- **Hospitalization length of stay for index procedure**

  LOS in hospitalizations due to index procedure will be summarized at the subject level per the following formula.

  Length of stay (days) = discharge date – admission date + 1.

  LOS will be summarized for subjects who were discharged alive following index procedure. The overall LOS, and LOS at ICU will be summarized separately. Further, the number and percentage of subjects with hospitalization length of stay will be summarized in categories: 0 to ≤1 day, >1 to ≤2 days, and >2 days.

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

- **Unscheduled re-hospitalizations post index procedure**

  The number and percentage of subjects with at least one re-hospitalization, the number of re-hospitalizations (including re-hospitalizations without discharge due to reasons such as death or early withdrawal), the maximum length of stay across re-hospitalizations will be summarized for subjects who were discharged alive from index procedure. The maximum length of stay is taken to be the maximum number of stay, in days, across all re-hospitalizations at the subject level.

7.7 Clot Analysis

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 using mITT analysis set. The clot weight (mg) and area (mm2) 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 (across all passes, %) 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 for each 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 across all subjects per pass and overall.

7.8 Analyses of Adverse Events (AEs)

AEs will be analyzed using safety analysis set. 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 adverse events (SAEs)
- Device and/or procedure related AEs
- Device related AEs
- Procedure related AEs
- Unanticipated serious adverse device effects (USADEs)

The independent clinical event committee will make adjudications for device and/or procedure related SAEs as specified in the PERFECT study Clinical Event Committee Charter.

7.9 Plans for Interim Analyses

Interim analyses will be conducted for regional (outside Europe, as well as for European MDR) regulatory submission purposes. Only descriptive statistics will be reported. Results of the interim analyses will not be used as a basis for stopping the trial early.

7.10 Handling of Missing Data

Missing data for the primary analysis of mRS ≤ 2 at 90 days (section 7.5.2.1) will not be imputed. The imputation of missing mRS scores at 90 days for sensitivity analysis is detailed in section 7.11.

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

7.11 Sensitivity Analyses

- mRS ≤ 2 at 90 days

  mRS sensitivity analyses will be based on mITT analysis set.

  Due to reasons other than all-cause mortality, missing mRS scores at 90 days (75 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. Subjects without any post-procedure mRS scores will be excluded from sensitivity analysis.

  The mRS ≤ 2 at 90 days will also be analyzed by the window of ± 15 days using observed data (without last observation carry forward imputation).

7.12 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 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.
  - Age at consent (years)
  - Vascular location
  - ASPECTS score
  - Baseline NIHSS
  - Aspiration device position when aspiration started in pass 1
- The following bullets will be analyzed for primary endpoint, secondary effectiveness and safety endpoints, demographic and baseline characteristics using the analysis set (as defined from section 7.3 to section 7.5). Descriptive statistics will be

presented based on observed data; CIs will not be presented due to limited sample size.

- System approach of EMBOVAC in combination with Cerebase (long sheath)

  Descriptive statistics will be presented if the number of subjects who have used CEREBASE at least once during the procedure is greater than 10 , by following category:

  EmboVAC + any LS (including Cerebase)

  EmboVAC + Cerebase only (no other LS other than Cerebase).

- Clots

  Descriptive statistics will be presented by following category: tough clots vs. other clots.

7.13 Additional Analyses

- Protocol deviations

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

- Device malfunctions/deficiency

  Subjects with at least one device malfunctions/deficiency will be listed.

- 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.

- mRS scores

  mRS scores by categories of 0, 1, 2, …, 6 will be summarized at scheduled visits using mITT analysis set. A shift table of mRS score from baseline to 90-day follow-up will be summarized as well.

7.14 Changes from 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 ±15 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 75 days. Analyses using the 90-day window of ±15 days will be considered part of the sensitivity analyses (section 7.11).

Other study endpoints at 90 days (e.g., all-cause mortality at 90 days, device and/or procedure related SAEs at 90 days) will still be based on the 90-day window of ±15 days considering the event days are not restricted by the compliance of the 90-day visit.

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