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Statistical Analysis Plan (SAP)

Study Name: AVENTUS

Protocol: CT-0001, Revision D

About

Overview

This Statistical Analysis Plan (SAP) is written to further describe the methods and procedures used in reporting data collected in the AVENTUS Study: Assessing the Safety and Efficacy of the treatment for Acute Pulmonary Embolism using the Inquis Medical Aventus Thrombectomy System™ (Protocol No. CT-0001). It was developed based on Revision D of the Protocol. Further updates to the protocol or the SAP may be required. In the event that SAP updates are required that do not impact the conduct of the study as written in the most recent version of the protocol, updates to the protocol may not be required and the SAP will serve as the primary guiding document for statistical related activities.

Statistical software such as STATA version 17.0 or higher will be used to prepare the tables, listings, and figures for the study.

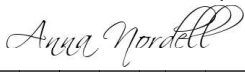
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1. Overview of Study Design

This study is a prospective, multi-center, single-arm, non-blinded clinical trial to evaluate the safety and efficacy of the Aventus Thrombectomy System™ for aspiration thrombectomy in subjects with acute pulmonary embolism (PE). The study will evaluate change in right ventricle/left ventricle (RV/LV) ratio from baseline to 48 hours post-index procedure as the primary efficacy endpoint, major adverse events (MAEs) within 48 hours of the index procedure as the primary safety endpoint, and a number of observational endpoints assessed at the time of the procedure, 48 hours post-index procedure, and within 30 days of the index procedure.

All subjects will be followed through 30 days with the following timepoints also being captured prior to study exit: screening, procedure (pre-, index, and post-), and 48 hours.

Up to 120 subjects will be enrolled at up to 35 United States (US) investigative sites. Each site can enroll a maximum of 30 subjects. In addition, each site may enroll up to 2 roll-in subjects for a total of 50 roll-in subjects.

2. Objectives and Endpoints

The primary objective of this trial is to evaluate the safety and efficacy of the Aventus Thrombectomy System™ for aspiration thrombectomy in subjects with acute pulmonary embolism.

ENDPOINT	DESCRIPTION
Primary	
Safety	Composite of device related MAEs within 48 hours (± 8 hours) of the index procedure, as adjudicated by the Clinical Events Committee (CEC), including: • Death • Major bleed • Clinical deterioration • Pulmonary vascular injury • Cardiac injury
Effectiveness	Core laboratory adjudicated change in RV/LV ratio from Baseline to 48 hours (± 8 hours) post-index procedure as measured by computed tomography angiography (CTA).
Observational	
	Length of stay in the Intensive care unit (ICU) related to index procedure
	Length of stay in the hospital (general ward) related to index procedure
	Core laboratory adjudicated change in Refined Miller Score from baseline to 48 hours (± 8 hours) post-procedure as assessed by CTA
	Use of thrombolytics within 48 hours (± 8 hours) of the index procedure
	Device related death within 48 hours (± 8 hours) of the index procedure*
	Device related major bleed within 48 hours (± 8 hours) of the index procedure*
	Device related clinical deterioration within 48 hours (± 8 hours) of the index procedure*
	Device related pulmonary vascular injury within 48 hours (± 8 hours) of the index procedure*
	Symptomatic pulmonary embolism (PE) recurrence within 30 days (± 7 days) of index procedure confirmed by imaging*
	Device related serious adverse events (SAEs) within 30 days (± 7 days) of the index procedure*
	All cause death within 30 days (± 7 days) of the index procedure
	Change in Six-Minute Walk Test (6MWT) from 48 hours (± 8 hours) to 30 days (± 7 days)
	Change in quality of life through 30 days (± 7 days) as measured by the PEmb-QoL Questionnaire ¹⁻⁴

*CEC Adjudicated

3. Statistical Considerations

3.1 Statistical Hypotheses

The primary safety and efficacy endpoint will be compared to a performance goal using a one-sided 2.5% significance level for each test, respectively. Additional hypotheses are not planned to be tested formally in order to control the overall type I error.

The study is considered a success when the test for the primary efficacy endpoint and the test for the primary safety endpoint are both statistically significant.

3.2 Sample Size Determination

The sample size is based off of the primary efficacy and primary safety endpoints both being compared to a performance goal using a one-sided significance level 2.5% for each test. Sample size calculations were performed using PASS 2019.

Primary Efficacy Endpoint:

An observed RV/LV ratio change from baseline to 48 hours post-index procedure of 0.30 with a standard deviation of 0.35 will be compared to a performance goal of 0.20. Using a t-test, 99 subjects will achieve power of 0.8 for the primary efficacy endpoint.

Statistical Hypothesis: $H_0: \mu_{\text{Inquis}} \leq \mu_{\text{Minimum}}$ versus $H_1: \mu_{\text{Inquis}} > \mu_{\text{Minimum}}$

where μ_{Inquis} is the average Change from Baseline in the RV/LV Ratio 48 hours after treatment, and μ_{Minimum} is the minimum efficacy threshold for the average Change from Baseline in the RV/LV Ratio 48 hours after treatment.

Primary Safety Endpoint:

The performance goal for the statistical testing of the primary safety endpoint is an MAE rate of 25%. It is estimated that the Aventus Thrombectomy System™ will demonstrate an MAE rate of 13.48% or less. Using a one-sided 2.5% significance level, 108 subjects will achieve 80% power.

Statistical Hypothesis: $H_0: \pi_{\text{Inquis}} \geq \pi_{\text{Maximum}}$ versus $H_1: \pi_{\text{Inquis}} < \pi_{\text{Maximum}}$

where π_{Inquis} is the percent of treated subjects with a composite MAE within 48 hours (± 8 hours) after treatment, and π_{Maximum} is the maximum safety threshold for the percent of treated subjects with a composite MAE within 48 hours (± 8 hours) after treatment

Assuming roughly a 10% attrition rate, including patients that were lost to follow-up, withdrawn, received thrombolytic agents within 48 hours (± 8 hours) of the procedure, or if a primary endpoint assessment is missing,

i.e., CTA at 48 hours (± 8 hours) post procedure, up to 120 subjects will be enrolled to ensure at least 108 subjects are evaluable for the primary safety and efficacy endpoints.

3.3 Populations for Analyses

The following analysis populations will be used:

Safety/Intention-to-Treat (ITT) analysis population: All subjects in whom the Aventus Thrombectomy System™ has been introduced into their body. The data from this population will be analyzed even if the subject did not follow the protocol until completion. Analyses for all safety related endpoints will be performed using the Safety/ITT Cohort.

Modified ITT (mITT) analysis population: A subset of the ITT analysis sample which excludes subjects that received adjunctive treatments for the purpose of reducing clot burden in the pulmonary arteries (intra-procedure and up to 48 hours (± 8 hours) post procedure) or had received any thrombolytics during the procedure and up to 48-hours (± 8 hours) post procedure. This population will be the primary population for all efficacy related endpoints.

Thrombolytic & Treatment population: A subset of the ITT analysis sample which includes subjects that received adjunctive treatments and/or thrombolytics during the procedure and up to 48-hours (± 8 hours) post-procedure. Subjects in this Cohort will be analyzed separately from the mITT analysis population with descriptive statistics.

Roll-In population: Sites will be permitted to use the investigational device in up to two (2) roll-in subjects per site. Subjects in this population will be analyzed separately from the ITT population, described using descriptive statistics, and are not included in the analysis of the endpoints. Up to 120 subjects will be enrolled, excluding the roll-in population.

3.4 Statistical Analyses

3.4.1 General Approach

The trial is anticipated to last two years, and each subject will be in the trial for approximately 30 days. A subject is considered enrolled if the informed consent form is signed by either the subject or the subject's legally authorized representative (LAR) and in whom the Aventus Thrombectomy System™ has been introduced into their body.

Subject follow-up days will be calculated by using the last reported date of the following: follow-up visit, adverse event start, death, PE recurrence, and study exit. Study day 0 will be the date of index procedure.

3.4.2 Descriptive Statistics

This section describes the descriptive statistics that will be provided with each analysis. The statistics depend on the type of variable (endpoint) that is analyzed. Descriptive statistics such as demographics, relevant medical history, vital signs, and pulmonary artery pressure will be tabulated.

The descriptive statistics that will be presented will depend on the data type:

- 1) Continuous data will be summarized using n, mean, standard deviation, median, minimum, and maximum values.
- 2) Categorical data will be summarized using frequency and percentage.

Change and percentage change from baseline to post-procedure follow-up timepoints will be calculated. Within-subject changes in a continuous endpoint (Change-from-Baseline) will be analyzed parametrically using the Paired t-test if the differences are normally distributed, or non-parametrically using the Signed-Rank Test if the differences are not normally distributed. Normality will be assessed with a Shapiro-Wilk test; a p-value of <0.05 for this test will be taken as evidence of non-normality. Exact binomial confidence intervals will be generated for estimates of proportions. Asymptotic confidence intervals based on the t-distribution will be generated for estimates of means. Confidence intervals will be presented when relevant.

3.4.3 Control of Type 1 Error

Type I error is controlled at an overall alpha of 0.05. Each of the two primary endpoints are tested at a significance level of 0.025.

3.4.4 Imputation of Missing Data and Sensitivity Analyses

Every attempt will be made to prevent missing data and the primary analyses are powered such that an analysis of complete data will be considered the primary analysis for this study. In the event that missing data occurs relating to the primary safety or efficacy endpoint, methods such as best case/worst case will be applied. If the conclusion of these analyses agrees with conclusion based on complete data (results of all hypothesis tests are significant/not significant), no additional analyses will be performed relating to missing data. If the conclusions are not in agreement, a tipping point analysis will be performed to understand the possible scenarios that would lead to either a significant/not significant result.

3.4.4.1 Sensitivity Analyses

An analysis of the primary and observational endpoints may be performed on the group of participants that met all inclusion/exclusion criteria if the population is different than the populations for analyses already previously defined.

3.4.5 Randomization and Blinding

There is no randomization or blinding that will occur as this is a single-arm clinical trial.

4. Primary Endpoints

4.1 Analysis of the Primary Safety Endpoint

The primary safety endpoint is the composite of device related MAEs within 48 hours (± 8 hours) of the index procedure, as adjudicated by the Clinical Events Committee (CEC), including:

- Death
- Major bleed
- Clinical deterioration
- Pulmonary vascular injury
- Cardiac injury

The MAE proportion will be reported as the number of subjects experiencing at least 1 MAE within 48 hours (± 8 hours) of the index procedure out of those subjects either experiencing an MAE within 48 hours (± 8 hours) of the index procedure or follow-up of at least that length of time.

Results will be summarized for the ITT population as the primary population of interest. Additional populations may be summarized with descriptive statistics only. Roll-in subjects will not be included in the ITT population.

4.1.1 Data Collection

Events will be classified and reported by the Clinical Events Committee. The CEC will also denote on the adjudication form whether or not the event occurred within 56 hours of the index procedure.

4.2 Analysis of the Primary Effectiveness Endpoint

Core laboratory adjudicated change in RV/LV ratio from Baseline to 48 hours (± 8 hours) post-index procedure as measured by CTA is the primary effectiveness endpoint. The measure at each time point, as well as the change, will be summarized as a continuous outcome.

The mITT population will be the primary population. The Thrombolytic & Treatment population and Roll-in population will be summarized separately with descriptive statistics only.

4.2.1 Data Collection

RV/LV ratio is reported on the Core Lab form at both screening and 48 hours/discharge. The value reported at screening will be subtracted from the value reported at 48 hours/discharge.

5. Observational Endpoints

5.1 Analysis of the Observational Endpoints

The table below summarizes the observational endpoints and the analysis that will be used to support the endpoint

	Endpoint	Analysis
1	Length of stay in the Intensive care unit (ICU) related to index procedure	Descriptive statistics for a continuous variable
2	Length of stay in the hospital (general ward) related to index procedure	Descriptive statistics for a continuous variable
3	Core laboratory adjudicated change in Refined Miller Score from baseline to 48 hours (± 8 hours) post-procedure as assessed by CTA	Descriptive statistics for a continuous variable as well as the percent reduction.
4	Use of thrombolytics within 48 hours (± 8 hours) of the index procedure	Descriptive statistics for a categorical variable
5	Device related death within 48 hours (± 8 hours) of the index procedure*	Descriptive statistics for a categorical variable
6	Device related major bleed within 48 hours (± 8 hours) of the index procedure*	Descriptive statistics for a categorical variable
7	Device related clinical deterioration within 48 hours (± 8 hours) of the index procedure*	Descriptive statistics for a categorical variable
8	Device related pulmonary vascular injury within 48 hours (± 8 hours) of the index procedure*	Descriptive statistics for a categorical variable
9	Symptomatic PE recurrence within 30 days (± 7 days) of the index procedure confirmed by imaging*	Descriptive statistics for a categorical variable
10	Device related SAEs within 30 days (± 7 days) of the index procedure*	Descriptive statistics for a categorical variable
11	All cause death within 30 days (± 7 days) of the index procedure*	Descriptive statistics for a categorical variable
12	Change in Six-Minute Walk Test (6MWT) from 48 hours (± 8 hours) to 30 days (± 7 days)	Descriptive statistics for a continuous variable
13	Change in quality of life through 30 days (± 7 days) as measured by the PEmb-QoL Questionnaire ¹⁻⁴	Descriptive statistics for a continuous variable

*CEC adjudicated

Endpoints related to safety (endpoints 5 through 11 above) will be reported for the ITT analysis population. Endpoints 1 through 4 and 12 through 13 above will be reported for the mITT and Thrombolytic & Treatment populations. The roll-in population will be summarized separately for all observational endpoints.

5.1.1 Data Collection

Endpoints relating to length of stay in the ICU and in the general ward related to the index procedure will use length of stay as reported on the hospital stay form at 48 hours/discharge.

The core lab CTA assessment will be used at screening and 48 hours/discharge to assess the change in Refined Miller Score.

Use of thrombolytics within 48 hours (± 8 hours) of the index procedure will be collected on the adjunctive treatments form at 48 hours/discharge.

Device related events, symptomatic PE recurrence and all cause death are all reported on the CEC adjudication form along with whether or not the event occurred within 56 hours or within 30 days.

The change in six-minute walk test is calculated from the 48 hours/discharge 6 Minute Walk Test Case Report Form (CRF) and the same CRF at 30 Days.

The change in quality of life is captured on the PEmb-QoL CRF at Screening and 30 Days.

6. Additional Reporting

6.1 Safety Analyses

The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints of the study, which are based on the protocol. The CEC will review regularly and adjudicate appropriate safety events for causality and attribution. The CEC data supersedes the investigator-reported data in all analyses of safety events.

Each reported adverse event (AE) will be assessed by the CEC for its primary suspected relationship to the study device or to the study procedure and will be summarized in the reporting of events. The following relationship categories will be used:

- Not Related
- Possibly Related
- Probably Related
- Related

Events will be classified as 'related' if they fall into the categories of 'probably related' or 'related'.

Events will also be summarized in the report based on seriousness.

6.2 Sub-group Analyses

Analyses of all endpoints may be repeated for the following subgroups:

- Gender
- Age (< 65 versus ≥ 65)
- Race
- Ethnicity
- Baseline RV/LV Ratio
- Baseline N-terminal pro B-type Natriuretic Peptide (BNP)
- Baseline Simplified Pulmonary Embolism Severity Index (sPESI) score
- Baseline Pulmonary Artery Pressure (PAP)
- Baseline Refined Miller Score

Unless otherwise noted, continuous values used to create subgroups will be cut at the median of the observed data. These analyses are exploratory in nature, and the results may be used when generating hypotheses for

future studies. Summary statistics will be generated for each of the subgroups without any hypothesis tests being performed. Confidence intervals may be generated to aid in the interpretation of the results.

A learning curve analysis comparing the primary outcomes of subjects where the procedure was performed as one of the first procedures for a physician as compared to later procedures for that same physician may be performed as well if the population is notably different than the roll-in versus ITT populations.

6.2.1 sPESI Scoring

Baseline sPESI will be scored using the following data reported at baseline:

- Age >80 years old (1 point)
- History of cancer (1 point)
- Chronic cardiopulmonary disease (1 point)
- Pulse ≥ 110 beats/minute (1 point)
- Systolic blood pressure <100 mmHg (1 point)
- Oxygen saturation <90% at diagnosis of PE (1 point)

The sum of these points will be used to calculate the overall sPESI score⁵. Subgroup analyses will be performed for those subjects scoring 0 as compared to those with a score of 1-6 points.

6.3 Additional Analyses

As an additional analysis, the number of subjects with blood return as well as the amount of blood returned to the patient during the procedure through the blood transfusion filter will be summarized and presented.

6.4 Pooling Data

Data will be pooled from multiple study sites for this analysis. The justification for pooling is made on a clinical basis. The basis for pooling comes from three critical factors: the study sites must implement one common protocol; the Sponsor must provide monitoring of study site compliance; the study sites must use common data collection procedures.

A test for site effect will be based on a regression approach for each of the primary endpoints. A p-value of 0.15 will be taken as potential evidence of site heterogeneity for an endpoint and exploratory analyses would then be performed to examine and quantify such heterogeneity.

Poolability across study sites will be assessed by presenting results across study centers. Differences in results between sites, if deemed to be only quantitative in nature as opposed to qualitative (i.e., if only due to a difference in magnitude of treatment effect across sites as opposed to a difference in direction of treatment effect across sites), will not necessarily disqualify study sites from being pooled. Site differences of a quantitative nature, (i.e., all sites show the treatment to be beneficial, but perhaps to a different degree by study site) will not be an impediment to pooling. Site differences of a qualitative nature (i.e., most sites show

the treatment to be beneficial, but one or more sites show the treatment to be detrimental), will require extensive evaluation of the sites with contrary results to attempt to determine what factors at those sites led to the result.

6.5 Tabulation of Individual Subject Data

Data listings of key subject level data will be used to support reporting and review of the study data as needed.

7. Report Timing

The Sponsor will prepare progress reports and a final study report in accordance with requirements established by local regulatory authorities. The sponsor will submit progress reports at least yearly to the central institutional review board (IRB) of record and to all participating study sites for submission to their IRBs per IRB reporting requirements. The final study report will be submitted within six (6) months of closing the database at the end of the study.

All information and data generated in association with this study will be held in strict confidence until the study is completed.

8. References

¹Cohn DM, Nelis EA, Busweiler LA, Kaptein AA, Middeldorp S. Quality of life after pulmonary embolism: the development of the PEmb-QoL questionnaire. *J Thromb Haemost.* 2009 Jun;7(6):1044-6.

²Klok FA, Cohn DM, Middeldorp S, Scharloo M, Büller HR, van Kralingen KW, Kaptein AA, Huisman MV. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. *J Thromb Haemost.* 2010 Mar;8(3):523-32

³Akaber A, Klok FA, Cohn DM, Hirsch A, Granton J, Kahn SR. Determining the minimal clinically important difference for the PEmbQoL questionnaire, a measure of pulmonary embolism-specific quality of life. *J Thromb Haemost.* 2018 Dec;16(12):2454-2461

⁴Cohn DM, Nelis EA, Busweiler LA, Kaptein AA, Middeldorp S. Quality of life after pulmonary embolism: the development of the PEmb-QoL questionnaire. *J Thromb Haemost.* 2009 Jun;7(6):1044-6.

⁵Jimenez D, Aujesky D, Moores L, et al., RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med.* 2010; 170:1383.

Changes

Summary of Changes

Affected Section(s)	Date	Revisions Made From (Note Previous Version)	Rationale