Statistical Analysis Plan (SAP)

A Prospective, Multi-center, Single Arm Study to Evaluate the Safety and Effectiveness of the CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System when Used in Conjunction with Endovascular Coil Embolization in the Treatment of Wide-necked Saccular Intracranial Aneurysms

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

Signature Page

Study Biostatistician:

[redacted]

(Print) (Sign) Date

Head of Biostatistics (or delegate):

[redacted]

(Print) (Sign) Date

Clinical Study Lead:

[redacted]

(Print) (Sign) Date

Franchise Head of Clinical Research:

[redacted]

(Print) (Sign) Date

Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
Version 1	26/FEB/2019	First edition.

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1. Study Design

This is a prospective, multi-center, single arm, clinical study to evaluate the safety and effectiveness of the ENTERPRISE stent when used in conjunction with endovascular coil embolization in the treatment of unruptured wide-neck, intracranial, saccular anterior circulation aneurysms (≤ 10 mm) arising from a parent vessel with a diameter of ≥ 2.5 mm and ≤ 4 mm. Due to low enrollment in the study, the Sponsor has decided to terminate the study early. The details regarding the length of follow-up for ongoing subjects are documented in the Close Out Plan.

2. Treatment Assignment

This is a single arm study with no comparator device, eligible subjects are expected to be treated with any of the following study devices.

- ENTERPRISE® Vascular Reconstruction Device and Delivery System (ENTERPRISE VRD system),
- ENTERPRISE® 2 Vascular Reconstruction Device and Delivery System (ENTERPRISE 2 VRD system).

3. Randomization and Blinding Procedures

No randomization or blinding is applied in the study.

4. Interval Windows

The following analysis intervals will be applied on the study.

Table 1: Analysis Intervals for Assessments

Visit	Description	Analysis Interval
Screening/Baseline	Screening/Baseline	Day -14 – Day 0
Immediate Pre-Procedure	Immediate prior to treatment	Within 12 hours prior to procedure
Index Procedure	Treatment	Day 0
Immediate Post-Procedure	Immediate post treatment	Within 12 hours post-procedure
Hospital Discharge	Hospital discharge	12 hours to 36 hours post-procedure
30-Day Follow-up	Telephone interview	Day 10 – Day 60
6-Month Follow-up	Clinic visit & Angiogram	Day 92 – Day 240
12-Month Follow-up	Clinic visit & Angiogram	Day 270 – Day 450
18-Month Follow-up	Telephone interview	Day 457 – Day 592
24-Month Follow-up	Clinic visit & MRA or Angiogram	Day 685 – Day 775

Unless specified otherwise, tables will be summarized by visit as defined in Table 1. Measurements outside the analysis windows will be considered as missing in the analysis. In the case of repeated measurements taken at the same analysis visit, the most recent measurement will be used.

5. Primary and Secondary Endpoints

5.1 Primary Endpoints

5.1.1 Primary Effectiveness Endpoint

- Rate of Complete Aneurysm Occlusion (RCAO) at 12-Month Follow-up according to the Raymond Scale as assessed by the Independent Core Laboratory.

  Complete aneurysm occlusion is defined as an aneurysm in which a score of 1 (complete obliteration) is achieved on the Raymond Scale at the relevant post-procedure angiogram, without additional procedures for treatment of the aneurysm since the index procedure. Subjects who are retreated (retreatment includes staged procedures) prior to the 12-Month aneurysm occlusion assessment will be considered not to have achieved this endpoint.

5.1.2 Primary Safety Endpoints

- Incidence of major ipsilateral stroke and/or death at 12-Month Follow-up.

  A major ipsilateral stroke is defined as a new neurological event which is ipsilateral and in the vascular distribution territory of the stenting procedure and that results in an increase of ≥ 4 on the National Institute of Health Stroke Scale (NIHSS) as compared to baseline and persists for greater than 24 hours.

- Incidence of in-stent stenosis at 12-Month Follow-up.

  In-stent stenosis is defined as greater than 50% narrowing of the vessel within the ENTERPRISE stent or within 10 mm of either end of the stent (i.e., in-stent stenosis).

5.2 Secondary Endpoints

5.2.1 Secondary Effectiveness Endpoint

- Procedure success rate

  The procedure success rate is defined to be the percentage of aneurysms in which coil mass position is maintained within the sac with parent artery patency, without additional procedures for treatment of the aneurysm since the index procedure. The procedure success rate will be summarized immediately post-treatment (acute), and at the 6-Month and 12-Month Follow-up assessments.

- Complete aneurysm occlusion as per the Raymond Scale

  The percentage of aneurysms in which a score of 1 (complete obliteration) is achieved on the Raymond Scale immediately post-procedure (acute) and at the 6-Month and 12-Month Follow-up angiographic assessments, respectively, will be evaluated.

- Complete/partial aneurysm occlusion as per the Raymond Scale

  The percentage of aneurysms in which a score of 1 (complete obliteration) or 2 (residual neck) is achieved on the Raymond Scale immediately post-procedure

(acute), and at the 6-Month and 12-Month Follow-up angiographic assessments will be evaluated.

- Percent aneurysm occlusion

  The percentage of subjects with aneurysms occlusion of 100%, 90%-99%, 70-89%, 50-69%, 25-49% or <25% occlusion in accordance with Consensus Grades 0-5, respectively, will be summarized immediately post-procedure (acute), and at the 6 and 12-Month Follow-up, respectively.

- Recanalization rate

  The percentage of aneurysms in which recanalization is documented at any time up to and including the 12-Month Follow-up visit, will be evaluated. Recanalization will be defined as an increase in aneurysm filling as compared to the previous study-specified angiographic assessment, resulting in a change in (i.e., worsening of) the Raymond classification. Changes in Raymond Scale will be classified as stable, improved, or recanalized based on the follow-up angiograms.

- Retreatment rate

  The percentage of target aneurysms that are retreated at any time up to and including the 12-Month follow-up visit will be evaluated. Retreatment will be defined as any additional treatment of the target aneurysm after the index procedure (retreatment includes staged procedures), or an additional procedure (regardless of whether retreatment is by surgery or endovascular treatment) due to recanalization, rupture or bleeding.

5.2.2 Secondary Safety Endpoints

- Rate of new neurological deficits as per the modified Rankin Scale (mRS)

  New neurological deficits will be evaluated in terms of mRS scores at baseline (pre-procedure) and follow-up (30 days, 6-Month and 12-Months post-procedure).

- NIH Stroke Scale (NIHSS) total score

  Neurological morbidity will be assessed using the NIHSS total score. The NIHSS, administered by the investigator, is a 15-item scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the subject's ability to answer questions and perform activities. Ratings for each item are scored on either zero to three or zero to five (with 0 as normal).

- Adverse events (AEs) and clinical complications

  AEs including complications associated with an untoward medical occurrence, from the start of the index procedure until completion of the 12-Month Follow-up will be evaluated, including serious adverse events (SAEs), device- or procedure-related AEs, unanticipated adverse device effects (UADEs) and deaths.

- Reduced TICI flow

The percentage of target aneurysms in which a new occurrence of unintentional and persistent reduced TICI flow (TICI score of 0 or 1) is observed at the target vessel during the index procedure as a result of a mechanical obstruction such as dissection or luminal thrombus will be evaluated.

- Bleeding complications

  The number and percentage of subjects who experience a procedure related hemorrhagic event which requires any of the following will be evaluated: blood transfusion, surgical intervention, a new hospitalization, or lengthening of hospital stay. The complications of hematoma requiring treatment (i.e., a hematoma > 5 cm in diameter occurring at the access site) and retroperitoneal bleeding will be reported as hemorrhagic events.

- In-stent stenosis

  The percentage of aneurysms in which in-stent stenosis is documented immediately post-procedure (acute) and up to and including 6 months post-procedure, will be evaluated.

  Acute in-stent stenosis will be further characterized by whether it results from vasospasm, and whether the vasospasm was responsive to medication.

- Thrombosis

  The percentage of aneurysms in which thrombosis is documented up to and including 6 and 12 months post-procedure will be evaluated. Thrombosis is defined as in-stent thrombosis.

5.3 Ancillary Endpoints

- Stent movement/migration

  Stent movement and/or migration will be evaluated from the start of the index procedure until completion of the 12-Month Follow-up.

5.4 Safety Follow-up after 12 Months Post-Procedure

According to the Close Out Plan, all enrolled and treated subjects will be required to complete follow-up visits through 12 months post-procedure. Hence, only a small number of subjects will have additional safety follow-up data post 12 months. AEs that started after 12-month follow-up will only be listed.

6. Levels of Significance

Protocol specified tests of hypotheses of the primary endpoints at the planned 2.5% significance level will not be conducted due to early termination of the study prior to enrollment of the planned sample size. Two-sided confidence intervals will be computed at a 95% confidence level but are not intended for inference.

7. Analysis Sets

The following analysis sets are defined for the study.

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

The mITT Analysis Set consists of all consented (enrolled) subjects who meet all pre-procedure angiographic eligibility criteria, and in whom treatment with the Enterprise device is attempted.

8. Sample Size Justification

This study was originally planned at a total sample size N=320, with an interim analysis for an early stop (either due to futility or tentative success) at N=160 when subjects were enrolled and followed for a minimum of 6-month post-procedure.

However, as the study will be terminated early due to low enrollment, the total sample size for the descriptive analyses in the final CSR will be based on the actual enrollment achieved. .

9. Data and Safety Monitoring Board (DSMB)

An independent DSMB was constituted for monitoring the accumulated interim data as the study progresses to ensure subject safety. All safety review procedures were established and agreed upon in the DSMB Charter prior to enrollment of the first subject.

10. Analyses to be Conducted

10.1 General Conventions

According to the Close Out plan, only descriptive statistics and listings will be presented, no inferential statistics will be performed for the primary and secondary endpoint. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum and maximum. Descriptive statistics for dichotomous/categorical variables will include the number and percentage of subjects. All summary tables will be presented overall. Unless specified otherwise, percentages are based on non-missing values, excluding missing data and subjects who early discontinued.

- Baseline

Baseline is defined as the last non-missing measurement prior to the index procedure.

- Study Day

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

- Date conversion

For the purposes of statistical analyses, a month is considered equivalent to 30 days and a year is considered equivalent to 360 days.

- SAS version

All statistical analyses will be performed using SAS®, Version 9.2 or later, unless otherwise noted.

10.2 Disposition of Study Subjects

- Disposition

The number and percentage of subjects who are included in and excluded from each analysis set (as defined in Section 7) will be presented, together with a summary of subjects who completed, died or discontinued the study with associated reasons.

10.3 Demographic, Baseline, Aneurysm and Procedure Characteristics

Subject demographics, aneurysms and procedure characteristics will be summarized and listed in mITT analysis set.

10.4 Primary and Secondary Endpoint Analyses

Protocol specified tests of hypotheses of the primary endpoints will not be performed due to the study terminating early for low enrollment. Descriptive analyses of the primary effectiveness and primary safety endpoint will be conducted in the mITT Analysis Set. Categorical data will be summarized with exact binomial confidence intervals for primary effectiveness and safety endpoints. Continuous data will be summarized with averages by visit and as average change from baseline at each visit.

Unless specified otherwise, the classification of adverse events will be based on the data from study case reported forms (CRFs). In the event the data are not captured or are missing, the DSMB and/or CEC adjudication data will be reported.

10.4.1 Primary Endpoints

10.4.1.1 Primary Effectiveness Endpoint

- Rate of RACO at 12 months post-procedure according to the Raymond Scale as assessed by the Independent Core Laboratory.

The number and percentage of subjects with RACO at 12-Month Follow-up will be summarized based on the assessment from the Independent Core Laboratory.

- Subjects who are retreated (retreatment includes staged procedures) prior to 12 months angiographic imaging will be considered as not achieving complete aneurysm occlusion;
- Subjects who have missing values in Raymond Scale at 12-Month Follow-up will be excluded from analysis.

10.4.1.2 Primary Safety Endpoints

- Incidence of major ipsilateral stroke and/or death

The incidence of major ipsilateral stroke and/or death will be evaluated from the start of the index procedure until the completion of the 12-Month Follow-up based on the assessment from DSMB adjudicated data.

The number and percentage of subjects with major ipsilateral stroke and/or death up to and including 12-Month Follow-up will be summarized.

- Incidence of In-sent stenosis

The number and percentage of subjects with in-stent stenosis up to and including 12 months post-procedure will be summarized based on the assessment from the Independent Core Laboratory. Subjects with missing data will be excluded from analysis.

10.4.2 Secondary Endpoints

All secondary endpoints will be summarized on mITT Analysis Set.

All angiographic imaging results will be based upon assessments by the independent Core Laboratory. A subject who is retreated (retreatment includes staged procedures) on or prior to the angiographic imaging assessment, is considered as a treatment failure for the evaluation of this endpoint. This applies to all secondary effective endpoints except the retreatment rate.

10.4.2.1 Secondary Effectiveness Endpoints

- Procedure success rate

The number and percentage of subjects who achieved procedure success will be summarized at immediately post-treatment (acute), 6-Month and 12-Month Follow-up visits.

- Rate of complete aneurysm occlusion

The number and percentage of subjects who have achieved complete aneurysm occlusion at immediately post-procedure (acute) and 6-Month Follow-up will be summarized based on the assessment from the Independent Core Laboratory.

- Complete/partial aneurysm occlusion as per the Raymond scale

The number and percentage of subjects who have reported a Raymond score of 1 (complete obliteration) or 2 (residual neck) will be summarized at immediately post-treatment (acute), 6-Month and 12-Month Follow-up Visits, based on the assessment from the Independent Core Laboratory.

- Percent aneurysm occlusion

The number and percentage of subjects by categories of aneurysm occlusion in percentage will be summarized at immediately post-procedure (acute), 6-Month and 12-Month Follow-up visits, based on the assessment from the Independent Core Laboratory.

- Recanalization rate

The number and percentage of subjects with recanalization up to and including 12-Month Follow-up Visit will be summarized based on the assessment from the Independent Core Laboratory.

- Retreatment rate

The number and percentage of subjects who received retreatments to the target aneurysms at any time up to and including 12-Month Follow-up will be summarized based on site reported data.

10.4.2.2 Secondary Safety Endpoints

- Rate of new neurological deficits as per mRS

The number and percentage of subjects with new neurological deficits, not related to stroke or death, will be summarized at baseline (pre-procedure) and follow-up visits, e.g., 30 days, 6 and 12 months post-procedure. Subjects who died prior to an evaluation will have an mRS score of 6 imputed at that timepoint for analysis purpose.

- NIHSS total score

The NIHSS total score and its change from baseline will be summarized at baseline (pre-procedure) and follow-up visits (6 months and 12 months post-procedure). In addition, the number and percentage of subjects who show a worsening from baseline (an increase of 4 points or more) will also be presented. Only the observed sores will be included in summaries.

- Adverse Events and Clinical Complications

AEs from the start of the index procedure until completion of the 12-Month Follow-up will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) into system organ class (SOC) and preferred terms (PTs). The number of events, the number and percentage of subjects with events and event rates by SOC and PT will be summarized for the following:

  - Any AEs
  - Study device or procedure related AEs
  - Any serious AEs (SAEs)
  - Unanticipated AEs
  - AEs leading to death

AEs related to device/procedure are defined as those with the relationship of definitely, probably or possibility related. AEs with miss relationship will not be imputed. Subjects with multiple relationships on the same AE will be reported by the events of the highest relationship. Only the relationship as determined by CEC will be used in the safety analysis.

In addition, device or procedure related AEs will be presented overall and by study period as follows:

Table 2: AEs by Study Period

Study Period	Lower Bound of AE Start Date	Upper bound of AE Start Date
Peri-procedure	from the beginning of the procedure	Until 24 hours post-procedure (Day 0)
12-Month Follow-up	After 24 hours post-procedure (i.e., from Day 1)	Until the date of: o early discontinuation in the study; or

Study Period	Lower Bound of AE Start Date	Upper bound of AE Start Date
		○ the upper bound of the12-Month analysis window (i.e., Day 450)

If the AE onset day is missing but the month and year is available, then the missing day will be imputed to be Day 1 of that month as a conservative approach. As an example, if the AE has an onset date of July of 2016, with an unknown day, the imputed onset day would be 01JUL2016. If the month and/or year is unknown, then, the AE will be categorized as unknown.

- Reduced TICI Flow

The number and percentage of subjects with a reduced TICI flow (TICI score of 0 or 1) at the target vessel during the index procedure will be summarized. Subjects with missing data on this endpoint will be excluded from analysis.

- Bleeding complications

The number and percentage of subjects who experience a procedure-related hemorrhagic event which requires any of the following will be summarized:

  - Blood transfusion
  - Surgical intervention
  - New hospitalizations
  - Lengthening of hospital stay for the index procedure

- In-stent stenosis

The number and percentage of in-stent stenosis at immediately post-procedure (acute), and up to and including 6-Month Follow-up (excluding acute events) will be summarized in the same way the primary safety endpoint (in-stent stenosis) at 12-Month Follow-up.

For subjects with acute in-stent stenosis, the number and percentage of subjects who have parent vessel stenosis caused by vasospasm, and whether vasospasm was responsive to medication will be summarized based on the assessment from the Independent Core Laboratory.

- Thrombosis

The number and percentage of subjects with thrombosis up to and including 6 months and 12 months post-procedure will be summarized based on the assessment from the Independent Core Laboratory. Subjects with missing data on thrombosis will be excluded from analysis.

10.4.3 Ancillary Endpoint Analyses

The ancillary endpoint analysis will be conducted on the mITT Analysis Set.

- Stent movement/migration

The number and percentage of subjects who experience stent movement/migration from the start of the index procedure until completion of the 12 Month Follow-up will be summarized. Subjects with missing data will be excluded from analysis.

10.4.4 Safety Follow-up after 12 months post-procedure

AEs that started post the upper bound of 12-Month follow-up (i.e., after Day 451) will be listed.

10.5 Plans for Interim Analysis

According to the Study Close Out Plan, the planned interim analyses will not be conducted.

10.6 Handling of Missing Data

Unless stated otherwise, missing data will not be imputed, percentages will be based on non-missing data.

10.7 Sensitivity Analyses

Sensitivity analyses will not be performed for the final CSR.

10.8 Subgroup Analysis

Subgroup analysis will not be performed for the final CSR.

10.9 Assessment of Site Homogeneity

Assessment of site homogeneity will not be performed for the final CSR.

10.10 Additional Endpoint Analyses

Please refer to section 10.4.3.

11. Appendix: Tables, Listings and Graphs Shells

The table, listing and graph shells will be provided in a separate document. The changes to the shells do not constitute a signature requirement on the statistical analysis plan.

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