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

This investigational protocol contains confidential information for use by the principal investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. It should not be copied or made available for review by any unauthorized person or firm.

Cerenovus
33 Technology Drive
Irvine, CA, U.S.A. 92618
Tel: + 1.888.783.7723

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

PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices, applicable FDA regulations, local regulations, the Declaration of Helsinki, the signed agreement with the Sponsor, and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB.

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in this protocol to the Sponsor and my reviewing IRB. I agree to permit the Sponsor, FDA, or other regulatory authority access to all records relating to the clinical investigation, whether paper-based or electronic data capture.

The below signature confirms I have read and understood this clinical investigational protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by the Sponsor.

Investigational product for this study will be sent to:

Name of Institution: _____
Attention/title: _____
Address: _____
_____
_____

Telephone: _____
Fax: _____
Email: _____

I, and any sub-investigator(s) participating in this study under my supervision as Principal Investigator (PI), **will conduct this protocol implant procedure and all follow-up procedures, including angiography, at the hospital/institution listed below:**

Name of Institution: _____
Address: _____
_____

Note: Subjects must return to the institution listed above for all related follow-up visits, assessments and procedure.

_____	_____	_____/_____/_____
Principal Investigator's Printed Name	Principal Investigator's Signature	Day / Month / Year

TABLE OF CONTENTS

Summary of Figures and Tables

OVERVIEW OF STUDY PROTOCOL

Title of Study: 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

Study Devices: CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System (CODMAN ENTERPRISE) and CODMAN ENTERPRISE® 2 Vascular Reconstruction Device (ENTERPRISE 2), hereafter referred to as ENTERPRISE.

Comparator Device: This is a single arm study with no comparator device.

Study Sponsor: Cerenovus
33 Technology Drive
Irvine, CA, U.S.A. 92618

Study Objectives: The primary objectives of the study are to evaluate the safety (as assessed by rates of major ipsilateral stroke and/or death and in-stent stenosis) and effectiveness (as assessed by the rate of complete angiographic occlusion) of ENTERPRISE when used in conjunction with endovascular coil embolization of unruptured wide-neck intracranial saccular anterior circulation aneurysms in a prospective, multi-center, single-arm clinical study.

Secondary effectiveness objectives include the evaluation of treatment outcomes for subjects treated with ENTERPRISE in the acute (procedure and immediate post-procedure time frames) and follow-up phases of patient management.

Secondary safety objectives include the evaluation of adverse safety outcomes for subjects treated with ENTERPRISE from the start of the procedure through the end of study participation (12 months or premature discontinuation of study participation).

	In addition, the rates of stent movement and migration in ENTERPRISE-treated subjects will be described.
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. A group sequential design will be utilized in which one primary endpoint interim analysis will be conducted after N=160 subjects have been enrolled and followed through 6 months post-procedure, to determine if the study should stop early for futility or a tentative determination of success; enrollment will pause after these 160 subjects have been enrolled. If the stopping rule is met for the trial to stop early for tentative success, a final confirmatory analysis will be conducted when all subjects have reached 12 months post-procedure. If the trial is not terminated early for futility or tentative success, then enrollment will continue up to a full enrollment sample size of N=320, and a final analysis will be conducted when all subjects have reached 12 months post-procedure. An analysis will be conducted to support a marketing application after all subjects have reached 12 months post-procedure. The remaining data out to 24 months post-procedure will be submitted as a post-approval study (PAS) report once all subjects have completed their 24 month follow-up.
Sample Size:	A group sequential design will be utilized in which N=160 subjects are enrolled and followed for a minimum of 6 months post-procedure, at which time an interim analysis will be conducted to determine whether or not to terminate the study early for futility or a tentative determination of success. If the trial is not terminated early for futility or tentative success, then enrollment will resume to a maximum enrolled sample size of N=320 (including the original N=160). Subjects who are enrolled but who are found to be ineligible for treatment with ENTERPRISE at the time of the pre-procedure angiogram will be replaced. Subjects in whom treatment with ENTERPRISE is

	attempted but who discontinue study participation prematurely will not be replaced.
Number of Sites:	Up to 25 institutions in the United States
Study Population:	Subjects with an unruptured wide-neck, intracranial saccular anterior circulation aneurysm (≤ 10 mm), arising from a parent vessel with a diameter of ≥ 2.5 mm and ≤ 4 mm, will be eligible for the study. Wide-necked is defined as having a neck width ≥ 4 mm or a dome-to-neck ratio < 2. Only one wide-necked aneurysm will be treated for each subject during the index procedure.
Study Procedures:	The study evaluation time points include: 1. Screening/Baseline 2. Procedure/Treatment Period 3. Hospital Discharge 4. Thirty Day Follow-up (Telephone Interview) 5. 6 Month Follow-up (Clinic Visit & Angiogram) 6. 12 Month Follow-up (Clinic Visit & Angiogram), 7. 18 Month Follow-up (Telephone Interview) 8. 24 Month Follow-up (Clinic Visit plus MRA or angiogram)
Primary Effectiveness Endpoint:	**Rate of Complete Aneurysm Occlusion (RCAO) according to the Raymond Scale:** The primary effectiveness endpoint is the rate of complete aneurysm occlusion (RCAO) at 12 months post-procedure 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 post-procedure follow-up visit will be considered <u>not</u> to have achieved complete aneurysm occlusion for the purpose of the primary endpoint analysis. The primary endpoint analysis will be to demonstrate that the RCAO is significantly greater than a performance goal

(PG) of 35%. The primary endpoint null and alternative hypotheses are:

Null hypothesis H_o: RCAO ≤ 35%

Alternative hypothesis H_A: RCAO > 35%

This analysis will be conducted on the modified intent-to-treat (MITT) population of subjects (subjects who are found to be eligible for treatment with ENTEPRISE at the time of the pre-procedure angiographic assessment, and in whom treatment is attempted). A supportive analysis will be conducted on the PP population.

Note: The study will be deemed to be a success if this primary efficacy endpoint null hypothesis (on the MITT population with data from all sites combined) is rejected in favor of the alternative hypothesis.

Primary Safety Endpoints:

There are two primary safety endpoints: Major Ipsilateral Stroke and/or Death at 12 months post-procedure and In-stenosis at 12 months post-procedure.

The analyses of these safety endpoints will be conducted on the MITT population. Supportive analyses will be conducted on the PP population.

Incidence of Major Ipsilateral Stroke and/or Death:

The incidence of a major ipsilateral stroke and/or death will be evaluated from the start of the index procedure until completion of the 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.

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the proportion of subjects who experience major ipsilateral stroke and/or death through 12 months post-procedure will be less than 25%.

Incidence of In-stent Stenosis:

The percentage of stents in which stenosis is assessed angiographically, at or prior to 12 months post-procedure will be evaluated. 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).

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the rate of in-stent stenosis at or prior to 12 months post-procedure will be less than 15%.

Secondary Effectiveness Endpoints:

The following secondary effectiveness endpoints have been defined. Observed rates will be described for both the MITT and PP populations. All angiographic imaging results will be based upon assessments by the independent Core Laboratory. A subject who is retreated (retreatment includes staged procedures) is considered to be a treatment failure for endpoints based on angiographic imaging.

a) **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 and 12 month follow-up assessments.

b) **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 and 12 month follow-up angiographic assessments, respectively, will be evaluated.

c) **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 and 12 month follow-up angiographic assessments will be evaluated.

d) **Percent Aneurysm Occlusion:**

The percentage of aneurysms with 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.

e) **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. Percentages of aneurysms falling into each of the categories will be presented.

f) **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.

Secondary Safety Endpoints:

The evaluation of the rate of new neurological deficits (increase in mRS > 2 from baseline not related to stroke or death) at 12 months will be a pre-specified, powered analysis. All other secondary endpoints will be presented as a group to better characterize the ENTERPRISE stenting procedure.

Unless otherwise stated, these secondary safety analyses will be conducted on the MITT population.

a) **Rate of New Neurological Deficits per the Modified Rankin Scale (mRS):**

Observed scores on the Modified Rankin Scale will be presented at baseline (pre-procedure) and follow-up (30 days, 6 and 12 months post-procedure). The number and percentage of subjects who have an increase in mRS > 2 from baseline not related to stroke or death will also be presented for each follow-up time point.

The evaluation of the rate of new neurological deficits at 12 months post-procedure will be a pre-specified, powered analysis. For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the rate of subjects with a new neurological deficit will be less than 15%. The analysis of new neurological deficits will exclude subjects who had a stroke or who died from the time of the index procedure to the time of the evaluation.

b) **NIH Stroke Scale (NIHSS) Total Score:**

The NIHSS Total Score evaluations will be summarized at baseline (pre-procedure) and follow-up (6 and 12 months post-procedure); change from baseline at 6 and 12 months will also be summarized. The percentage of subjects who show a worsening from baseline (increase of 4 points or more) will also be presented.

Observed scores and change from baseline will also be presented for NIHSS excluding scores on the aphasia subscale.

c) **Adverse Events and Clinical Complications:**

Adverse Events (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 coded using the MedDRA system and summarized with frequencies. Serious adverse events (SAEs), device- or procedure-related AEs, unanticipated adverse device effects (UADEs) and deaths will be presented.

AEs will be presented for the following study periods: 1) peri-procedure – i.e., from the start of the procedure until 24 hours post-procedure; and, 2) through 12 month follow-up – i.e., from 24 hours post-procedure through the 12 month visit or premature termination.

d) **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.

e) **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.

f) **In-stent Stenosis (Acute, and 6 Months):**

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 or not the vasospasm was responsive to medication.

g) **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.

Ancillary Endpoint **Stent Movement/Migration:**

	Incidence of stent movement and/or migration from the start of the index procedure until completion of the 12 month follow-up
Safety Follow-up through 24 months post-procedure	Subjects will be followed through 24 months post-procedure, and their outcomes will be summarized in a supplemental safety follow-up report: • All adverse events • Rupture of the index aneurysm beyond 24 hours post-treatment • Major ipsilateral stroke more than 1 month post-treatment • Ipsilateral parenchymal hemorrhage more than 1 month post-treatment
Sample Size Determination:	Both primary effectiveness and primary safety endpoint analyses will be conducted on the MITT population, where subjects with missing data at the time of endpoint analysis will be imputed as last observation carried forward (LOCF). Hence all subjects in the MITT population with post-procedure data are deemed to be evaluable for the purpose of MITT analyses. Subjects who receive the device but in whom there is no post-procedure data will be treated as failures for the primary effectiveness analysis; subjects who do not receive the device because of treatment failure due to reasons associated with the device will also be treated as failures. Subjects with no post-procedure endpoint data upon which to base a LOCF imputation will be excluded from the primary safety endpoint analyses; it is anticipated that fewer than 7% of MITT subjects will be excluded from either primary effectiveness or primary safety endpoint analyses. Subjects who are enrolled but who are found to be ineligible for treatment with ENTERPRISE at the time of the pre-procedure angiogram will be replaced. Subjects in whom treatment with ENTERPRISE is attempted but who discontinue study participation prematurely will not be replaced. The study design is a group sequential design, wherein after N=160 subjects have been enrolled, treated, and followed for a minimum of 6 months post-procedure, an interim analysis will be conducted to determine whether or not to terminate the study early for futility or tentative success.

The study will terminate early for tentative success if the unadjusted 2-sided normal approximation p-value for testing the primary effectiveness endpoint (RCAO vs. the PG of 35%) is less than 0.031, and will terminate early for futility if this p-value is greater than 0.358. If the stopping rule is met for the trial to stop early for tentative success, a final confirmatory analysis will be conducted when all subjects have reached 12 months post-procedure; a p-value threshold of 0.031 will be used for this final confirmatory analysis. If neither of these interim analysis criteria for stopping the trial early is met, or if the confirmatory analysis for early success is not satisfied, then enrollment will commence until a total sample of N=320 subjects have been enrolled (including the original N=160), and all subjects will be followed for a minimum of 12 months post-procedure at which time the final primary endpoint analysis will be conducted. In this final primary endpoint analysis, the study will be deemed to be successful if the unadjusted 2-sided normal approximation p-value for testing the primary effectiveness endpoint (RCAO vs. the PG of 35%) is less than 0.031.

The statistical power to stop early for success at the interim analysis is approximately 79% if the true RCAO is 47% in the general population and there are at least 150 evaluable MITT subjects (with post-procedure data) for this interim analysis. The statistical power at the final endpoint (if the study continues to full enrollment) is 87.7% if the rate of complete occlusion in the general population is 44% and there are 300 evaluable MITT subjects (with post-procedure data) for this final analysis. With the group-sequential design of this study and the specified interim and final analyses for the primary endpoint, including the sample sizes at which analyses will be conducted and the p-value thresholds for determining study success in the respective analyses, the overall probability of a Type 1 error in this study (α, 2-sided) is maintained below 0.05.

There are two primary safety endpoints with formal hypotheses that will be tested, and the following are estimates of statistical power for each of these respective endpoints at the time of the interim analysis. For each respective endpoint, the purpose of the hypothesis test is to ensure that the 2-sided 95% upper confidence limit for the estimate is less than a stated performance goal for the

endpoint. The performance goal, expected outcome, and estimated statistical power based upon a sample size of N=150 evaluable subjects (with post-procedure data) are provided for each respective endpoint.

a) Major ipsilateral stroke/death at 12 months:
   - Performance goal = 25%. The upper confidence limit of a 2-sided 95% confidence interval for the proportion of subjects who experience major ipsilateral stroke and/or death through 12 months post-procedure will be observed to be less than 25%.
   - Expected rate of major ipsilateral stroke and/or death is not greater than 14%.
   - Statistical power ≥ 92.5%.

b) In-stent Stenosis at 12 months
   - Objective performance criterion = 15%. The upper confidence limit of a 2-sided 95% confidence interval for the rate of in-stent stenosis will be observed to be less than 15%.
   - Anticipated rate of in-stent stenosis is not greater than 6%.
   - Statistical power = 95.5%.

Enrollment Start Date, Enrollment Phase and Follow-up Schedule:

The study is expected to start Q3 2015. The initial enrollment phase is expected to take 48 months. A 6-month pause in enrollment will occur after 160 subjects have been enrolled for an interim analysis to be conducted to determine if the study should stop early for futility or tentative success. If the trial is not terminated early, then enrollment will continue up to a full enrollment of 320 subjects, which is anticipated to take an additional 12 months.

Subjects will be followed through 24 months with assessments at discharge, 30 days, 6 months, 12 months, 18 months and 24 months with a follow-up angiography (digital subtraction angiography) being performed at 6, 12 and 24 months for all subjects.

If a subject experiences indications that in-stent stenosis or delayed hydrocephalus is occurring, additional follow-up

may be required, including MRI or CT at the Investigator's discretion.

SCHEDULE OF EVENTS

Table 1: Summary of Study Procedures and Assessments

Assessments	Screening/ Baseline (-14 to 0 days)	Pre-treatment [5] (day 0)	Intra-procedure [5] (day 0)	Post-treatment [5] (day 0)	Angiographic Screening Failure [9] (day 0)	Hospital discharge [5]	30 Days ☎ (16 - 44 days)	6 Months (92-212 days)	12- Months (320-410 days)	18 Months ☎ (457-592 days)	24 Months [7] (685-775 days)	Stroke or Suspected Stroke [6]
Study approved informed consent	X											
Medical history	X											
Clinical assessment & physical exam	X					X		X	X		X	
NIH Stroke Scale Score (NIHSS)	X					X [1]		X	X		X	X
Modified Rankin Scale (mRS)	X					X [1]	X	X	X	X	X	X
Clinical neurological evaluation	X					X [1]	X	X	X	X	X	
Hunt and Hess Scale (HHS) for subarachnoid hemorrhage						X [1]		X	X		X	
Vital Signs	X	X		X	X	X		X	X		X	
Relevant prior and concomitant medications [2]	X					X	X	X	X	X	X	
Serum creatinine	X											
Pregnancy test [3]	X											
Index Procedure			X									
Procedural Medications [(2)]		X	X	X	X							
Imaging:												
CT or MRI performed within 10 years [8]	X [8]											
Angiogram [11]	X[12]	X	X	X [10]	X			X	X		X	
MRI/MRA or Angiogram											X [7]	
MRI for Stroke/Suspected Stroke (within 24 hrs.)												X
Record of adverse events [4,6]		X	X	X	X	X	X	X	X	X	X	
Record of protocol deviation [4]	X	X	X	X	X	X	X	X	X	X	X	
Record device malfunction/product complaint [4]		X	X	X		X	X	X	X	X	X	
End of Study (occurring once at any timepoint)		X	X	X	X	X	X	X	X	X	X	

1. At 12 to 36 hours after end of the index procedure.
2. Procedural and relevant concomitant medications include: Antithrombotic (including anti-platelet, anticoagulant, and fibrinolytics), inhibitors of ADP-induced platelet aggregation, IIb-IIIa Inhibitor, vasoactive medications, contrast and medication associated with AEs.
3. For females of childbearing potential as assessed per investigator.
4. As needed.
5. Collect at the index procedure and any subsequent procedures, if applicable.
6. Assess for stroke or suspected stroke at each visit. Within 24 hours of symptom(s) onset, conduct MRI. If Investigator doesn't learn of event within 24 hours, conduct MRI immediately as well as mRS and NIHSS. 30 day follow up (window 16 - 44 days) required in the event of confirmed stroke; complete mRS and NIHSS.
7. MRI/MRA or angiogram to assess for in-stent stenosis, thrombosis and hydrocephalus, or if an angiogram is performed, then also obtain MRI or CT to assess for hydrocephalus (angiogram must be performed if any stent or coils are not MRA/MRI compatible).
8. Obtain an axial CT or MRI of the subject (performed within the last 10 years provided that the CT or MRI was not performed before the subject's 20th birthday), that shows the orbital anatomy. The CT/MRI should contain a valid centimeter marker and be uploaded to Image Management Vendor.
9. If the subject signed the study informed consent but meets any of the angiographic exclusion, the subject is considered an angiographic screening failure (ASF) and may not continue in the study.
10. Completed post-treatment (after treatment with stent/coils) prior to end of procedure.
11. Unscheduled angiograms are those not required for the study. If needed, they should be performed using the same orthogonal views used during the index procedure and submitted to the core lab.
12. Baseline angiography (either CTA or angiogram) within 90 days).

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
ADP	Adenosine Diphosphate
ADPKD	Autosomal Dominant Polycystic Kidney
AE	Adverse Event
ACT	Activated Clotting Time
APTT	Activated Partial Thromboplastin Time
ASA	Aspirin
ASF	Angiographic Screening Failures
AVM	Arteriovenous Malformation
CFR	Code of Federal Regulations
CI	Confidence Interval
CF	Continued Follow-up
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomography Angiography
DS	Delivery System
DSA	Digital Subtraction Angiography
DW	Delivery Wire
eCRF	Electronic Case Report Forms
EDC	Electronic Data Collection
EDNRA	Endothelin Receptor Type A
EVT	Endovascular Treatment
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GI	Gastrointestinal
HDE	Humanitarian Device Exemption
HHS	Hunt and Hess Scale
HUD	Humanitarian Use Device
ICES	Interstate Collaboration of Stent Coiling
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board (United States)
IVRS	Interactive Voice Response System
ITT	Intent-to-Treat
LAR	Legal Authorized Representative
LOCF	Last Observation Carried Forward
LR	Logistic Regression
MI	Myocardial Infarction
MITT	Modified Intent-to-Treat
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIH	National Institute of Health
NIHSS	National Institute of Health Stroke Scale
NiTi	Nitinol
OR	Odds Ratio
PP	Per Protocol
PTFE	Polymeric Tube
PSF	Preliminary Screen Fail
QCA	Standard Quantitative Angiography
RCAO	

SAC	Rate of Complete Aneurysm Occlusion according to the Raymond Scale
SAE	Stent-Assisted Coiling
SAH	Serious Adverse Event
SAP	Subarachnoid Hemorrhage
SAS	Statistical Analysis Plan
SDV	Statistical Analysis Software
TICI	Source Data Verification
UADE	Thrombolysis in Cerebral Infarction
UIA	Unanticipated Adverse Device Effect
US	Unruptured intracranial aneurysms
VRD	United States
WBC	Vascular Reconstruction Device
	White Blood Cell

1.0 INTRODUCTION

1.1. Literature Summary and Background

1.1.1 Background

Intracranial saccular aneurysms are common acquired lesions. Imaging studies have reported frequencies of 0.5% to 2%, while autopsy studies have reported frequencies of 1% to 9% (Burns et al., 2009a). Findings from an analysis of 68 prevalence studies reporting data from 83 study populations showed an overall prevalence of intracranial saccular aneurysms of 3.2% (Vlak, 2011). Findings from imaging studies in which arteriography and MRI were used suggest that the frequency of intracranial saccular aneurysms in the general population is 0.5–3% (Winn, 1983; Atkinson, 1989). In a European population-based prevalence study (Vernooij et al., 2007), about 1.8% of adult participants had an aneurysm detected on screening MRI. In a cross-sectional study in China (Li et al., 2013), 7% of adults between the ages of 35 and 75 years had an aneurysm detected on widespread screening with brain magnetic resonance angiography (MRA). In Norway, the prevalence of intracranial saccular aneurysms on MRA was 1.9% and the incidence of subarachnoid hemorrhage in the same population was 16.4 per 100 000 person-years (Müller et al., 2013).

The inherent threat of unruptured intracranial aneurysms (UIAs) is rupture and subsequent subarachnoid hemorrhage (SAH). Studies of aneurysmal SAH, which accounts for around 80% of non-traumatic SAH, have reported 1-month case mortality rates as high as 30% to 50% (Burns et al., 2009b; Broderick et al., 1993; Fogelholm et al., 1993); these devastating outcomes are still extraordinary. Poor neurologic and functional outcomes among patients whom have suffered SAH are due to initial hemorrhage, early rebleeding, and delayed cerebral ischemia resulting from cerebral vasospasm, microvascular dysfunction, and complex neuronal-glial interactions (Laskowitz and Kolls, 2010). The overall economic effect is substantial; data from the late 1970s and 1980s suggest that lifetime costs of management exceed US$500 million annually in the USA (Wiebers et al., 1992).

Intracranial saccular aneurysms have to be considered as an important disease due to the severe morbidity and mortality associated with SAH that result from rupture of cerebral aneurysms. The most important objective of the treatment is to prevent rupture or rebleeding by isolating an aneurysm from the normal blood circulation without narrowing the parent vessel

1.1.2 Pathophysiology of Aneurysms

An intracranial aneurysm is a focal bulging in the wall of an artery in the brain that results from a weakening of the internal muscular layer of a blood vessel. Due to certain histopathologic and hemodynamic factors, aneurysms most commonly occur in arteries that supply blood to the brain.

Several risk factors affecting both aneurysm formation/growth and risk of rupture have been identified: aneurysm shape and location, gender, age, family history, genetic conditions, cigarette smoking, hypertension, and alcohol and drugs consumption.

Intracranial aneurysms are classified as saccular, fusiform, or dissecting. Nearly 90 percent are saccular aneurysms. Intracranial saccular aneurysms are responsible for most of the morbidity and mortality caused by SAH (Yong-Zhong and van Halphen, 1990).

Intracranial saccular aneurysms occur primarily in proximal arterial bifurcations in the circle of Willis, and 85% of these lesions are located in the anterior circulation (Kassel et al., 1990) including the following sites: the internal carotid artery sidewall and bifurcation, the anterior communicating artery to anterior cerebral artery junction, the middle cerebral artery branch points and the ophthalmic artery origin. In the posterior vertebrobasilar distribution, the most common locations include the tip of the basilar artery, the superior cerebellar artery branch from the basilar artery, the anterior inferior cerebellar artery branch from the basilar artery, and the posterior inferior cerebellar artery branch from the vertebral artery. About 20% of patients have more than one aneurysm (Rinne et al., 1994).

Unruptured intracranial aneurysms are more common in women than in men, with a 3:1 ratio of women to men with aneurysms in a large cohort (Chason and Hindman, 1958; ISUIA, 1998). Unruptured intracranial aneurysms are also more common in elderly people (Inagawa and Hirano, 1990) and are uncommon in children (Meyer et al., 1989; Storrs et al., 1982).

Occurrence of Intracranial saccular aneurysms is increased in some inherited disorders compared with the general population. Autosomal dominant polycystic kidney (ADPKD) disease is the most common inherited disorder associated with intracranial saccular aneurysm (Chapman et al., 1992; Gibbs et al., 2004; Mariani et al., 1999; Schievink 1997). In this disease, the risk of aneurysm detection is higher when other family members have had brain aneurysm (Mariani et al., 1999) and with increasing age; the overall prevalence is about 10% (Chapman et al., 1992). Other inherited disorders that have been associated with brain aneurysm include multiple endocrine neoplasia type I (Schievink, 1998), hereditary hemorrhagic telangiectasia (Maher et al., 2001), Ehlers-Danlos syndrome type IV (Edwards and Taylor, 1969), Marfan's syndrome (Schievink 1999), and neurofibromatosis type I (Schievink et al., 2005), although the overall frequency of association of these disorders with unruptured intracranial saccular aneurysms rather than fusiform aneurysms is uncertain. Increased occurrence of brain aneurysm has also been associated with moyamoya disease (Yasargil and Smith, 1976), intracranial arteriovenous malformations (Brown et al., 1990), sickle-cell disease (Batjer et al., 1991), systemic lupus erythematosus (Nagayama et al., 1991), fibromuscular dysplasia (Palubinskas et al., 1966), and coarctation of the aorta (Connolly

et al., 2003). Overall, among all unruptured intracranial aneurysms detected, the proportion that is associated with these disorders is low (ISUIA, 1998; Wiebers et al., 2003).

The specific genetic abnormality associated with intracranial saccular aneurysm formation is not clear, but a large meta-analysis (Alg et al., 2013) of genetic studies identified 19 single nucleotide polymorphisms associated with sporadic intracranial aneurysm. The strongest associations were found on chromosome 9 within the CDKN2B antisense inhibitor gene, on chromosome 8 near the SOX17 transcription regulator gene, and on chromosome 4 near the EDNRA gene (Alg et al., 2013; Foroud et al., 2012). Findings from a meta-analysis of the Familial Intracranial Aneurysm cohort (Foroud et al., 2012) showed significance for single nucleotide polymorphisms on chromosome 9p and supported an association between intracranial aneurysm and single nucleotide polymorphisms in SOX17 on chromosome 8q. About 20% of patients with an aneurysm or subarachnoid hemorrhage will report a family history of these diagnoses (Kissela et al., 2002). However, not all cases of familial aneurysm are necessarily genetic in cause; some represent a co-occurring familial history of hypertension or a higher occurrence of smoking in members of a family. In families with two or more members affected with intracranial saccular aneurysm or subarachnoid hemorrhage, there is an increased occurrence of these disorders in first-degree and possibly second-degree relatives of those with either diagnosis. The mean age of subarachnoid hemorrhage is younger in familial than in non-familial cases (Bromberg 1995) and the overall outcome is often poorer (Bromberg et al., 1995). The overall occurrence of unruptured intracranial aneurysm or subarachnoid hemorrhage in the relatives of someone affected with subarachnoid hemorrhage is available from population-based data. In one such study of patients with subarachnoid hemorrhage (Kissela et al., 2002), 9.4% of patients had a first-degree relative with subarachnoid hemorrhage or intracranial aneurysm and 14% had a second-degree relative with these diagnoses. In a screening study of the relatives of 193 patients with subarachnoid hemorrhage aged 20–70 years (Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group, 1999; Raaymakers, 1999) 4% of screened first-degree relatives had an unruptured intracranial aneurysm on MRA and subsequent intra-arterial angiography.

Several treatable risk factors seem to increase the occurrence of aneurysms including cigarette smoking (Juvela et al., 1993; Shiue et al., 2012) and hypertension (Shiue et al., 2012; Knekt et al., 1991; Longstreth et al., 1992). Findings from some studies that assessed risk factors for subarachnoid hemorrhage suggested that heavy alcohol use (Shiue et al., 2012; Longstreth et al., 1992; Klatsky et al., 1989) increases the risk of subarachnoid hemorrhage. Drugs containing high dose oestrogen increase the risk of subarachnoid hemorrhage, but the risk might be lower with drugs containing low-dose oestrogen (Bonita, 1986; Longstreth et al., 1994; Johnston et al., 1998). Cocaine use has been associated with subarachnoid hemorrhage in young people (Broderick et al., 2003). Finally, low body-mass

index has been associated with increased risk of subarachnoid hemorrhage, but the cause of this is unclear (Zacharia et al., 2010).

1.1.3 Treatment Options for Intracranial Saccular Aneurysms

The most appropriate treatment option for any UIAs is that which provides an optimal balance of procedural safety and long-term efficacy based on patient and aneurysm characteristics. Currently, there are two available options for treating UIAs, microsurgical clipping and endovascular coiling.

Traditionally, surgical clipping has been viewed as being highly efficacious, but carrying greater risk due to the neurological complications associated with open neurosurgery. Efficacy of this treatment is illustrated by a study performed between 1998 and 2001 that explored the need for cerebral angiography following surgery for saccular aneurysms. Of the 315 surgically clipped UIAs in this study, 287 were completely occluded, a 91% complete occlusion rate (Kivisaari et al., 2004). On the other hand, safety concerns associated with surgical treatment are shown in a report analyzing data from twenty-one single-center and eight multicenter studies of surgical clipping from 1991 to 2003 (Lee and Kolls, 2005). In this study, mortality rates ranged from 0% to 6.9%. The same study found the adverse outcome rate (AOR) to range between 0% and 25.1% with a cumulative AOR of 17.8%. The largest multicenter study of UIAs at the time, the ISUIA (International Study of Unruptured Intracranial Aneurysms), aimed to characterize the natural history of unruptured aneurysms. One of the goals of the prospective branch of the ISUIA was to obtain a more comprehensive assessment of the surgical risks of aneurysm clipping. Among the 1917 patients who underwent surgical clipping, the study found a 1-year mortality rate of 2.3% and a 1-year morbidity rate of 12.1%. The study also found that increasing aneurysmal size and patient age as well as location in the posterior circulation (particularly basilar tip and posterior communication artery) are indicators of poor outcome following surgical treatment (Wiebers et al., 2003). Consequently, older patients with large, posterior circulation aneurysms are most likely better candidates for endovascular treatment.

More recent studies are showing that refinement of microsurgical technique is leading to safer, more efficacious treatment of UIAs. One study followed a series of 450 aneurysms treated with surgical clipping by one neurosurgeon immediately upon completion of neurosurgery training. With 6-month morbidity and mortality rates of 1.06% and 0.27%, respectively, it is clear that, given proper mentorship and resources prevailing neurosurgeons can achieve acceptable results when treating UIAs surgically (Nussbaum et al., 2007).

Since its conception and implementation about two decades ago (Guglielmi et al., 1991a; Guglielmi et al., 1991b), endovascular coil embolization has become a primary treatment in the management of unruptured intracranial saccular aneurysms. In many institutions worldwide, endovascular coiling has become the preferred treatment for unruptured intracranial saccular

aneurysms for which intervention is indicated (Moyle and Patel, 2010). To confirm the notion that endovascular procedures provide a safe alternative for treating unruptured intracranial saccular aneurysms, many studies have investigated the morbidity and mortality rates of patients who underwent endovascular coiling. As part of the prospective branch of the ISUIA, 451 patients were chosen to undergo endovascular coiling. Among these patients, there was a 1-year surgery-related mortality rate of 3.1% and a 1-year morbidity rate of 9.5% (Wiebers et al., 2003). A year later, Lanterna et al. (2004) analyzed thirty studies of endovascular coiling, published between 1990 and 2002, and revealed case-fatality and permanent morbidity rates of 0.6% and 7.0%, respectively. To appreciate the effect of advancing technology and technical refinement, the investigators divided the publications by midyear of the study and found that studies before 1995 reported a morbidity rate of 8.6%, while the morbidity rate of studies after 1995 had dropped to 4.5% (Lanterna et al., 2004). Another more recent meta-analysis performed by Naggara et al. (2010) looked at similar studies performed in 17 different countries from 2003 to 2008 and found unfavorable outcomes occurred at a rate of 4.8%. Ultimately, these data do seem to indicate that endovascular coiling provides a safe alternative to clipping by imparting lower complication rates upon patients.

While endovascular treatment of unruptured intracranial saccular aneurysms is now widely used, certain aneurysmal morphologies and anatomical features, particularly a wide neck, render some aneurysms technically difficult to treat endovascularly. To facilitate endovascular coiling of aneurysms with broad necks, Moret et al. (1997) extended a previously utilized temporary balloon inflation technique to the treatment of unruptured intracranial saccular aneurysms and named it balloon remodeling. One part of the ATENA (Analysis of Treatment by Endovascular Approach of Nonruptured Aneurysms) Study explored the safety of the balloon remodeling technique. The morbidity and mortality rates of UIAs treated with balloon remodeling were 2.3% and 1.4%, respectively, compared to 2.2% and 0.9% for those receiving standard endovascular coiling, a difference which was not statistically significant (Pierot et al., 2009). In terms of efficacy, a review comparing aneurysms treated with balloon remodeling versus standard endovascular treatment, in studies published from 1997 to 2006, revealed significantly higher initial and follow-up aneurysm occlusion rates for those aneurysms treated with balloon remodeling (Shapiro et al., 2008).

Another adjunctive therapy for wide-neck UIAs is microcatheter-delivered stenting. The hope among neurosurgeons is that stent-assisted coil embolization (SAC) may improve long-term durability and effectiveness by minimizing herniation and increasing packing density (Gounis et al., 2010). After establishing procedural safety and periprocedural effectiveness (Fiorella et al., 2004), Sedat et al. (2009) reported that long-term complete aneurysmal occlusion occurred in 71% of patients, with aneurysmal regrowth in 4 out of 38 patients at first angiographic follow-up and no regrowth in any other follow-ups. In order to value the safety and efficacy of SAC, the Interstate Collaboration of Stent Coiling (ICES) was conducted. Data on

consecutive patients treated with Enterprise stent-assisted coiling of ruptured and unruptured aneurysms from 9 high-volume neurointerventional centers was compiled. Initial results of the ICES study concluded that this technique was helpful for treatment of unruptured intracranial aneurysms but not ruptured intracranial aneurysms and produced morbidity and mortality rates of 2.8% and 2.0%, respectively (Mocco et al., 2009). The final report of the ICES study, which then encompassed 229 SAC-treated aneurysms with a mean follow-up of 655.7 days, reported that 59% of aneurysms demonstrated complete occlusion and 81% had≥90% aneurysm occlusion, illustrating that SAC is a viable option for wide-neck aneurysms (Fargen et al., 2012).

Even though the ICES trial provides valuable information on stent-assisted coiling in general, a monitored trial evaluating the safety and efficacy of Enterprise assisted coiling in the treatment of intracranial, unruptured, wide-necked aneurysms has not been conducted up to date. This study is designed to evaluate the safety and effectiveness of ENTERPRISE when used in conjunction with endovascular coil embolization of unruptured wide-necked saccular intracranial aneurysms in a prospective, single arm clinical study.

1.2. Investigational (Study) Device Description

1.2.1 CODMAN ENTERPRISE® Vascular Reconstruction Device

The CODMAN ENTERPRISE® Vascular Reconstruction Device (CODMAN ENTERPRISE) is intended for use in the neurovasculature with embolic coils to provide treatment to a population of intracranial aneurysms where aneurysm geometry alone cannot support embolic coils. This aneurysm geometry, known as the wide-necked aneurysm, does not naturally support a coil mass. The wide-neck aneurysm is defined as having a neck width ≥ 4 mm or a dome-to-neck ratio < 2. The stent serves the specific purpose of supporting a coil mass in a scenario where the shape of the aneurysm does not do so naturally, by providing a scaffold to prevent coil protrusion into the parent vessel lumen.

The CODMAN ENTERPRISE consists of a nitinol stent pre-loaded on a delivery wire and constrained within an introducer that facilitates transfer of the stent into a microcatheter. The recapturable and repositionable stent bridges and reconstructs the neck of an aneurysm from within the lumen of a parent artery in the neurovasculature in order to support embolic coils deployed into the aneurysm. The stent is also coated with Parylene C, an insulating polymer that enhances the stent's resistance to corrosion caused by dissimilar metal contact between nitinol and platinum/tungsten embolic coils. The delivery wire is used to advance and subsequently deploy and release the stent into the neurovasculature.

1.2.2 CODMAN ENTERPRISE® 2 Vascular Reconstruction Device

The CODMAN ENTERPRISE VRD System and ENTERPRISE 2 VRD System serve the specific purpose of supporting a coil mass in a scenario where the shape of the aneurysm does not do so naturally, by providing a scaffold to prevent coil protrusion into the parent vessel lumen. The ENTERPRISE 2 VRD System incorporates several minor modifications, bench top testing showed that it met or exceeded the same acceptance criteria as the ENTERPRISE VRD System.

The modifications are further described in Section 5.1.2. There is no change to the intended use as a result of the modifications.

1.3. Previous Codman Sponsored Clinical Studies

1.3.1 Feasibility studies: United States and Europe

Cordis Neurovascular/Codman Neuro, Inc., conducted two multi-center, prospective, non-randomized, feasibility studies evaluating the CODMAN ENTERPRISE® Vascular Reconstruction Device (stent) and Delivery System. The CODMAN ENTERPRISE stent size 4.5 X 22 mm was used in both of these studies. One study was conducted in Europe at three medical institutions and the other was conducted in the United States at five medical institutions. Both studies were conducted according to local regulatory requirements and in accordance with the principles of the Declaration of Helsinki as enforced at the time the study was conducted.

The studies demonstrated the safety and probable benefit of the CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System to facilitate endovascular coil embolization of wide neck saccular or fusiform intracranial aneurysms. The studies involved a more rigorous design than studies involving the use of stents to treat intracranial aneurysms currently found in the literature. Notable study design features include the use of an independent Clinical Events Committee (CEC), the use of an independent angiographic core lab, independent neurological assessment, and collection of all adverse events, whether or not related to the device or procedure, confirmed via routine study monitoring.

European Data

The European clinical study began with the first implant on 19 December 2003. Thirty-one subjects were enrolled into the study. The database was closed on 01 February 2006.

Baseline data were collected on 31 subjects who enrolled into the study, which received the CODMAN ENTERPRISE stent and were followed through six months. The majority (87.1%) of the subjects was female, and the average age was 54.5 years. A medical history of hypertension was reported in 38.7% of the subjects enrolled and 25.8% had endocrine / metabolic disease. The most commonly reported neurological event was

subarachnoid hemorrhage (38.7%) and 16.1% had a history of cranial nerve palsy and pounding / pulsatile headache. Fourteen subjects (45.2%) had undergone a prior intracranial embolization procedure for their cerebral aneurysm.

All serious adverse events were reviewed and adjudicated by the independent Clinical Events Committee. Six subjects (16.1%) experienced one or more device or procedure related serious adverse events. Eighteen subjects experienced 25 adverse events that were judged by the site to be at least possibly related to the device or procedure. The majority of these events occurred within 30 days. Neurological assessments included NIH Stroke score, modified Rankin score and clinical neurological examination. Most subjects experienced no change or improved neurological assessment ratings from pre-procedure to six months.

The mean NIH Stroke score was 0.3 pre-procedure and was 0.3 at six months. The majority of subjects (96.8%) were rated Grade 0 or Grade 1 on the modified Rankin scale pre-procedure, and 96.7% of subjects were Grade 0 or Grade 1 at six months (a Rankin scale of “0” indicates no neurological disability).

Angiographic measurements were performed by an angiographic core lab. At pre-procedure, the mean aneurysm dome height and width was 6.3 mm and 7.0 mm, respectively. The mean neck width was 4.8 mm, and mean dome width-to-neck ratio was 1.47. The mean proximal/distal diameter of the parent vessel pre-procedure was 3.1/2.8, and 2.8/2.5 at six months.

The technical success measures were also assessed using the angiographic core lab. Successful stent placement angiographically assessed immediately post-procedure was 96.8%. Successful stent placement was defined as stable stent placement with complete coverage across the aneurysm neck and parent artery patency, while satisfactory coil mass position was defined as stent maintains coil position within the sac with parent artery patency. Procedural success, defined as successful stent placement with satisfactory coil mass position without occurrence of procedural serious adverse events, was 90.0%. Maintenance of coil mass position was 96.7% at six months. The mean percent aneurysm occlusion post-procedure was 93.0% and 93.9% at six months.

United States Data

The US clinical study includes data on subjects enrolled between 22 June 2004 and 12 October 2004. Subjects were followed for six months. The database was closed on 13 July 2005.

Baseline data were presented on 30 subjects who enrolled into the study and on 28 subjects who received the CODMAN ENTERPRISE stent and followed through six months. Two subjects were enrolled into the study but did not receive the device due to pre-procedure angiographic disqualification. In one case, the parent vessel was too large in diameter

and in the other, the aneurysm neck was too wide. The majority (76.7%) of the subjects was female, and the average age was 57.8 years. A medical history of hypertension was reported in 66.7% of the subjects enrolled and 40.0% had cardiovascular disease. The most commonly reported neurological event was pounding/pulsatile headache (43.3%) and 26.7% had a history of Altered Mental Status. Five subjects (16.7%) had previously suffered a subarachnoid hemorrhage, and 23.3% of the subjects had undergone a prior intracranial embolization procedure for their cerebral aneurysm.

All serious adverse events were reviewed and adjudicated by the Clinical Events Committee. Seven subjects (25%) experienced one or more device or procedure related serious adverse events. One subject died as a result of an intracerebral hemorrhage post-operatively. This death was classified as secondary to the presenting intracerebral hemorrhage. Eighteen subjects experienced 47 other adverse events that were judged to be at least possibly related to the device or procedure. The majority of these events occurred within 30 days.

Neurological assessments included NIH Stroke score, modified Rankin score and clinical neurological examination. Most subjects experienced no change or improved neurological assessment ratings from pre-procedure to six months.

The mean NIH Stroke score was 1.4 pre-procedure and was 0.3 at six months. This indicates that there was benefit for both neurological and overall clinical improvement following treatment, since an NIH stroke scale core of “0” is an indication of being completely normal. The majority of subjects (75.9%) were rated Grade 0 or Grade 1 on the modified Rankin scale pre-procedure, and 80.7% of subjects were Grade 0 or Grade 1 at six months (a Rankin scale of “0” indicates no neurological disability).

Angiographic measurements were made by an angiographic core lab. At pre-procedure, the mean aneurysm dome height and width was 8.2 mm and 8.6 mm, respectively. The mean neck width was 5.3 mm, and mean dome width-to-neck ratio was 1.43. The mean proximal/distal diameter of the parent vessel pre-procedure was 3.4/3.0, and 3.3/2.9 at six months.

The technical success measures were also assessed using the angiographic core lab. Successful stent placement with satisfactory coil mass position assessed immediately post-procedure was 100%. Successful stent placement was defined as stable stent placement with complete coverage across the aneurysm neck and parent artery patency, while satisfactory coil mass position was defined as stent maintains coil position within the sac with parent artery patency. Maintenance of coil mass position was 95.8% at six months. The mean post-procedure percent aneurysm occlusion was 87.9%, and improving to 92.0% at six months.

1.3.2 Feasibility study: Argentina

A Feasibility Study of the Codman Neurovascular Self Expanding Stent System in Intracranial Arteries was conducted in Argentina. This was a prospective, single-arm, single-center study sponsored by Codman Neuro. The study was completed 09 March 2009.

The purpose of the study was to assess both effectiveness and safety. The CODMAN ENTERPRISE stent size 4.5 X 22 mm was used in this study. The two components of the effectiveness evaluation include:

a) Technical feasibility

For all subjects with a deployed stent:

- Successful stent placement/coil mass position angiographically assessed immediately post-procedure, and
- Evaluation of the percent occlusion assessed immediately post-procedure and at six months after treatment.

b) Clinical/neurological outcome

For all subjects with a deployed stent, clinical/neurological outcome using independent neurological evaluations (NIH Stroke Scale, Modified Rankin Scale) by independent, qualified personnel immediately after the procedure, at discharge, at thirty days and six months after treatment compared to the baseline evaluation.

Safety

Adverse Events (AEs)

For all enrolled subjects, incidence of AEs assessed immediately following the pre-procedure angiogram through hospital discharge.

For subjects with a deployed stent, incidence of AEs assessed immediately following the pre-procedure angiogram through hospital discharge, at thirty days and six months after treatment.

Results:

Ten (10) subjects were enrolled, all of whom were entered into the study and evaluable at the 6 month follow-up.

Effectiveness:

This study demonstrated the technical feasibility of the CODMAN ENTERPRISE system for the treatment of wide-necked intracranial aneurysms. Stable stent placement with complete neck coverage and parent artery patency post-procedure was observed in 9/10 (90%) subjects; since due to poor angiographic image quality the Core Lab was unable to confirm stable stent placement immediately post-procedure and therefore this one subject was reported not to have stable stent placement immediately post-procedure. Immediately post-procedure and at the 6 month follow-up, the

stent was reported to maintain coil mass position within the aneurysm sac with parent artery patency in 10/10 (100%) subjects.

The mean post-procedure aneurysm occlusion was 86.8%, and improved to 88.8% at six months.

Safety:

The CODMAN ENTERPRISE system was demonstrated to be safe for the treatment of wide-necked aneurysm in this study population. Only 3 SAEs were reported in 3 subjects, and no SAEs were reported to be related to the device. There were no deaths and no event caused the stenting/coiling procedure to be discontinued.

1.3.3 Study of ENTERPRISE in the Japanese Clinical Setting

Johnson & Johnson Medical Company in Japan conducted a multicenter, single-arm study evaluating the CODMAN ENTERPRISE® Vascular Reconstruction Device. The study period was November 2007 through October 2008.

Since the probable benefit and safety of CODMAN ENTERPRISE had already been demonstrated in clinical studies in the United States and European countries, and since no device with similar functions of those to ENTERPRSISE was commercially available, Japan conducted the study to evaluate the applicability of CODMAN ENTERPRISE assisted procedure in the Japanese clinical setting. In this study, procedural success was the primary endpoint in patients with a non-ruptured intracranial wide-neck (defined as a neck width ≥ 4 mm or a dome-to-neck ratio < 2) saccular aneurysm with a greatest diameter of at least 10 mm that is refractory to surgeries (e.g., clipping) or coil-only embolization. Four stent sizes were used in the study (4.5 mm x 14 mm, 4.5 mm x 22 mm, 4.5 mm x 28 mm, or 4.5 mm x 37 mm) according to lesion findings. Fifteen (15) patients were enrolled and reported on in the study submission to the Shonin. It was approved in Japan on 08 January 2010 under the product name CODMAN ENTERPRISE Stent.

1.3.4 Sunrise Registry: European Post Market Surveillance

The Sunrise Registry is a multicenter, prospective, observational registry to evaluate the safety and performance of the CODMAN ENTERPRISE System in routine clinical practice.
This study demonstrates the safety and performance of the CODMAN ENTERPRISE System to facilitate endovascular coil embolization of wide neck saccular intracranial aneurysms. The study design featured the use of an angiographic core lab as well as study monitoring.

One hundred and nine (109) Subjects were enrolled in 15 centers (1 center in Australia and 14 centers in Europe) where the CODMAN ENTERPRISE

System is approved for commercial use. Three subjects who did not give consent prior to data entry are omitted from analysis (consent forms were signed after the procedure had been performed). One subject did not receive treatment and was excluded as well.

Data is presented on 105 subjects who were enrolled into the study and signed informed consent before stent placement. Per protocol, the study period for each subject was 6 months. The majority (71.6%) of the subjects was female, and the average age was 55.3 years. A medical history of hypertension was reported in 36.2% of the subjects enrolled and 3.8% had cardiovascular disease. The most commonly reported neurological event at baseline was TIA/CVA (20.0%), and 17.1% had a history of recurrent headaches. At baseline, 34.3% of the subjects had undergone a prior intracranial embolization procedure or clipping for their cerebral aneurysm.

All serious adverse events were adjudicated by the participating investigators. Based on the adjudication, two subjects experienced a device- or procedure-related serious adverse event for an estimated rate of 1.9%. Seventeen subjects (16.2%) experienced 17 at least possibly device or procedure adverse events (including the two SAEs reported above). The majority (70.6%) of these events occurred before hospital discharge.

Angiographic measurements were made by an angiographic core lab. At pre-procedure, the mean aneurysm dome height and width was 7.8 mm and 6.9 mm, respectively. The mean neck width was 4.9 mm. The mean proximal/distal diameter of the parent vessel pre-procedure was 3.6/3.3.

The technical success measures were also assessed using the angiographic core lab. Successful intracranial device placement (defined as stable CODMAN ENTERPRISE placement with complete coverage of the aneurysm neck and parent artery patency) was achieved in 85.7% of the cases. Satisfactory coil mass position (defined as CODMAN ENTERPRISE maintains coil position within the sac with parent artery patency as defined angiographically) was 83.5% immediately post-procedure and 83.3% at six months. Complete aneurysm occlusion was achieved in 20.2% of cases immediately post-procedure and in 58.2% of the subjects with 6 months follow-up.

1.4. Commercial Approval of ENTERPRISE

"Conformité Européene" (CE-mark):
Outside of the United States (U.S.), the CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System and the CODMAN ENTERPRISE® 2 Vascular Reconstruction Device are released by meeting the European medical device regulations for use with occlusive devices in the treatment of intracranial aneurysms.

Humanitarian Use Device (HUD) approved through Humanitarian Device Exemption (HDE) No. H060001:
In the United States, the CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System and the CODMAN ENTERPRISE® 2 Vascular Reconstruction Device are authorized by the Federal Law for use with embolic coils for the treatment of wide-neck, intracranial, saccular or fusiform aneurysms arising from a parent vessel with a diameter of ≥ 2.5 mm and ≤ 4 mm. Wide neck is defined as having a neck width ≥ 4 mm or a dome-to-neck ratio < 2.

Japanese Government:
In January 2010, Johnson & Johnson Medical Company in Japan received SHONIN approval from Japan's Ministry of Health, Labor and Welfare to market the CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System in Japan.

2.0 STUDY OBJECTIVES

The primary objectives of the study are to evaluate the safety (as assessed by rates of major ipsilateral stroke and/or death and in-stent stenosis) and effectiveness (as measured by the rate of complete angiographic occlusion) of ENTERPRISE when used in conjunction with endovascular coil embolization of unruptured wide-neck, intracranial, saccular anterior circulation aneurysms (≤ 10 mm) in a prospective, multi-center, single arm clinical study.

Secondary effectiveness objectives include the evaluation of treatment outcomes for subjects treated with ENTERPRISE in the acute (procedure and immediate post-procedure time frames) and follow-up phases of patient management.

Secondary safety objectives include the evaluation of adverse safety outcomes for subjects treated with ENTERPRISE from the start of the procedure through the end of study participation (12 months or premature discontinuation of study participation).

In addition, the rates of stent movement and migration will be described.

3.0 STUDY DESIGN

3.1 General Design

This is a prospective, single arm, multicenter 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, saccular anterior circulation intracranial aneurysms (≤ 10 mm) arising from a parent vessel with a diameter of ≥ 2.5 mm and ≤ 4 mm.

This study will be conducted at a maximum of 25 centers in the United States (US). The study will be registered and results will be reported to the U.S. database maintained by the United States National Institutes of Health (NIH) on the United States National Library of Medicine's ("NLM") website www.clinicaltrials.gov under Title VIII of the Food and Drug Administration Act of 2007 ("FDAAA").

It is anticipated that fewer than 15% of entered subjects will be unevaluable at the 12 month follow-up visit due to loss to follow-up and/or missing primary angiographic occlusion or safety data. However, subjects with missing data at the time of endpoint analysis will have primary effectiveness and primary safety endpoint data imputed as last observation carried forward (LOCF). Subjects who receive the device but in whom there is no post-procedure data will be treated as failures for the primary effectiveness analysis; subjects who do not receive the device because of treatment failure due to reasons associated with the device will also be treated as failures. Subjects with no post-procedure endpoint data upon which to base a LOCF imputation will be excluded from the primary safety endpoint analyses; it is anticipated that fewer than 7% of MITT subjects will be excluded from either primary effectiveness or primary safety endpoint analyses. Thus, although the primary endpoint analyses will be in the Modified Intent to Treat (MITT) population for primary effectiveness and safety endpoints, up to 320 subjects will be enrolled to achieve approximately 300 subjects with post-procedure data in the MITT population. A group sequential design will be employed in which one primary endpoint interim analysis will be conducted after N=160 subjects have been enrolled and followed through 6 months post-procedure, to determine if the study should stop early for futility or tentative success; it is anticipated that there will be at least N=150 subjects with post-procedure data in the MITT population for this analysis. If the stopping rule is met for the trial to stop early for tentative success, a final confirmatory analysis will be conducted when all subjects have reached 12 months post-procedure. If the trial is not terminated early for futility or tentative success, then enrollment will continue up to the full enrollment sample size of N=320.

Patients who experience an AE of Special Interest and who have an MRS >2 at any clinical evaluation will be followed through 24 months post-procedure.

An independent core laboratory will perform the quantitative analysis for the primary and secondary effectiveness endpoints, as well as for subjects where the 12 month angiogram is an endpoint assessment. A medical monitor will adjudicate the relationship of AEs to the device, procedure, and/or underlying disease in accordance with the definitions specified within this protocol.

3.2 Study Endpoints

3.2.1 Primary Effectiveness Endpoint

- The primary effectiveness endpoint is the Rate of Complete Aneurysm Occlusion (RCAO) at 12 months post-procedure 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 post-procedure follow-up visit will be considered not to have achieved complete aneurysm occlusion for the purpose of the primary endpoint analysis.

The primary endpoint analysis will be to demonstrate that the RCAO is significantly greater than a performance goal (PG) of 35%. The primary endpoint null and alternative hypotheses are:

Null hypothesis H_o: RCAO ≤ 35%

Alternative hypothesis H_A: RCAO > 35%

This analysis will be conducted on the modified intent-to-treat (MITT) population of subjects (subjects who are found to be eligible for treatment with ENTEPRISE at the time of the pre-procedure angiographic assessment, and in whom treatment is attempted). A supportive analysis will be conducted on the PP population.

Note: The study will be deemed to be a success if this primary efficacy endpoint null hypothesis (on the MITT population with data from all sites combined) is rejected in favor of the alternative hypothesis.

3.2.2 Primary Safety Endpoints

There are two primary safety endpoints: the of rate of Major Ipsilateral Stroke and/or Death at 12 months post-procedure and In-stent Stenosis at 12 months post-procedure.

The analyses of these safety endpoints will be conducted on the MITT population. Supportive analyses will be conducted on the PP population.

3.2.2.1 Incidence of Major Ipsilateral Stroke and/or Death

The incidence of a major ipsilateral stroke and/or death will be evaluated from the start of the index procedure until completion of the 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.

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the proportion of subjects who experience major ipsilateral stroke and/or death through 12 months post-procedure will be less than 25%.

3.2.2.2 Incidence of In-Stent Stenosis

The percentage of aneurysms in which in-stent stenosis is assessed angiographically, at or prior to 12 months post-procedure will be evaluated. 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).

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the rate of stenosis at or prior to 12 months post-procedure will be less than 15%.

3.2.3 Secondary Effectiveness Endpoints

The following secondary effectiveness endpoints have been defined. Observed rates will be described for both the MITT and PP populations; All angiographic imaging results will be based upon assessments by the independent Core Laboratory. A subject who is retreated (retreatment includes staged procedures) is considered to be a treatment failure for endpoints based on angiographic imaging.

3.2.3.1 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 and 12 month follow-up assessments.

3.2.3.2 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 and 12 month follow-up angiographic assessments, respectively, will be evaluated.

3.2.3.3 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, and 12 month follow-up angiographic assessments will be evaluated.

3.2.3.4 Percent Aneurysm Occlusion

The percentage of aneurysms with 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.

3.2.3.5 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. Percentages of aneurysms falling into each of the categories will be presented.

3.2.3.6 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.

3.2.4 Secondary Safety Endpoints

The evaluation of the rate of new neurological deficits (increase in mRS > 2 from baseline not related to stroke or death) at 12 months will be a pre-specified, powered analysis. All other secondary endpoints will be presented as a group to better characterize the ENTERPRISE stenting procedure.

Unless otherwise stated, these secondary safety analyses will be conducted on the MITT population.

3.2.4.1 Rate of New Neurological Deficits as per the Modified Rankin Scale (mRS)

Observed scores on the Modified Rankin Scale will be presented at baseline (pre-procedure) and follow-up (30 days, 6 and 12 months post-procedure). The number and percentage of subjects who have an increase in mRS > 2 from baseline not related to stroke or death will also be presented for each follow-up time point.

3.2.4.2 NIH Stroke Scale (NIHSS) Total Score

The NIHSS Total Score evaluations will be summarized at baseline (pre-procedure) and follow-up (6 and 12 months post-procedure); change from baseline at 6 and 12 months will also be summarized. The percentage of subjects who show a worsening from baseline (increase of 4 points or more) will also be presented. Observed scores and change from baseline will also be presented for NIHSS excluding scores on the aphasia subscale.

3.2.4.3 Adverse Events and Clinical Complications

Adverse Events (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 coded using the MedDRA system and summarized with frequencies. Serious adverse events (SAEs), device- or procedure-related AEs, unanticipated adverse device effects (UADEs) and deaths will be presented.

AEs will be presented for the following study periods: 1) peri-procedure – i.e., from the start of the procedure until 24 hours post-procedure; and, 2) through 12 month follow-up – i.e., from 24 hours post-procedure through the 12 month visit or premature termination.

3.2.4.4 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.

3.2.4.5 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.

3.2.4.6 In-stent Stenosis (Acute, and 6 Months)

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 or not the vasospasm was responsive to medication.

3.2.4.7 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.

3.2.5 Ancillary Endpoint

3.2.5.1 Stent Movement/Migration

Incidence of stent movement and/or migration from the start of the index procedure until completion of the 12 month follow-up

3.2.6 Safety Follow-up through 24 months post-procedure

Subjects who experience any of the following AEs of Special Interest and who have an MRS > 2 at any clinical evaluation will be followed through 24 months post-procedure, and their outcomes will be summarized in a supplemental safety follow-up report:

- All adverse events
- Rupture of the index aneurysm beyond 24 hours post-treatment
- Major ipsilateral stroke more than 1 month post-treatment
- Ipsilateral parenchymal hemorrhage more than 1 month post-treatment

4.0 ELIGIBILITY OF SUBJECTS, EXCLUSIONS AND REMOVAL OF SUBJECTS

Subjects eligible for initial study screening are subjects who present with unruptured wide-neck, intracranial, saccular anterior circulation aneurysms and who are judged to be candidates for stenting. Every effort will be made to establish eligibility of the participants prior to enrollment.

Subjects who agree to voluntarily sign a study informed consent will be considered “enrolled” in the study, and will comprise the subject populations for this study.

Enrolled subjects who meet all of the general inclusion criteria and none of the general exclusion criteria described in this protocol will proceed with confirmation of angiographic inclusion/exclusion criteria.

Pre-treatment angiography performed during the index procedure will be utilized for final assessment of angiographic eligibility criteria. Subjects, who meet all of the general and angiographic inclusion/exclusion criteria, including the requirement for only one aneurysm to be treated, may be treated with ENTERPRISE. Subjects will be "entered" in the study (if the intent is to proceed with stent deployment) at the time of the start of the index procedure as defined in this protocol (see definitions). All subjects entered will be evaluated, regardless of sequence of treatment that ensues.

Subjects who are enrolled but not entered due to angiographic ineligibility resulting from either a pre-procedure angiogram or a pre-treatment angiogram will be considered an Angiographic Screening Failure (ASF) and will be followed for the period 72 hours following the end of the angiogram, or until discharge, whichever comes first, or to resolution of any adverse event, whichever is longer, and then will be discontinued from the study.

All subjects "entered" in the study are considered follow-up eligible and will be required to adhere to the follow-up schedule outlined in this protocol. Subjects who withdrew consent after treatment will be followed until the time of their withdrawal. Subjects who receive a retreatment of the study aneurysm will be followed for safety until the completion of their 24 month follow-up or premature study termination. These aneurysms will not be assessed for effectiveness beyond the retreatment.

Subjects who were determined by the investigator to meet the angiographic eligibility criteria, and received treatment with ENTERPRISE, but upon core lab review do not meet these criteria will be included in the effectiveness analysis in the Modified Intent-to-Treat population. However, the subject will be excluded from the Per Protocol population.

4.1 Criteria for Eligibility

4.1.1 General Inclusion Criteria

Prior to entry in this study, candidates must meet ALL of the following criteria:

1. Subject is 21 to 70 years, inclusive.

2. Subject whose target aneurysm is an unruptured wide-neck, intracranial, saccular anterior circulation aneurysm (≤ 10 mm) arising from a parent vessel with a diameter of ≥ 2.5 mm and ≤ 4 mm who is referred for endovascular treatment. Wide-necked is defined as width ≥ 4 mm or a dome-to-neck ratio < 2.
    i. For aneurysms < 5mm, subject must have another factor that increases the risk of rupture, specifically:

1. Aneurysm is irregular in shape (e.g. multi—lobulated/with daughter sac)
2. Interval increase in aneurysm size
3. Subject with history of subarachnoid hemorrhage (non-target aneurysm)
4. Subject with 2 first degree relatives with history of aneurysmal SAH

3. Subject whose target aneurysm is located in the anterior circulation.

4. Subject understands the nature of the procedure and provides voluntary written informed consent prior to the treatment.

5. Subject is willing to comply with specified follow-up evaluation and is willing to return to the investigational site for the thirty day, 6 month and 12 month, 18 month and 24 month follow-up evaluations.

4.1.2 General Exclusion Criteria

Candidates must be excluded from this study if ANY of the following criteria are met:

1. A planned staged procedure (a staged procedure is a procedure where entire treatment with the device (e.g., coils/stents) is completed over separate sessions).

2. Currently enrolled in another investigational device or drug study that has not reached the primary endpoint or that clinically interferes with the current study endpoints.

3. Two or more aneurysms (> 2 mm) in associated distribution.

4. More than 2 aneurysms (> 2 mm) total, previously treated or untreated.

5. Target aneurysm that has been previously treated

6. A non-target intracranial aneurysm expected to require treatment during the 12 month follow-up period.

7. A previous neuro-interventional or neuro-surgical procedure of any kind within 30 days prior to the study procedure.

8. A ruptured aneurysm.

9. Mycotic, fusiform or dissecting aneurysm.

10. Arteriovenous malformation (AVM) in the territory of the target aneurysm.

11. A Barthel Index < 80 from baseline condition not secondary to index aneurysm.

12. An intracranial mass (tumor, abscess, or other infection).

13. Dementia.

14. Admission platelet <50,000 or any known hemorrhagic diathesis, coagulation deficiency, or on oral anticoagulant therapy with an INR >3.0

15. A serum creatinine level > 2.5 mg/dL within 14 days prior to index procedure which the investigator determines restricts the use of contrast agents.

16. Known hypersensitivity/allergies or contraindication to aspirin, bivalirudin, clopidogrel or ticlopidine, cobalt, nitinol metal, nickel, or sensitivity to contrast media, which cannot be adequately pre-medicated or subject unable/unwilling to undergo therapy.

17. Cannot receive heparin during the study procedure.

18. A previously implanted intracranial stent associated with the symptomatic distribution within the past 12 weeks.

19. A previously implanted carotid stent associated with the symptomatic distribution within the past 12 weeks.

20. Evidence of an acute myocardial infarction (MI) within 31 days of the intended study procedure.

21. Currently has uncontrolled atrial fibrillation or known cardiac disorders likely to be associated with cardioembolic symptoms.

22. Females who are currently pregnant or intend to become pregnant during the study.

23. Patients with ongoing treatment of cancer or any patient who does not have a 5 year life expectancy from congestive heart failure, renal failure or other significant medical problems.

24. A history of stroke, cerebrovascular accident or transient ischemic attack in the last 6 months.

25. Active peptic ulcer or active gastrointestinal (GI) bleeding.

26. Otherwise determined by the investigator to be medically unsuitable for participation in this study.

27. A prisoner.

28. Evidence of active infection (WBC >10x109 /L)

29. Target aneurysm is an extradural aneurysm(s)

30. Current substance-abuse /illicit drug use

4.1.3 Angiographic Inclusion Criteria

Candidates must meet ALL of the following criteria:

1. An unruptured wide-neck, intracranial, saccular anterior circulation aneurysm
   (target aneurysm)

2. Aneurysm size is ≤ 10 mm.
   i. For aneurysms < 5mm, subject must have another factor that increases the risk of rupture, specifically:
      1. Aneurysm is irregular in shape (e.g. multi—lobulated/with daughter sac)
      2. Interval increase in aneurysm size
      3. Subject with history of subarachnoid hemorrhage (non-target aneurysm)
      4. Subject with 2 first degree relatives with history of aneurysmal SAH

3. Target aneurysm for the study treatment arises from a parent vessel with a diameter of ≥ 2.5 mm and ≤ 4 mm.

4. A wide-necked aneurysm. Wide-necked is defined as width ≥ 4 mm or a dome-to-neck ratio < 2.

4.1.4 Angiographic Exclusion Criteria

Candidates must be excluded if ANY of the following criteria are met:

1. Angiogram demonstrates that the target aneurysm is not appropriate for endovascular treatment (i.e.: severe intracranial vessel tortuosity or stenosis, intracranial vasospasm not responsive to medical therapy).

2. Aneurysm is expected to require more than one stent.

3. Aneurysm will or may be treated with a Hydrocoil(s) (the use of all other polymer coils is not an exclusion criteria).

4.2 Early Withdrawal of Subjects

4.2.1 Withdrawal Criteria

A subject can stop his or her participation by withdrawing his/her consent or when he/she is no longer able to participate in the study. Withdrawing consent will not result in any penalty whatsoever for the subject. Further treatment will be performed according to local practice. In case of a device-related or procedural-related adverse event that occurred as a result of participating in this study, the subject will be treated according to local practice.

The data of the subject who withdraws his/her informed consent will not be discarded, and will be used in the final analysis of the study, unless the subject specifically requests that the data not be used.

If a subject decides to withdraw from the study, he/she may do so at any time. However, the reason for discontinuation must be recorded in the source documentation and on the CRF. Possible reasons for premature discontinuation may include, but are not limited to, the following:

- Subject decides to withdraw from the study
- Investigator decides to withdraw subject from the study
- Lost to follow-up: after three attempts to reach the subject by telephone have failed, a certified letter will be sent to the subject. The subject will be considered lost to follow-up if this communication is unsuccessful.

5 STUDY DEVICE

5.1 ENTERPRISE Investigational (Study) Device Description

5.1.1 CODMAN ENTERPRISE® Vascular Reconstruction Device

The CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System (may be referred to as ENTERPRISE) is comprised of a self-expandable stent pre-loaded in a delivery system. The delivery system is composed of an introducer and a delivery wire. The self-expanding stent is pre-loaded on the delivery system inside the introducer.
The CODMAN ENTERPRISE Vascular Reconstruction Device and Delivery System is available in 2 versions. A first version with a 12 mm radio opaque tip at the distal part of the delivey wire, and a second version without the12 mm radio opaque tip at the distal part of the delivery wire (referred as “no-tip”).

Stent:

The stent is the implantable segment of the system. It has a tubular mesh structure, which is laser-cut from a Nickel Titanium (NiTi) hypotube. The proximal and distal ends of the stent are flared and are designed to enhance apposition of the implanted stent to the wall of the vessel. Once exposed to body temperature and upon release from the microcatheter constraint into vessels with smaller diameters than that of the stent, it expands to the vessel lumen diameter. In its expanded shape, the stent creates a proprietary, highly flexible, closed-cell structure that provides support for coils inside the aneurysm. The stent's pattern provides the flexibility necessary to navigate the tortuous neurovasculature as well as sufficient radial strength and adequate cell size to provide reliable embolic coil support. Refer to Figure 1.

The stent has radiopaque markers on 4 struts at either end of the device. This allows the physician to visualize the device *in vivo* under fluoroscopy. The markers are mechanically attached to the struts and covered with an adhesive. The adhesive enhances the marker-strut bond and creates a smooth, continuous surface. The stent and markers are covered with an insulating polymer.

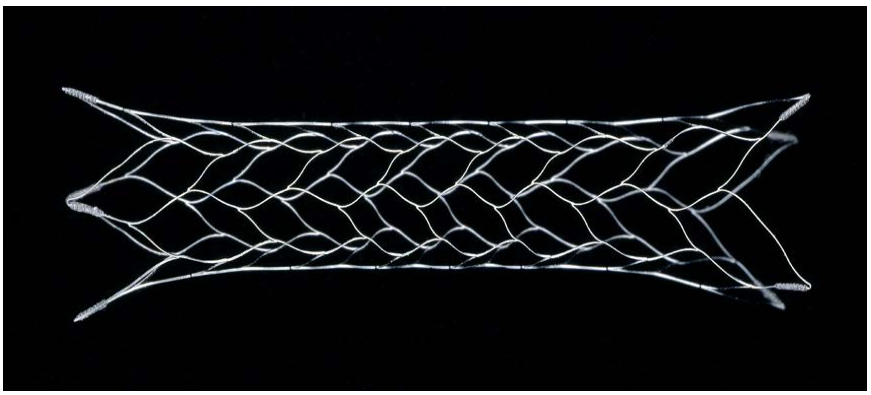


Figure 1: Expanded Stent

Refer to Table 2 for a list of stent sizes.

Table 2: CODMAN ENTERPRISE Stent Sizes and Parent Vessel Diameter

Unconstrained Target Expanded Stent Diameter (mm)	Unconstrained Target Stent Length (mm)	Lumen Diameter of Vessel Treated (mm)
4.5	14	2.5 – 4
4.5	22	2.5 - 4
4.5	28	2.5 - 4

4.5	37	2.5 - 4

Delivery System:

As previously stated, the delivery system of the CODMAN ENTERPRISE Vascular Reconstruction Device and Delivery System is comprised of an introducer and a delivery wire. The CODMAN ENTERPRISE Vascular Reconstruction Device and Delivery System is available in 2 versions. A first version with a 12mm radio opaque tip at the distal part of the delivery wire, and a second version without the12mm radio opaque tip at the distal part of the delivery wire (referred as “no-tip”).

The No distal tip delivery wire configuration has the same materials as the Enterprise with the 12mm distal tip delivery wire configuration. Refer to Figure 2.

Introducer:

The introducer consists of a polymeric tube (PTFE) .021″ inner diameter, with a tapered distal end. Its inner diameter matches that of the microcatheter and the taper angle and diameter match corresponding parameters of the microcatheter hub. The introducer is designed to protect the stent from damage and, when properly positioned in the microcatheter hub, creates an uninterrupted passage for the stent during its transition from the introducer into the microcatheter.

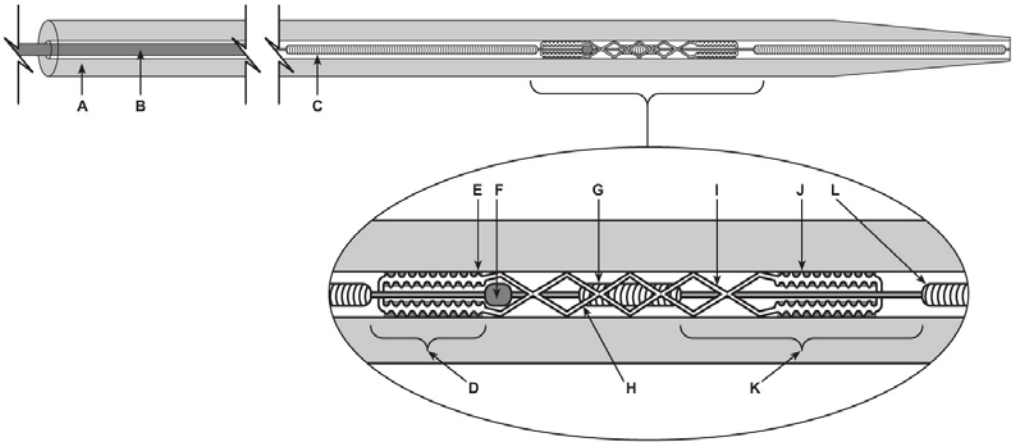
Delivery Wire:

The delivery wire (DW) is made of a Nitinol corewire that tapers down from the proximal to the distal end. The tapering of the corewire provides different stiffness zones along its length, stiffest at the proximal end and most flexible at the distal tip in order to facilitate navigation into the distal neurovasculature.

For the Enterprise with the 12 mm distal tip delivery wire configuration, the distal section of the delivery wire has three radiopaque zones. They are created by platinum/tungsten coils soldered (95% Sn / 5% Ag solder alloy) to the corewire. Each of the three radiopaque zones is of a specific length with gaps between them designed to serve different functions. These radiopaque zones are referred to as the proximal marker, stent positioning marker and the distal marker of the delivery wire. A stent retraction bump is located between the proximal marker and the stent positioning marker. Grinding the Nitinol corewire to a larger diameter than the adjacent corewire creates the stent retraction bump. The space between the proximal stent marker of the delivery wire and the stent retraction bump is referred to as the stent marker engagement gap. The proximal stent markers rest within this gap, which engages the stent with the delivery wire as long as the stent is compressed within the lumen of the introducer or microcatheter. The gap

between the distal and stent positioning markers of the delivery wire is referred to as the resting gap. The distal stent markers reside over the resting gap of the delivery wire.

The Enterprise “No-Tip” delivery wire configuration has the same materials as the Enterprise, but without the 12mm distal tip on the delivery wire.



Note: Items are not drawn to scale.

Figure 2: CODMAN ENTERPRISE Vascular Reconstruction Device and Delivery System

A: Introducer
B: Proximal delivery wire
C: Proximal marker of delivery wire
D: Stent marker engagement gap
E: Proximal stent markers
F: Stent retraction bump
G: Stent positioning marker of delivery wire
H: Recapture limit point
I: Stent body
J: Distal stent markers
K: Resting gap
L: Distal marker of delivery wire (*Not applicable for the Enterprise No-Tip configuration*)

The Enterprise stent is also available in a No Distal Tip configuration (Figure 3). This configuration eliminates the 12mm tip segment which will allow physicians to place stents in vasculature where additional distal stability is not required or desired (e.g., severe distal tortuosity, small distal diameter tapering vessels of the presence of perforator vessels that may be impacted by the distal coil.

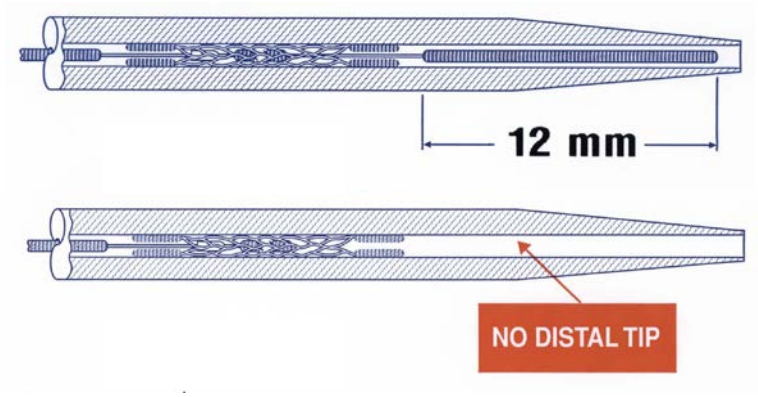


Figure 3: Enterprise Stent With Distal Tip and Without Distal Tip

Principles of Operations:

As described above, the proximal stent markers are engaged in the delivery wire stent marker engagement gap between the proximal markers of the delivery wire and the stent retraction bump and rest within the constraint of the microcatheter lumen. Within the constraint of the microcatheter lumen, this mechanical interlocking of the stent marker engagement gap, located between the proximal marker and the stent retraction bump, gives the physician the ability to deploy, retract, and reposition the stent. During deployment, the distal end of the delivery wire proximal marker pushes the proximal end of the stent markers. During retraction, the proximal end of the delivery wire stent retraction bump pulls against the distal end of the proximal stent markers.

The stent is advanced through the microcatheter to the intended location. The delivery wire's stent positioning marker is positioned in the desired location across the neck of the aneurysm. Once accurate placement is confirmed, the microcatheter is slowly retracted while the delivery wire is held in place. As the stent exits the tip of the microcatheter, it expands and takes the shape of the vasculature. The stent may be re-sheathed until the position at which the recapture limit point is aligned with the distal end of the distal microcatheter marker band. Once the proximal markers of the stent exit the tip of the microcatheter, the stent is fully deployed into the vessel.

5.1.2 CODMAN ENTERPRISE® 2 Vascular Reconstruction Device

The modifications to the CODMAN ENTERPRISE Vascular Reconstruction Device are described below. Table 3 provides additional information on the similarities and differences between the two devices.

All changes are applicable to the CODMAN ENTERPRISE 2 Vascular Reconstruction Device only and do not impact the current Codman Enterprise Vascular Reconstruction Device and Delivery System.

Design Changes

- The outer diameter (OD) of the stent (unconstrained) was expanded from 4.5 mm to 5 mm to improve stent wall apposition;
- The tantalum Coil Marker was replaced by a platinum 92%-tungsten 8% (PtW8) alloy marker band to improve stent marker radiopacity;
- The marker retention feature on the stent crowns was modified to accommodate the new marker bands;
- The nominal engagement gap diameter of the delivery wire assembly was increased minimally to increase the robustness of the delivery wire;
- The minimum engagement gap length of the delivery wire assembly was increased minimally to accommodate new marker retention feature;
- The corewire engagement gap length was increased minimally and a change was made to ensure a flatter joint surface on the distal end of the proximal coil distal joint, improving stent insertion;
- Flushing holes were added to the Introducer to facilitate ease of use.

Table 3: Similarities and differences between Enterprise and the Enterprise 2

	Component	ENTERPRISE VRD	ENTERPRISE 2 VRD Design Modifications	ENTERPRISE 2 VRD Process Modifications
Stent Assembly	Stent	50.8% Nickel / 49.2% Titanium (Nitinol)	No change	• Use of a new cutting laser • Low oxide tubing with a new mechanical polishing step • Addition of an etching solution • Modification to the electropolishing solution and parameters. • Modification in heat treatment steps. • Passivation step and a new constraining fixture added.
	Radiopaque Stent Markers	Tantalum R05400	92% Platinum, 8% Tungsten	Changed from wound coils to solid marker bands
	UV Curable Adhesive (for Stent Marker attachment)	Dymax Adhesive 1128A-M-VT	No change	Added crimping process for marker bands

	Component	ENTERPRISE VRD	ENTERPRISE 2 VRD Design Modifications	ENTERPRISE 2 VRD Process Modifications
	Stent Coating	Parylene-C	No change	None
Delivery Wire Assembly	Corewire	50.8%Nickel / 49.2% Titanium (Nitinol)	No change	See below for Delivery Wire dimensional modifications:
	Corewire Engagement gap length	0.058 + 0.007 / - 0.003	0.068 + 0.007/- 0.003	No change, same grinding process
	Corewire Engagement Gap (EG) OD Increase	0.0033 +/- 0.0003	0.0036 +/- 0.0003	No change, same grinding process
	Constant ground section between EG and distal coil marker	0.0033 +/- 0.0003 (1)[1] 0.0032 +.0007 / - .0002 (2)[2]	0.00345 +/- 0.00045	No change, same grinding process
	Corewire Surface finish	No Requirement	Requirement	No process change; inspection added to monitor surface finish
	Distal Marker (coil)	92% Platinum / 8% Tungsten	No change	No change
	Stent Positioning Marker (coil)	92% Platinum / 8% Tungsten	No change	No change
	Proximal Marker (coil)	92% Platinum / 8% Tungsten	No change	No change
	Solder/Flux (for Delivery Wire Marker attachment)	Solder: EutecRod 157 (95% Sn, 5% Ag, Cadmium free) Flux: Indalloy flux #2	No change	Removed buffing of the proximal coil distal join
	Delivery Wire Engagement Gap Length	0.045” Min	0.050” Min	Placement of proximal delivery wire marker
	Delivery Wire – Solder Station and Ultrasonic Bath	Operations performed in Clean Room Building 340	Operations to be performed in Clean Room in Building 304 with other ENTERPRISE manufacturing	A duplicate solder station and ultrasonic bath were purchased and qualified in order to move these operations from Building 340 to the clean room located in Building 304 within the same LRM facility, thus consolidating all ENTERPRISE 2 operations into Building 304.
Introducer	Introducer	Natural PTFE	Same material but with the addition of flushing holes	The taper and punch hole operations are performed by a new vendor.
Final Assay	Final Inspection	Fixture constrains introducer only	Fixture constrains introducer and delivery wire simultaneously	Final inspection fixture changed; inspection process did not change

	Component	ENTERPRISE VRD	ENTERPRISE 2 VRD Design Modifications	ENTERPRISE 2 VRD Process Modifications
Stent Design	Closed cell, flared ends, 4-cell design	Closed cell, flared ends, 4-cell design, 4.5mm unconstrained	Closed cell, flared ends, 4-cell design, 5.0mm unconstrained; dogbone features to accommodate new markers	See item 1
Packaging	Hoop	HDPE	No change	No change
	Cavity Clips	60% HDPE / 40% LDPE	No change	No change
	Wire Retention Clip	TPV 8271-75	No change	No change
	Pouch	Perfecseal 35721-K Nylon to Du Pont 1073B Tyvek coated with BB2000	No change	No change
	Carton	Paperboard	Same material as current, modified graphics	No change

Table 4: CODMAN ENTERPRISE 2 Stent Sizes and Parent Vessel Diameter

Unconstrained Target Expanded Stent Diameter (mm)	Unconstrained Target Stent Length (mm)	Lumen Diameter of Vessel Treated (mm)
5.0	16	2.5 – 4
5.0	23	2.5 - 4
5.0	30	2.5 - 4
5.0	39	2.5 - 4

5.2 ENTERPRISE Instructions for Use (IFU)

5.2.1 ENTERPRISE General Use and Study Protocol

The CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System is currently approved under a Humanitarian Device Exemption as a Humanitarian Use Device in the United States. Only ENTERPRISE devices that are specifically packaged and labeled for this clinical study are allowed to be used to treat subjects entered under this study protocol. There is no change to the instructions for use as

a result of the modifications to the CODMAN ENTERPRISE Vascular Reconstruction Device.

[NOTE: Per the protocol, subjects are only expected to have one ENTERPRISE stent implanted, however, if it becomes necessary to place an additional stent(s) during the Index Procedure:

- ***ENTERPRISE IDE stent should be used if placed in the target aneurysm***
- ***ENTERPRISE HDE stent should be used if placed in a non-target aneurysm]***

The investigator should follow the study specific Instructions for Use (IFU) that is packaged with the ENTERPRISE study device for general information, and follow the inclusion/exclusion criteria and procedures as outlined in this study protocol.

5.3 ENTERPRISE Packaging

The ENTERPRISE Device is protected by the dispenser hoop and extension tube. The loaded dispenser hoop is packaged in the primary and the secondary packaging components, comprised of the Nylon/Tyvek® pouch and the carton respectively. The carton will be a solid white carton sealed with the closure label. The white carton is used to distinguish the clinical trial units it from the bronze carton of the current product.

The No-Tip configuration packaging will employ red pigmented dispenser clips and a Tyvek tag to help the user identify the product. The Tyvek tag is attached to the dispenser hoop with one of the red clips and has a printed image of the No-Tip design, as well as the words “No Distal Tip” on a red background.

Product labeling includes inner and outer product information labels. Temperature monitoring labels are used to indicate exposure of the product to temperatures exceeding 60°C. Prior to introducing the CODMAN ENTERPRISE Stent into the sterile field, observe the temperature exposure indicator label found on the product’s inner pouch. The acceptance criterion for the product is delineated by the graphic below the indicator label with the green check mark. The reject criterion for the label is delineated by the graphics marked with a red “X”. Do not use if the temperature exposure indicator mirrors the reject criterion graphics, as the constrained stent diameter may have been compromised by exposure to high temperature. The inner pouch and unit carton will also include an Investigational Device Sticker to identify it as clinical trial inventory.

.

5.4 ENTERPRISE Receiving, Storage, Dispensing and Return

5.4.1 Receipt and Accountability of Study Device

The investigator is responsible for device accountability at the study site.

The investigator may assign some of the investigator's duties for device accountability at the study site to an appropriate staff member. This staff member must be listed on the Study Personnel Authorization Form.

The investigator should maintain a record that documents receipt of study device at the study site, the inventory at the site, administration to each subject, and return to the Sponsor and submit the required forms to the study monitor. These records include dates, quantities, lot numbers, expiration dates, and the unique code numbers assigned to the investigational device and study subjects. Study devices must be recorded on the Investigational Device Disposition Log. For any investigational devices destroyed at the site, the date, mode and method of destruction along with the name of the person destroying the device must be recorded.

5.4.2 Storage of Study Device

All study devices must be stored in a locked storage facility to which only the investigator, or designated assistants, will have access.

5.4.3 Dispensing of Study Device

The investigator agrees not to supply the investigational device(s) to any person except those named as sub-investigators on the study personnel authorization form. The investigator must ensure that the investigational devices are used only in accordance with the IFU and study protocol.

5.4.4 Return or Destruction of Study Device

Unused investigational devices being reclaimed for excess inventory, following study completion or due to product expiration, damage, or defect should be returned to Sponsor or designee.

For unopened sterile device/product being returned for excess inventory, study completion and product expiration, the investigator must complete the Sterile Returned Clinical Device Form. The investigator must notify the Sponsor or designee prior to shipment and return the device to the address printed on the Sterile Returned Clinical Device Form.

For device malfunctions and product complaints, the device should be kept at the site until the Sponsor provides instructions for return of the

device to the analysis lab. Non-sterile devices will be returned to Crum Glenn (CG) Laboratories, 1410 Southtown Drive, Granbury, TX 76048. The investigator must notify the Sponsor or designee of device malfunction and product complaints with 10 business days of knowledge.

6 STUDY PROCEDURES

6.1 Screening/Baseline

6.1.1 Screening and Enrollment Procedures

Investigators will be encouraged to screen consecutive subjects who, in the Investigator's judgment are candidates for stenting, as they present for treatment of wide-necked aneurysms, thus decreasing the risk of selection bias in this study. All subjects who are screened for the study will be entered on a screening eCRF. Subjects who are screened will be assigned an identification number (see Section 6.1.2, Subject Identification). The screening eCRF will include age, gender, race and ethnicity. If the subject is not enrolled (the subject is enrolled in the study at the time they sign the study informed consent), the reason will be recorded on the screening eCRF.

Subjects who meet all of the general inclusion criteria and none of the general exclusion criteria described in this protocol will be asked to participate in the study. If the subject declines to participate, or if the investigator decides that the subject will not be asked to participate, then the reason must be documented on the study screening eCRF.

The benefits and risks of the study will be explained and voluntary written informed consent must be obtained from all subjects. The study informed consent should be signed as close to the index procedure as possible, but must be signed prior to any study-specific tests or procedures that are not routine standard of care. Pre-treatment angiography will be performed at the start of the index procedure for the final determination of anatomic and angiographic eligibility. The subject is enrolled in the study at the time they sign the study informed consent. The initial angiogram used to assess angiographic eligibility may or may not be at the same time as the index procedure. A pre-procedure angiography may be performed up to 90 days prior to the index procedure (The pre-procedure angiographic inclusion/exclusion criteria can be taken from either a CTA angiogram or an angiogram).

If the subject signed the study informed consent, but meets any of the angiographic exclusion criteria as the screening procedure progresses, the subject is considered an angiographic screening failure (ASF) and may not continue in the study. For ASF subjects, the signed informed consent must be filed and all eCRF up to and including the

Investigator's angiographic assessment must be completed and entered in the database along with the reason why the subject was not eligible to participate in the study. Any AEs that occurred from the time written consent was obtained through the period 72 hours following the end of the angiogram or until discharge, whichever comes first, must be documented. If any adverse event has not resolved by the 72-hour safety evaluation or discharge, follow-up must continue up to 30 additional days until resolution of the adverse event or the Investigator documents in the subject's medical record that a stable clinical endpoint has been reached, or that the subject's status is not associated with the device or procedure. After the safety evaluation has been conducted, the ASF subject will be discontinued from the study.

Subjects who meet all of the general and angiographic inclusion/exclusion criteria will actually be "entered" in the study (if the intent is to proceed with stent deployment) at the time of the start of the index procedure as defined in this protocol (see definitions) and pre-treatment angiogram confirms subject still meets angiographic eligibility criteria.

6.1.2 Subject Numbering

Subjects who are screened for the study will be assigned an identification number (subject study number). The first two digits assigned represent the site identification; this is followed by a hyphen, and three subsequent digits which represent the sequential identification. For example, ID: 10-001 would represent the first subject screened at site 10. If a subject is screened for the study but is not enrolled, the site will document the reason for not signing the consent.

At the time the subject is enrolled (signs the study informed consent), the five digit identification number (subject study number) is also maintained for these subjects. The first two digits assigned represent the site identification; this is followed by a hyphen, and three subsequent digits which represent the sequential enrollment number. For example, ID: 01-005 would represent the fifth subject at site 01.

Subjects who are enrolled but who are found to be ineligible for treatment with ENTERPRISE at the time of the pre-procedure angiogram will be replaced. Subjects in whom treatment with ENTERPRISE is attempted but who discontinue study participation prematurely will not be replaced.

6.1.3 Baseline Medication and Assessments

The following pre-procedure medications are a requirement of this protocol. Confirmation of correct antiplatelet therapy prior to the procedure must be documented. If confirmation of the correct antiplatelet therapy is not available, the procedure should be delayed.

- Aspirin (ASA): At least 81 mg/day for a minimum of 7 days prior to the procedure

- P2Y12 Platelet Inhibitor: Daily for a minimum of 7 days prior to the procedure

All patients must have platelet reactivity testing performed. Record the test results in the applicable eCRF.

The following baseline data must be collected for all subjects prior to the treatment procedure (within 14 days prior to index procedure). Note that the study informed consent must be signed prior to any study protocol required assessments or procedures that are not routine standard of care by the investigation.

Neurological assessments and subject interview:
*(*Within 14 days prior to index procedure)

- Medical History
- Clinical Assessment/Physical Exam/Vital Signs
  - Within 14 days prior to the index procedure, and during the index procedure (both pre-treatment and immediately post-treatment)
- Relevant prior medications: indicate all antithrombotic (including anti-platelets, anticoagulants, and fibrinolytics) and inhibitors of ADP-induced platelet aggregation medications the subject has taken within14 days prior to index procedure:
- Neurological evaluations performed by qualified personnel. Included as part of this examination are the NIH Stroke Scale Score (NIHSS), Modified Rankin Scale (mRS), and clinical neurological evaluations.

Clinical Laboratory Tests:
*(*Within 14 days prior to index procedure)

- Serum creatinine

CT or MRI

- Obtain an axial CT or MRI of the patient (performed within the last 10 years provided that the CT or MRI was not performed before the subject's 20th birthday) that shows the orbital anatomy of the skull. The CT/MRI should contain a valid centimeter marker and upload to Image Management Vendor (to be used for calibrating images). The CT/MRI scans are needed only for calibration and will not need interpretation.

6.2 Procedure

6.2.1 Indications for Use – Study Device

The CODMAN ENTERPRISE Vascular Reconstruction Device and Delivery System is intended for use with embolic coils for 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. Wide-neck is defined as having a neck width ≥ 4 mm or a dome-to-neck ratio < 2. The device must be used according to the Instructions for Use packaged with the study device, the study protocol inclusion and exclusion criteria, and the study procedures outlined in this study protocol.

6.2.2 Index Procedure

For the ENTERPRISE Device see accompanying IFU for complete instructions including warnings and precautions, on intracranial stent preparation and usage. The index procedure (pre-treatment, intra-procedure, and immediate post-treatment of the index), 6 month and 12 month follow-up, any unscheduled and any pre-retreatment angiograms must be performed according to the study Core Lab Manual. Per the study protocol, the stenting and coiling must both be performed during the index procedure, and the embolization coils must be placed after the stent is deployed. Staged procedures are not allowed under this study protocol. If it becomes medically necessary to stage the stenting and coiling procedures this will be considered a treatment failure.

<u>General Overview for ENTERPRISE Stent-Assisted Coiling</u>
When delivering the stent under fluoroscopic visualization, the interventionist must slowly advance the delivery system to deploy the stent (See IFU for complete directions for use). Do not recapture the stent more than once. Optimal expansion requires the stent to be in full contact with the artery wall, with the stent internal diameter matching the vessel diameter. Stent wall contact should be verified through routine angiography. The interventionist must fully cover the entire aneurysm with the stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion (to maintain a minimum of 5 mm on either side of aneurysm neck). All efforts should be taken to assure that the stent is completely apposed to the vessel wall. Once the stent has been deployed, using the best orthogonal catheter arteriographic projections profiling the aneurysm relative to the parent artery, three orthogonal plane images of the stented artery must be obtained for independent core laboratory review. For size calculations using planar projections, sizing markers must be placed on both sides of the head due to the significant magnification that occurs.

After the stent has been deployed, remove and discard the delivery system. Verify that the stent has remained patent and properly positioned. After completing the procedure, withdraw and discard all

applicable accessory devices. The embolization coils must be placed after the stent is deployed, during the index procedure.

6.2.3 Embolic Devices

For the embolic device, refer to the enclosed labeling packaged with the embolic coils.

Embolization Coils: The embolization coils must be placed after the stent is deployed, during the index procedure. The protocol does not allow the use of Hydrocoils (the use of all other polymer coils, except Hydrocoils, are allowed). Any subject in whom a Hydrocoil is implanted will be considered a protocol deviation.

6.2.4 Procedure Assessments

(This is applicable to the index procedure as well as any other subsequent procedures)

Start/End of Procedure:

The following definitions apply to the index procedure.

- The start of the procedure is the time the femoral artery is accessed.
- The end of the procedure is the time the guiding catheter is removed from the subject.

Procedural Study Assessments:

- Procedural medications
- Event assessment during index procedure (pre-treatment, intra-procedure, and post-treatment), i.e. adverse events, protocol deviations, device malfunction/product complaint
- Angiogram
  - Upload or send the pre-treatment, intra-procedure, and post-treatment images to the study Image Management System

6.2.5 Procedural Medications

Procedural Medications:
Procedural medications administered in the pre-procedural, intra-procedural, and immediate post-procedural timeframes will be recorded on the eCRF. Procedure medications will include, antithrombotic, (including anti-platelet, anticoagulant, and fibrinolytics), and inhibitors of ADP-induced platelet aggregation medications that were administered within 7 days prior to the start of the procedure (femoral artery access) and up to and including 24 hours after end of the procedure (time guiding catheter is removed from the subject). Additionally, please indicate all ***vasoactive*** medications and ***contrast***

that were administered intra-procedurally until the end of the index procedure.

Post-Procedural Medications:
Medications administered 24 hours after end of the index procedure will be recorded on the eCRF. Post-procedural medications will include all antithrombotics (including anti-platelet, anticoagulant, and fibrinolytics), and inhibitors of ADP-induced platelet aggregation medications.

The following post-index procedure medications are a requirement of this protocol.

- ASA (at least 81 mg/day) must be continued for a minimum of 12 months.
- P2Y12 Platelet Inhibitor must be taken daily for a minimum of 3 months

Please refer to Section 8 for further information concerning concomitant medications.

6.3 Follow-up

6.3.1 Follow-up of Angiographic Screening Failures

An angiographic screening failure is any subject who signed the study informed consent but meets any of the angiographic exclusion criteria as the screening procedure progresses. These subjects will not be entered in the study and will be followed for the period 72 hours following the end of the angiographic procedure to determine study angiographic eligibility or until discharge, whichever comes first. Any AEs that occur during this period must be documented. If any AE has not resolved by the 72-hour safety evaluation or discharge, follow-up must continue until resolution of the adverse event, after which they will be discontinued from the study.

For angiographic screening failures:

- Complete and enter onto Screening Log the reason why the subject was not eligible to participate in the study
- File the signed informed consent
- Complete and enter into database all eCRF up to and including the Investigator's angiographic assessment, these forms shall include:
    - Screening/Baseline
    - Pre-Procedure Angiography (and Pre-Treatment Angiography, if applicable)
    - Study Completion
    - Protocol Deviations, as applicable
    - Adverse Events, as applicable

- Complete and entered in the Adverse Event (AE) eCRF any AEs that occurred from the time the study informed consent was signed through the period 72 hours following the end of the angiographic procedure to determine study angiographic eligibility, or until discharge, whichever comes first, or to resolution of any adverse event, whichever is longer.

6.3.2 Follow-up After Stroke or Suspected Stroke (Unscheduled Visit)

If a subject experiences a stroke, or if there is any suspicion of a stroke, the subject needs to have an MRI completed within a time window of **24 hours after symptom(s) onset**.

Additionally, if the subject experiences a stroke they will need to return to visit the investigator 30 days (window 16 - 44 days) after the stroke for a neurological assessment to include, at a minimum, a modified Rankin Score (mRS) assessment and the National Institute of Health Stroke Scale (NIHSS).

In the event, that the subject experienced a stroke but the investigator did not learn about the stroke at the time it occurred, and thus an MRI was not done within 24 hours of the stroke, then site must obtain an MRI immediately upon learning of the stroke, as well perform the modified Rankin Score (mRS) assessment and the National Institute of Health Stroke Scale (NIHSS).

6.3.3 Post-Procedure through Hospital Discharge

All subjects entered into the study will undergo the following tests or procedures while in the hospital.

Assessment and subject interview

- Vital Signs (Blood pressure, Heart Rate, and Respirations)
    - Immediately Post-Treatment
    - Hospital discharge
- Relevant Concomitant Medications (daily): indicate <u>all</u> antithrombotics (including anti-platelets, anticoagulants, and fibrinolytics), and inhibitors of ADP-induced platelet aggregation medications that were administered <u>after 24 hours post-procedure through hospital discharge.</u>
- Neurological assessment and evaluations performed by qualified personnel at 12-36 hours after end of procedure (removal of the guiding catheter from the subject). Included as part of this examination are the NIH Stroke Scale Score, Modified Rankin Scale, clinical neurological evaluation, and if applicable, the Hunt and Hess Scale (HHS) for subarachnoid hemorrhage

- Event assessment (daily) as applicable (i.e. adverse events, protocol deviations, device malfunction/product complaint).

6.3.4 **Thirty-Day Follow-up** (Telephone Interview)

The thirty-day follow-up visit must occur between 16 days to 44 days from the date of the index procedure and may be conducted via telephone.

All subjects entered into the study will be followed for adverse event assessment at thirty days.

All subjects entered into the study will be submitted to the following interview about their health condition and medications:

Subject interview

- Relevant Concomitant Medications (daily since hospital discharge): indicate any antithrombotics (including anti-platelets, anticoagulants, and fibrinolytics) and inhibitors of ADP-induced platelet aggregation medications administered more than 24 hours post-procedure through end of study participation.
- Neurological evaluation performed by qualified personnel. Included as part of this examination is the Modified Rankin Scale.
- Event assessment (since discharge evaluation) (i.e., adverse events, protocol deviations, device malfunction/product complaint)

6.3.5 **6 Month Follow-up** (Clinic Visit & Angiogram)

The 6 month follow-up visit must occur between 92 days and 212 days from the date of the index procedure.

All subjects entered into the study will be followed for adverse event assessment at 6 months post-procedure.

The 6 month follow-up evaluations must be performed at the investigational site. All subjects entered into the study will be submitted to the following:

Assessment and subject interview

- Vital Signs (Blood pressure, Heart Rate, and Respirations)
- Relevant Concomitant Medications (daily since 30 day follow-up): Indicate any antithrombotics (including anti-platelets, anticoagulants, and fibrinolytics) and inhibitors of ADP-induced platelet aggregation medications administered more than 24 hours post-procedure through end of study participation.
- Clinical Assessment and Physical Exam

- Neurological assessment and evaluations performed by qualified personnel. Included as part of this examination are the NIH Stroke Scale Score, Modified Rankin Scale, clinical neurological evaluation, and, if applicable, the Hunt and Hess Scale (HHS) for subarachnoid hemorrhage
- Event assessment (since 30 day follow-up) (i.e., adverse events, protocol deviations, device malfunction/product complaint)
- Angiogram
    - Upload or send the follow-up angiogram images to the study Image Management System
    - The 6 month follow-up angiogram shall be performed using the same orthogonal views as used during the index procedure, and according to the study Core Lab Manual.

6.3.6 **12 Month Follow-up** (Clinic Visit & Angiogram)

The 12 month follow-up must occur between 320 days and 410 days from the date of the index procedure.

All subjects entered into the study will be followed for adverse event assessment at 12 months.

The 12 month follow-up evaluations must be performed at the investigational site. All subjects entered into the study will be submitted to the following:

Assessment and subject interview

- Vital Signs (Blood Pressure, Heart Rate, and Respirations)
- Relevant Concomitant Medications (since 6 month follow-up): indicate any antithrombotics (including anti-platelets, anticoagulants, and fibrinolytics) and inhibitors of ADP-induced platelet aggregation medications administered more than 24 hours post-procedure through end of study participation.
- Clinical Assessment and Physical Exam
- Neurological assessment and evaluation performed by qualified personnel. Included as part of this examination are the NIH Stroke Scale Score, Modified Rankin Scale, clinical neurological evaluation, and, if applicable, the Hunt and Hess Scale (HHS) for subarachnoid hemorrhage.
- Event assessment (since 6 month follow-up) (i.e., adverse events, protocol deviations, device malfunction/product complaint)
- Angiogram
    - Upload or send the follow-up angiogram images to the study Image Management System
    - The 12 month follow-up angiogram shall be performed using the same orthogonal views as used during the

index procedure, and according to the study Core Lab Manual.

6.3.7 18 Month Follow-up (Telephone Interview)

The 18 month follow-up visit telephone interview must occur between 457 days and 592 days from the date of the index stenting procedure.

The 18 month follow-up evaluations may be conducted via a telephone interview. All subjects entered into the study will be submitted to the following:

Subject interview

- Relevant Concomitant Medications (since 12 month follow-up): indicate any antithrombotics (including anti-platelets, anticoagulants, and fibrinolytics) and inhibitors of ADP-induced platelet aggregation medications administered more than 24 hours post-procedure through end of study participation.
- Neurological evaluations performed by qualified personnel. Included as part of this examination is the Modified Rankin Scale.
- Event assessment (since 12 month follow-up) (i.e. adverse events, protocol deviations, device malfunction/product complaint)

6.3.8 24 Month Follow-up (Clinic Visit & MRA or Angiogram)

The 24 month follow-up visit must occur between 685 days and 775 days from the date of the index stenting procedure.

The 24 month follow-up evaluations must be performed at the investigational site. All subjects entered into the study will be submitted to the following:

Assessment and subject interview

- Vital Signs (Blood pressure, Heart Rate, and Respirations)
- Relevant Concomitant Medications (since 18 month follow-up): indicate any antithrombotics (including anti-platelets, anticoagulants, and fibrinolytics) and inhibitors of ADP-induced platelet aggregation medications administered more than 24 hours post-procedure through end of study participation
- Neurological evaluations performed by qualified personnel. Included as part of this examination are the NIH Stroke Scale Score, Modified Rankin Scale, clinical neurological evaluation, and, if applicable, the Hunt and Hess Scale (HHS) for subarachnoid hemorrhage
- MRI/MRA or angiogram (an angiogram must be performed if any stent or coils are not MRA/MRI compatible) to assess for in-stent stenosis, thrombosis and hydrocephalus, or if an angiogram is

performed to assess for in-stent stenosis and thrombosis, then also obtain MRI or CT to assess for hydrocephalus)
- Event assessment (since 18 month follow-up) (i.e. adverse events, protocol deviations, device malfunction/product complaint)

Following the 24 month study visit, the subject will be discharged from the study. However, if the investigator determines there are indications of delayed hydrocephalus or in-stent stenosis occurring, additional follow-up may be required, including MRI or CT at the Investigator's discretion. If this should this occur the investigator will determine the additional follow-up required at that time and inform the study sponsor.

If a subject presents with an adverse event at the 24 month follow-up, he/she will receive appropriate treatment for that condition. If the subject's condition precludes him or her from undergoing any 24 month evaluation specified by the protocol, the subject would be discharged from the study after the Investigator documents in the subject's medical record that a stable clinical endpoint has been reached, or that the subject's status is not associated with the device or procedure.

Subjects entered into the study will be considered eligible for follow-up unless they have died or withdrawn their consent to be contacted. The study center will review the follow-up requirements with the subject to help ensure compliance with the follow-up schedule. Telephone numbers should be obtained from the subject to ensure the ability to contact him or her at the required follow-up times. These phone numbers should include all home numbers, work numbers and primary physician numbers. A phone number of a relative or friend should also be requested.

6.3.7 Safety Follow-up (Subjects with Adverse Events of Special Interest)

All subjects entered into the study who experience any adverse event of special interest and who have an MRS > 2 at any clinical evaluation will be followed through 24 months post-procedure, and their outcomes will be summarized in a supplemental safety follow-up report.

Adverse Events of Special Interest include:

- rupture of the index aneurysm beyond 24 hours post-treatment
- major ipsilateral stroke more than 1 month post-treatment
- ipsilateral parenchymal hemorrhage more than 1 month post-treatment
- device migration at the 6 month angiogram

6.4 Placement of Second ENTERPRISE Stent

Per the study protocol inclusion and exclusion criteria, subjects are only expected to have one ENTERPRISE stent implanted. However, if upon initiating the index procedure, the Investigator deems it necessary to place an additional stent(s), the investigator must use an ENTERPRISE IDE stent. Placement of an additional stent(s) will be considered a protocol deviation.

- ***ENTERPRISE IDE stent should be used if placed in the target aneurysm***
- ***ENTERPRISE HDE stent should be used if placed in a non-target aneurysm]***

6.5 Retreatment of the Target Aneurysm

Retreatment in this study protocol, regardless whether by surgery or endovascular treatment, is defined as any additional treatment of the target aneurysm after the index procedure due to recanalization, rupture or bleeding, or as part of a staged procedure.

6.6 Unscheduled Angiogram

If a subject undergoes an angiogram that is not required as part of this study protocol, it is considered an unscheduled angiogram. If a subject has an unscheduled angiogram, it should be performed using the same orthogonal views as used during the index embolization procedure, and according to the study Core Lab Manual. The angiogram images should be uploaded or sent to the study Image Management System.

6.7 Summary of Follow-up Schedule and Time Windows

Table 5: Follow-up visits: Schedule & Time Windows

Follow-up Visit	Time Window (days)	Timeframe
30 days*	16 - 44	days after index procedure
6 month	92 - 212	days after index procedure
12 month	320 - 410	days after index procedure
18 month*	457 - 592	days after index procedure
24 month	685 - 775	days after index procedure
Stroke or suspected stroke visit	16 - 44	days after stroke or suspected stroke**

* May be a Telephone Visit

** If a subject experiences a stroke, or if there is any suspicion of a stroke, the subject needs to have an MRI completed within a **time** window of 24 hours **after** symptom(s) onset. In the event, that the subject experienced a stroke but the investigator did not learn about the stroke at the time it occurred, and thus an MRI was not done within 24 hours of the stroke, then site must obtain an MRI immediately upon learning of the stroke, as well perform the modified Rankin Score (mRS) assessment and the National Institute of Health Stroke Scale (NIHSS).

All follow-up assessments will be performed at the specified times indicated unless a subject suffers an adverse event that prevents evaluation. Under these

circumstances, only clinically indicated assessments will be performed at the discretion of the attending physician.

7 CORE LABORATORY

An independent core laboratory will perform the quantitative angiographic measurements for the primary and secondary effectiveness endpoints and the 24 month follow up using the Raymond scale assessment. These measurements will be performed by an independent reader.

All subjects are to have procedural angiograms (at pre-treatment, intra-procedure, and immediate post-treatment), as well as 6 and 12 and (if applicable) 24 month angiograms. The angiograms need to be performed according to the study Core Lab Manual. Standard quantitative angiography (QCA) acquisition procedures will be followed for QCA analysis. All angiographies must provide angiograms that are suitable for quantitative analysis, based on optimal orthogonal catheter arteriographic projections. Refer to the study Core Laboratory Manual for further angiographic methods and requirements.

8 CONCOMITANT MEDICATIONS

The following concomitant medications are a requirement of this protocol. Regardless of the therapy administered, the concomitant medication(s) will be documented on the eCRF.

8.1 Pre-procedure Medications

- Aspirin (ASA): At least 81 mg/day for a minimum of 7 days prior to the procedure
- P2Y12 Platelet Inhibitor: Daily for a minimum of 7 days prior to the procedure

  Note: Confirmation of correct antiplatelet therapy prior to the procedure must be documented; If not available, the procedure should be delayed.

8.2 Intra-procedure

- General anesthesia is required for the procedure.

- Heparin: A bolus of intravenous heparin will be given that is weight adjusted to maintain the activated clotting time (ACT) near 250-300 seconds throughout the procedure. If a GP IIb-IIIa Inhibitor (Reopro or Integrilin) is given during the procedure, then the ACT should be maintained at less than 220 to minimize the risk of bleeding. GP IIb-IIIa Inhibitors should not be given if the subject has a recent history (less than 30 days) of hemorrhage. It is required that the ACT be checked during the procedure at intervals of no longer than 60 minutes, as well as at the

end of the procedure to verify conformity with this requirement. It is recommended to discontinue heparin at the end of the procedure and the arterial sheath removed after the ACT has returned to < 140 seconds.

The use of vascular closure devices is recommended, but sheath removal on the day following the procedure is acceptable.

8.3 Post-procedure

The following post-procedure medications are required per this protocol.

• ASA (at least 81 mg/day) must be continued for a minimum of 12 months.

• P2Y12 Platelet Inhibitor must be taken daily for a minimum of 3 months.

9 STATISTICAL METHODS

The following sections provide a general description of the statistical plan for the analysis of study data. A separate Statistical Analysis Plan (SAP) document that provides greater detail on data derivations and the analyses to be performed will be developed prior to the planned interim analysis. The SAP will reflect the protocol and any amendments that have been implemented at the time the SAP is finalized. Any deviations from the final SAP will be noted in the final clinical summary report.

9.1 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. A group sequential design will be utilized in which one primary endpoint interim analysis will be conducted after N=160 subjects have been enrolled and followed through 6 months post-procedure. Enrollment will pause after these 160 subjects have been enrolled and will not resume until after the interim analysis has been conducted. The purpose of the interim analysis will be to determine whether or not to terminate the trial early for futility or tentative success. If the stopping rule is met for the trial to stop early for tentative success, a final confirmatory analysis will be conducted when all subjects have reached 12 months post-procedure. If the trial is not terminated early for futility or tentative success, then enrollment will continue up to a full enrollment sample size of N=320. After all 320 subjects have reached 12 months post-procedure, a final analysis will be conducted.

9.2 Treatment Assignment

This is a single arm study; all subjects will be treated with the CODMAN ENTERPRISE device.

9.3 Levels of Significance

A 2-sided alpha of 0.05 will be used for statistical testing and confidence intervals unless otherwise noted. There will be no adjustment to p-values or alpha levels for testing primary safety, secondary effectiveness, or secondary safety endpoints.

A primary efficacy endpoint interim analysis will be conducted to determine whether or not to stop the trial early for futility or tentative success. This analysis will be based solely on the primary efficacy endpoint, and will be conducted after N=160 subjects have been enrolled and have reached 6 months post-procedure. In this interim analysis, the two-sided unadjusted p-value threshold for stopping the trial early for success will be 0.031. If the stopping rule is met for the trial to stop early for tentative success, a final confirmatory analysis will be conducted when all subjects have reached 12 months post-procedure; a p-value threshold of 0.031 will be used for this final confirmatory analysis. If this early stopping rule is not met, then enrollment will commence until the total sample of N=320 subjects have been enrolled (including the original N=160). The final endpoint analysis with all be conducted with a 2-sided p-value threshold of 0.031 for determining study success. These p-value thresholds have been established in order to maintain an overall 2-side alpha (probability of a Type 1 error) below 0.05 for the primary endpoint.

9.4 Interval Windows

The baseline/screening evaluation is to be done between14 days prior to the procedure and the day of the index procedure, which is considered to be day 0. The immediate pre-procedure evaluation (which includes angiographic assessment) and immediate post-procedure assessment will be considered within window if they occur within 12 hours (before and after, respectively) of the start of the index procedure (groin stick). The assessment at hospital discharge will occur between 12 and 36 hours after the start of the index procedure. The 30 day, 6 month, 12 month, 18 month and 24 month assessments will occur in the time intervals (days) indicated in the following table:

Study Interval Windows [days or hours, as indicated]	
Baseline/Screening	-14 to 0
Immediate Pre-Procedure	Within 12 hours prior to procedure
Index Procedure	Day 0
Immediate Post-Procedure	Within 12 hours after procedure
Hospital Discharge	12 to 36 hours after procedure
30 Days	16 to 44 days after procedure
6 Months	92 to 212 days after procedure

12 Months	320 to 410 days after procedure
18 Months	457 to 592 days after procedure
24 Months	685 to 775 days after procedure

9.5 Handling of Missing Data

Primary effectiveness and primary safety endpoint analyses will be conducted on the modified intent-to-treat (MITT) population, where subjects with missing data at the time of endpoint analysis will be imputed as last observation carried forward (LOCF); see Section 9.8 for analysis set definitions. Note that the immediate post-procedure evaluation will be utilized in this LOCF methodology if this is the last observation on file. MITT subjects who receive the device but in whom there is no post-procedure data will be treated as failures for the purpose of the primary effectiveness endpoint analysis; these subjects will be excluded from all other endpoint analyses. Subjects who do not receive the device because of treatment failure due to reasons associated with the device will also be treated as failures for the primary effectiveness endpoint analysis; these subjects will be excluded from all other endpoint analyses. MITT subjects who do not receive the device because of an intra-operative surgeon decision based on patient anatomy (e.g. vessel tortuosity) will be treated as missing (and not as failures) in all endpoint analyses, including the primary effectiveness and primary safety endpoint analysis.

All subjects who have died prior to an evaluation will have a mRS score of 6 imputed for that time point for analysis purposes.

All other analyses based upon MITT or PP population data will be based upon actual data, with no data imputation.

9.6 Primary and Secondary Endpoints

Primary Endpoint

Efficacy:
The primary effectiveness endpoint is the rate of complete aneurysm occlusion (RCAO) at 12 months post-procedure 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 post-procedure follow-up visit will be considered not to have achieved complete aneurysm occlusion for the purpose of the primary endpoint analysis.

Safety:

There are two primary safety endpoints: The incidence of Major Ipsilateral Stroke and/or Death at 12 months post-procedure and the incidence of In-stent stenosis at 12 months post-procedure.

Incidence of Major Ipsilateral Stroke and/or Death:

Major ipsilateral stroke and/or death will be evaluated from the start of the index procedure until completion of the 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:

In-stent stenosis at or prior to 12 months post-procedure will be assessed angiographically. 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.

Secondary Endpoints

Secondary Effectiveness Endpoints:

Procedure Success: Procedure Success is defined as 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. Procedure success will be summarized immediately post-treatment (acute), and at the 6 and 12 month follow-up assessments.

Acute and 6 Month 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 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, and 12 month follow-up angiographic assessments will be evaluated.

Percent Aneurysm Occlusion: The percentage of aneurysms with 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 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. Percentages of aneurysms falling into each of the categories will be presented.

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), and (regardless of whether retreatment is by surgery or endovascular treatment) due to recanalization, rupture or bleeding.

Secondary Safety Endpoints:

Rate of New Neurological Deficits per the Modified Rankin Scale (mRS): Observed scores on the Modified Rankin Scale will be presented at baseline (pre-procedure) and follow-up (30 days, 6 and 12 months post-procedure). Subjects who have died at the prior to an evaluation will have an mRS score of 6 imputed for that time point for analysis purposes.

The number and percentage of subjects who have an increase in mRS > 2 from baseline not related to stroke or death will also be presented for each follow-up time point.

NIH Stroke Scale (NIHSS) Total Score: NIHSS Total Score evaluations will be summarized at baseline (pre-procedure) and follow-up (6 and 12 months post-procedure); change from baseline at 6 and 12 months will also be summarized. The percentage of subjects who show a worsening from baseline (increase of 4 points or more) will also be presented.

Observed scores and change from baseline will also be presented for NIHSS excluding scores on the aphasia subscale.

Adverse Events and Clinical Complications:

Adverse Events (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 coded using the MedDRA system and summarized with frequencies. Serious adverse events (SAEs), device- or procedure-related AEs, unanticipated adverse device effects (UADEs) and deaths will be presented.

AEs will be presented for the following study periods: 1) peri-procedure – i.e., from the start of the procedure until 24 hours post-procedure; and, 2) through 12 month follow-up – i.e., from 24 hours post-procedure through the 12 month visit or premature termination

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 (Acute, and 6 Months):

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 or not 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.

Ancillary Endpoints

Stent Movement/Migration: Incidence of stent movement and/or migration from the start of the index procedure until completion of the 12 month follow-up

Follow-up through 24 months: Subjects will be followed through 24 months post-procedure, and their outcomes will be summarized in a supplemental safety follow-up report:

- All adverse events through 24 months post-procedure
- rupture of the index aneurysm beyond 24 hours post-treatment
- major ipsilateral stroke more than 1 month post-treatment
- ipsilateral parenchymal hemorrhage more than 1 month post-treatment

Note: Although a supplemental safety report will be written to summarize safety outcomes through 24 months, there are no formal primary or secondary endpoints regarding outcomes at this time-point.

9.7 Hypotheses

Primary Efficacy Endpoint: Rate of Complete Occlusion (RCAO) according to the Raymond Scale

The primary efficacy endpoint analysis will be to demonstrate that the RCAO is significantly greater than a performance goal (PG) of 35%. The null and alternative hypotheses for this endpoint are as follows:

Null hypothesis H_o: RCAO ≤ 35%

Alternative hypothesis H_A: RCAO > 35%

Decision Criterion: The decision will be made to reject the null hypotheses H_o and conclude the alternative hypothesis H_A either of the following occur:

1. At the interim analysis (when the first N=160 enrolled subjects have reached a minimum of 6 months post-operatively), the unadjusted 2-sided normal approximation p-value for testing the primary effectiveness endpoint (RCAO vs. the PG of 35%) is less than 0.031. The conclusion of this analysis will be a tentative conclusion; if this stopping rule for tentative success is met, a final confirmatory analysis will be conducted when all subjects have reached 12 months post-procedure, and a p-value threshold of 0.031 will be used for this final confirmatory analysis.
2. At the final analysis when all N=320 subjects have been followed for a minimum of 12 months post-procedure, the unadjusted 2-sided normal approximation p-value for testing the primary effectiveness endpoint (RCAO vs. the PG of 35%) is less than 0.031.

This primary efficacy endpoint analysis will be conducted on the MITT population.

Note: The study will be deemed to be a success if this primary efficacy endpoint null hypothesis (on the MITT population with data from all sites combined) is rejected in favor of the alternative hypothesis.

Primary Safety Endpoint: Incidence of Major Ipsilateral Stroke and/or Death

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the proportion of subjects who experience major ipsilateral stroke and/or death through 12 months post-procedure will be less than 25% (regardless of whether this analysis is conducted at the interim analysis with N=160 subjects at 6 months follow-up or the final analysis with N=320 subjects at 12 months follow-up). The null and alternative hypotheses for this endpoint are as follows:

Null Hypothesis H_o: $p_{Major\ Sroke/Death} \geq 25\%$

Alternative Hypothesis H_A: $p_{Major\ Sroke/Death} < 25\%$

where $p_{Major\ Sroke/Death}$ represents the proportion of subjects in the treatment population who experience major ipsilateral stroke/death.

Decision Criterion: The null hypothesis will be rejected and the alternative hypothesis will be concluded if the upper confidence limit of a 2-sided 95% confidence limit (normal approximation) is less than 25%.

Primary Safety Endpoint: Incidence of In-Stent Stenosis

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the rate of in-stent stenosis will be observed to be less than 15% (regardless of whether this analysis is conducted at the interim analysis with N=160 subjects at 6 months follow-up or the final analysis with N=320 subjects at 12 months follow-up). The null and alternative hypotheses for this endpoint are as follows:

Null Hypothesis H_o: $p_{Stenosis} \geq 15\%$

Alternative Hypothesis H_A: $p_{Stenosis} < 15\%$

where $p_{Stenosis}$ represents the proportion of subjects in the treatment population who experience in-stent stenosis.

Decision Criterion: The null hypothesis will be rejected and the alternative hypothesis will be concluded if the upper confidence limit of a 2-sided 95% confidence limit (normal approximation) is less than 15%.

9.8 Analysis Sets

The following analysis sets have been defined for this study: a Preliminary Screen Fail (PSF) analysis set, an Intent-to-Treat (ITT) analysis set, an

Angiographic Screen Fail (ASF) analysis set, a Modified Intent-to-Treat (MITT) analysis set, a Per Protocol (PP) analysis set, and a Continued Follow-up (CF) analysis set. The primary effectiveness, primary safety, and all secondary endpoint analyses will be carried out on available data in the MITT analysis set; supportive analyses of certain endpoints will be carried out on the PP analysis set. Interim analyses for early stopping are based on available data in the MITT analysis set. Demographic summaries will be provided for all analysis sets; a brief safety summary will be provided for the ASF analysis set. Clinical outcomes and safety summaries will be provided for the MITT, PP, and CF analysis sets, as specified for the various endpoint analyses, respectively.

PSF Analysis Set

The PSF analysis set consist of screening log data for all patients who are determined to be ineligible for the study based upon the initial screening information (including information from a preliminary angiographic assessment, which is distinct from the pre-treatment angiographic assessment at the time of the index procedure).

ITT Analysis Set

The ITT analysis set consists of all subjects who are consented (enrolled) into the study. Note that at the time of consent, a screening angiographic assessment will have taken place to facilitate an initial determination regarding study treatment eligibility.

ASF Analysis Set

Angiographic Screen Fail Subjects are comprised of all ITT analysis set subjects who are determined to be ineligible for treatment at the time of the pre-procedure angiographic evaluation (which is more thorough than the screening angiographic assessment upon which treatment eligibility was initially determined). These subjects are not treated with the ENTERPRISE device due to a failure to meet all angiographic eligibility criteria. Angiographic Fail Subjects will be followed for 72 hours following the end of the pre-procedure angiogram, or until hospital discharge, or to resolution of any adverse event, whichever is longer.

MITT Analysis Set

The MITT analysis set consists of all ITT subjects who meet all pre-procedure angiographic eligibility criteria, and in whom treatment with the Enterprise device is attempted.

PP Analysis Set

The PP analysis set is a subset of the MITT analysis set that includes all subjects who meet the following criteria:

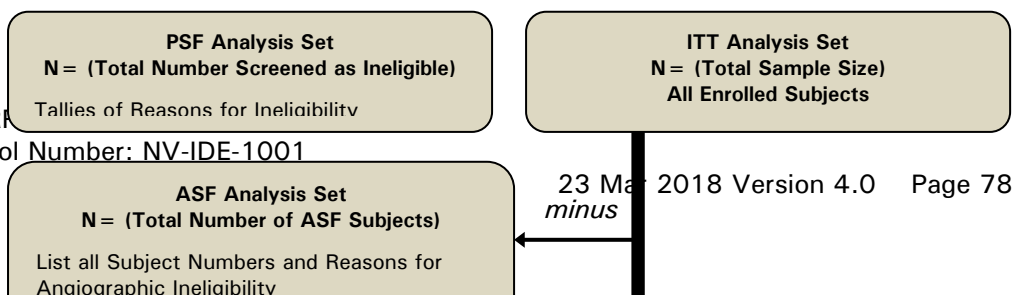
- there are no clinically meaningful deviations from the protocol eligibility criteria,
- the subject receives treatment with the Enterprise device,
- the subject has either a 6 month or a 12 month angiographic assessment.

CF Analysis Set

The CF analysis set is a subset of the MITT analysis set that is comprised of all subjects who are followed through 24 months post-procedure.

9.9 Dataset Flow Diagram

A detailed account of all subjects who are consented (enrolled) will be presented in a dataset flow diagram to display the analysis datasets, beginning with the set of enrolled subjects and explicitly listing the subjects with distinguishing reasons for exclusion from the other datasets. A template of this dataset flow diagram is given in Figure 3 below.



4: Dataset Flow Diagram for Enrolled Subjects

True RCAO in the Patient Population	Overall Power to demonstrate Primary Efficacy (at Interim or Full Enrollment)	Probability of Stopping Early for Success (Interim Analysis)	Probability of Study Success at Full Enrollment if Not Stopped at Interim Analysis	Probability of Stopping Early for Futility (Interim Analysis)
0.35	2.70%	1.40%	2.90%	60.80%
0.37	10.60%	4.60%	12.40%	54.80%
0.4	41.40%	18.00%	40.90%	32.20%
0.42	68.10%	33.90%	62.60%	17.60%
0.43	79.10%	43.30%	72.10%	12.10%
0.44	87.70%	53.20%	80.50%	8.00%
0.45	93.30%	62.70%	86.90%	4.90%
0.46	96.80%	71.70%	91.80%	2.90%
0.47	98.60%	79.30%	95.00%	1.60%
0.5	99.90%	93.90%	99.30%	0.20%

An estimate of the overall Type 1 error rate for this study design can be seen in the first row of this table, where the true RCAO in the patient population is equal to the performance goal of 35% for the Primary Efficacy Endpoint; this estimated Type 1 error rate is 2.7% (2-sided), which is below 5%. An estimate of overall statistical power is 87.7% if the true RCAO is 44% in the patient population, and the likelihood of stopping early for tentative study success is approximately 79.3% if the RCAO in the patient population is 47%. The likelihood of stopping early for futility is approximately 54.8% if the RCAO in the patient population is 37%.

There are two primary and secondary safety endpoints with formal hypotheses that will be tested, and the following are estimates of statistical power for each of these respective endpoints at the time of the interim analysis. For each respective endpoint, the purpose of the hypothesis test is to ensure that the 2-sided 95% upper confidence limit for the estimate is less than a stated performance goal for the endpoint. The performance goal, expected outcome, and estimated statistical power based upon a sample size of N=150 evaluable subjects (with post-procedure data) are provided for each respective endpoint.

Statistical Power for Primary Safety Endpoints

Primary Safety Endpoint: Incidence of Major Ipsilateral Stroke and/or Death

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the proportion of subjects who experience major ipsilateral stroke and/or death through 12 months post-procedure will be less than 25% (regardless of whether this

analysis is conducted at the interim analysis with N=160 subjects at 6 months follow-up or the final analysis with N=320 subjects at 12 months follow-up). The anticipated rate of major ipsilateral stroke and/or death in the population is not greater than 14%, so it is estimated that the statistical power to demonstrate this endpoint with a sample size of N=150 evaluable subjects (MITT subjects with post-procedure data) is approximately 92.5%. This power estimate was calculated with the following SAS code:

SAS Code for Power Estimation:
Incidence of Major Ipsilateral Stroke and/or Death

```
proc power;
   onesamplefreq test=z method=normal
      nullproportion = 0.25
      proportion = .14
        alpha = 0.05
        sides = 2
      ntotal = 150
      power = .;
      title 'z Test, uses null proportion for
variance estimate';
run;
```

Primary Safety Endpoint: Incidence of In-Stent Stenosis

For a successful evaluation of this endpoint, the upper confidence limit of a 2-sided 95% confidence interval for the rate of in-stent stenosis will be observed to be less than 15% (regardless of whether this analysis is conducted at the interim analysis with N=160 subjects at 6 months follow-up or the final analysis with N=320 subjects at 12 months follow-up). The anticipated rate of in-stent stenosis at 12 months in the population is not greater than 6%, so it is estimated that the statistical power to demonstrate this endpoint with a sample size of N=150 evaluable subjects (MITT subjects with post-procedure data) is approximately 95.5%. This power estimate was calculated with the following SAS code:

SAS Code for Power Estimation:
Incidence of In-stent Stenosis

```
proc power;
   onesamplefreq test=z method=normal
      nullproportion = 0.15
      proportion = .06
        alpha = 0.05
        sides = 2
      ntotal = 150
      power = .;
      title 'z Test, uses null proportion for
variance estimate';
run;
```

9.10 Analysis Plan

9.10.1 General Considerations

All statistical processing will be performed using SAS® Version 9.2 or higher, unless otherwise noted. A separate Statistical Analysis Plan (SAP) document that provides greater detail on data derivations and the analyses to be performed will be developed prior to the planned interim analysis.

Summary tables will be provided for subject demographics and baseline variables for each dataset which has been defined. Effectiveness and safety endpoints will be summarized at each protocol-specified evaluation. Endpoint analyses will be conducted on pooled data from all sites. In addition, endpoint data will be presented by investigator/site; sites having fewer than 6 subjects will be pooled to comprise one group of all small sites.. For the primary effectiveness and primary safety endpoints, the homogeneity of study endpoint data will be assessed with a chi-square test of proportions across sites.

Descriptive statistics for continuous variables will include number of subjects, mean, standard deviation, median, minimum, and maximum. Descriptive statistics for dichotomous/categorical variables will include number and percent of subjects.

A 2-sided alpha of 0.05 will be used for statistical testing and confidence intervals unless otherwise noted. Detail on the level of significance for testing the primary endpoint analysis in this group sequential design is addressed in Section 10.3 (Levels of Significance).

9.10.2 Subject Disposition

All subjects who are screened or enrolled (consented) into the study will be accounted for in Subject Disposition, overall and by study site; see section 10.8 (Analysis Sets).

9.10.3 Aneurysm and Procedure Characteristics

For aneurysms in which an ENTERPRISE procedure is attempted, baseline characteristics to be summarized will include presenting symptom and results of the pre-procedure treatment cerebral angiogram – i.e., parent vessel diameter (distal and proximal), percent occlusion, aneurysm location, aneurysm shape, dome height, neck width, dome-to-neck ratio. Where the aneurysm is located at a distal vessel bifurcation, the number of vessels with a bifurcation will be reported; measurements of the parent vessel diameter will be taken in

both distal vessels and summarized by the total number of distal vessels. A summary of aneurysm characteristics will be presented overall and by study site.

The following data will be summarized for the index procedure:

- the number of procedures (index), attempted and successful
- the number and duration of procedures to treat the target aneurysm (treatment with stenting and coiling)
- the number of stent recaptures
- total index procedure duration from time the femoral artery is accessed until the time the guiding catheter is removed from the subject,
- procedure technique to include catheter type and technique, guide wire type, guiding catheter type, adjunctive techniques
- number, size, diameter, length and type of coils deployed into the target aneurysm.

In addition, procedure resource utilization will be described for the following parameters:

- contrast use, in particular, the amount of contrast used
- fluoroscopy time
- length of in-patient hospital stay – i.e. days from the date of the index procedure to the hospital discharge date
- re-hospitalization or prolongation of hospitalization
- number of days in each hospital ward/floor
- discharge location of the subject
- total number of days in the hospital and days in each hospital ward/floor

9.10.4 Analysis of Angiographic Screening Failures

Data will be collected from the time of consent through a 72-hour safety evaluation or hospital discharge (whichever comes first) or, in the case of an AE that has not resolved by 72 hours post-angiogram or discharge, the resolution of the AE. Demographics, baseline subject and aneurysm characteristics, procedural and safety data will be listed and summarized separately from the other analysis populations.

9.10.5 Analysis of Primary and Secondary Endpoints

Primary effectiveness and primary safety endpoint analyses will be conducted on the modified intent-to-treat (MITT) population, where subjects with missing data at the time of endpoint analysis will be imputed as last observation carried forward (LOCF); some MITT subjects who receive the device but in whom there is no post-procedure data will also be included in the primary effectiveness endpoint analysis as failures; see section 9.5 on the handling of missing data. Subjects with no post-procedure endpoint data upon

which to base a LOCF imputation will be excluded from all other analyses.

All subjects who have died prior to an evaluation will have an mRS score of 6 imputed for that time point for analysis purposes.

All other analyses based upon MITT or PP population data will be based upon actual data, with no data imputation.

Supportive analyses the Primary effectiveness and primary safety endpoint analyses will be conducted on the.

All secondary efficacy endpoints will be summarized on both the MITT and PP analysis sets. All secondary safety endpoints will be summarized on the MITT analysis set.

9.10.6 Supplemental Safety Follow-up Report on Continued Follow-up Subjects

A supplemental safety follow-up report will be written to summarize safety outcomes for CF subjects through the 2 year follow-up evaluation. There are no formal primary or secondary endpoints regarding these outcomes.

9.10.7 Subgroup Analyses

Data summaries of the primary safety and effectiveness endpoints and the secondary safety endpoint regarding increase in mRS at 12 months post-procedure will be presented for the ITT and PP populations, as appropriate, in the following subgroups:

- study site
- gender
- age category (21-39, 40-49, 50-59, 60-69, and 70-80 years).
- subject has <u>any</u> (1 or more) Hydrocoil implanted vs no Hydrocoil implanted.

9.11 Plans for Interim Analysis

This study is a group sequential design in which one primary endpoint interim analysis will be conducted after N=160 subjects have been enrolled and followed through 6 months post-procedure. The purpose of the interim analysis will be to determine whether or not to terminate the trial early for futility or tentative success. This analysis will be a test of the primary efficacy endpoint only, and will be conducted after N=160 subjects have been enrolled and have reached 6 months post-procedure. LOCF imputation methodology will be utilized for subjects who do not have 12 month post-procedure data, so that 6 month primary endpoint data will serve as a surrogate for 12 month data for subjects who have not yet reached 12 months post-procedure.

The trial will stop early and will be deemed to be tentatively successful if the two-sided unadjusted p-value for this primary efficacy endpoint analysis is below 0.031. If the stopping rule is met for the trial to stop early for tentative success, a final confirmatory analysis will be conducted when all subjects have reached 12 months post-procedure; a p-value threshold of 0.031 will be used for this final confirmatory analysis. The trial will stop early for futility and it will be decided that the study would not have been successful even if the study would have continued to an enrollment of N=320 if the two-sided unadjusted p-value for this primary efficacy endpoint analysis is above 0.358. If neither of these criteria are met, or if the confirmatory analysis for early success is not satisfied, then enrollment will commence until the total sample of N=320 subjects have been enrolled (including the original N=160), and the final endpoint analysis will be conducted after all 320 subjects have reached 12 months post-procedure. In the case that the study continues to a full enrollment of N=320, the study will be deemed to be a success if the two-sided unadjusted p-value for the final primary efficacy endpoint analysis is below 0.031.

If a decision is made to stop the trial early for either futility or tentative success, follow-up will continue through 12 months post-procedure for all enrolled subjects. Further details of this planned interim analysis are provided in sections 9.1 (Study Design), 9.3 (Levels of Significance), 9.7 (Hypotheses), and 9.9 (Sample Size Justification).

The interim analysis for determining whether to stop the trial early for futility or tentative success will be conducted by the sponsor, and will be carried out on the MITT dataset.

There are no other planned interim analyses for the purpose of stopping the trial early. In addition to the annual progress report, interim reports will be provided to the FDA every four months (or an additional two interim reports) in effort to provide regular assessments of the progress and safety of the study.

A study report will be filed for evaluation of the primary endpoint after all subjects have completed their 12 Month follow-up visit or prematurely terminated study participation prior to 12 months post-procedure. The remaining data out to 24 months post-procedure will be submitted as a post-approval study (PAS) report once all subjects have completed their 24 Month follow-up visit or prematurely terminated study participation prior to 24 months post-procedure. No adjustment for multiplicity is proposed since the primary analysis will be the analysis at 12 months post-procedure.

10 SAFETY AND ADVERSE EVENTS

10.1 Adverse Events/Complications

10.1.1 Potential or Anticipated Adverse Events/Complications - ENTERPRISE

The study is designed to minimize potential risks and complications in the subjects. However the following adverse events associated with intracranial catheterization or intracranial stent placement have been identified as possible (anticipated) adverse events associated with the use of the CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System or with the procedure:

- Allergic reaction including, but not limited to, contrast, Nitinol metal and medications
- Aneurysm Bleed or Rebleed
- Aneurysm recanalization or regrowth
- Arm cramps
- Arrhythmia
- Arteriovenous fistula
- Cerebral edema
- Cerebral infarct
- Coil migration or prolapse into normal vessel adjacent to aneurysm
- Cold hands and feet
- Confusion
- Cranial nerve II deficit
- Cranial nerve palsy
- Death
- Deployment Difficulty
- Dissection
- Edema
- Emboli (air, tissue or thrombotic)
- Emergent neurosurgery
- Eyes fixed unable to focus
- Facial numbness
- Failure to deliver stent
- Fever
- Floaters, blurry vision
- Fracture of delivery wire
- Groin Hemorrhage
- Headache
- Hip pain
- Incomplete aneurysm occlusion
- Infection
- Infection at insertion site

- Insertion site hematoma / bleeding
- Injury to normal vessels or tissue
- Intracerebral hemorrhage
- Ischemia
- Laboratory abnormality
- Left, right-sided weakness
- Mid, low back pain
- Myocardial Infarction
- Nausea
- Neck pain
- Neurological deficits
- Not feeling right
- Occlusion of side branch
- Pain at insertion site
- Panic attack
- Perforation
- Pseudoaneurysm
- Radiation effects that include alopecia, cataracts, tissue burns ranging in severity from skin reddening to ulcers and delayed neoplasia[1]
- Renal failure
- Retroperitoneal Hematoma
- Rupture, vessel or aneurysm
- Stenosis of stented segment
- Seizures
- Stent migration / embolization
- Stent thrombosis / occlusion
- Stroke
- Total occlusion of treated segment
- Transient elevation or decrease in blood pressure
- Transient ischemic attack
- Upset stomach
- Vasospasm
- Vessel thrombosis
- Visual field decrease

10.1.2 Adverse Event Definitions

An **Adverse Event** is any untoward medical occurrence in a study subject, and which does not necessarily have a causal relationship with the product or treatment; any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study devices, whether or not considered related to the devices. A preexisting

[1] Radiation risk increases with exposure time and can be reduced by limiting exposure by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.

condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period.

An **Adverse Device Effect (ADE)** is a device-related Adverse Event.

A **Serious Adverse Event (SAE)** is any significant adverse experience, including those that may be either life-threatening or involving permanent or long term injuries but excluding injuries that are non-life-threatening and/or that are temporary and reasonably reversible. A Serious Adverse Event includes any of the following events that may or may not be considered related to the device;

- Results in Death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Serious Adverse Events may or may not be related to the device.

An **Unanticipated Adverse Device Effect (UADE)** is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that affects the rights, safety, or welfare of study subjects may also be considered UADEs.

All Adverse Events, Adverse Device Effects, Serious Adverse Events, and Unanticipated Adverse Device Effect must be recorded, as applicable, on the eCRF.

Note:

- Recanalization is not considered an adverse event since this is not an untoward medical occurrence to the subject, but rather an anticipated occurrence in the evolution of aneurysms

- Adverse events include abnormalities in physiological testing or physical examination that require clinical intervention or further investigation.

- Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g. “how has your health been since the last visit?”). Any time during the clinical investigation, the subject may volunteer information that resembles an

AE. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE form.

10.1.3 Adverse Event Severity and Causal Relationship Ratings

The Investigator will record the nature, severity, treatment and outcome of the AE, and will determine the relationship to device, procedure or underlying disease. This classification of the event determines the reporting procedures to be followed. The sponsor may upgrade the classification as required for reporting purposes.

For purposes of this protocol, the following definitions will apply.

Adverse Event Severity Rating
The following categories of adverse event severity are to be used:

- Mild: Awareness of sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae,
- Moderate: Interferes, but does not hinder, the subject's usual activity and/or may require treatment,
- Severe: Symptom(s) causing severe discomfort and significant impact on the subject's usual activity and requires treatment or intervention.

Causal Relationship Rating

The causal relationship to study device, study procedure, and underlying disease will be evaluated as follows:

- Definitely Related: The adverse event is clearly related to the test product.
- Probably Related: The adverse event is temporally associated and plausibly related to the product/procedure but there are also potential alternative explanations, though the alternatives are not likely.
- Possibly Related: The adverse event may be related, scientifically plausible, but there are also alternative explanations.
- Unlikely Related: The adverse event is doubtfully related.
- Not Related: The adverse event is clearly not related. The adverse event is most plausibly explained by the subject's underlying medical condition or their concomitant therapy, or the adverse event has no

plausible relationship to study treatment, or the adverse event has no plausible biological relationship to the study treatment.

10.2 Unanticipated Adverse Device Effects

The investigator shall submit to the Sponsor a report of any unanticipated adverse device effect (UADE) occurring during the investigation as soon as possible but no later than 72 hours after the investigator first learns of the effect. Additionally, if a UADE occurs in a device other than the study device (ENTERPRISE), follow FDA and manufacturer's instructions for reporting the UADE.

Unanticipated adverse device effects are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that affects the rights, safety, or welfare of study subjects may also be considered UADEs.

If the Sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, all or parts of investigations presenting that risk will be terminated as soon as possible. Termination will occur not later than five working days after the Sponsor makes this determination and not later than fifteen working days after the Sponsor first receives notice of the effect.

10.3 Management of Post-procedure Symptoms

If clinical symptoms deteriorate, the subject must be seen and assessed by the study investigator immediately. This does not exclude the subject from the study and follow-up should continue. All subjects entered into the study remain in the study until the 24 month post procedure study follow-up visit has been reached.

If a subject presents with an adverse event at the 24 month study visit, he/she will receive appropriate treatment for that condition. If the subject's condition precludes him or her from undergoing any 24 month evaluation specified by the protocol, the subject would be discharged from the study after the Investigator documents in the subject's medical record that a stable clinical endpoint has been reached, or that the subject's status is not associated with the device or procedure.

Following the 24 month study visit, the subject will be discharged from the study. However, if at the 24 month study visit the investigator determines there are indications of delayed hydrocephalus or in-stent stenosis

occurring, additional follow-up may be required, including MRI or CT at the Investigator's discretion. If this occurs, the investigator will determine the additional follow-up required at that time and inform the study sponsor.

10.4 Subject Death

Subject death during the investigation must be reported to the Sponsor as soon as possible but no later than 72 hours of the investigator's knowledge of the death. Notification of death must include a brief statement of the pertinent details and be signed by the investigator. A copy of the death records, death certificates and an autopsy report (if performed) must be sent to the Sponsor.

10.5 Adverse Event Reporting Period

10.5.1 Adverse Event Reporting for Angiographic Screening Failure

Any subject, who had an angiogram, but was not entered, will be followed for the period 72 hours following the end of the angiographic procedure to determine study angiographic eligibility, or until discharge, whichever comes first, or to resolution of any adverse event, whichever is longer. Any AEs that occurred from the time written consent was obtained through the period described must be entered into the eCRF database.

10.5.2 Adverse Event Reporting for Entered Subjects

The adverse event reporting period for this study begins at the time the study informed consent is signed and ends at the twenty-four month follow-up unless noted otherwise in Section 11.3. Adverse events that occur in subjects during the adverse event reporting period must be entered into the eCRF database. All required treatments and outcomes of the adverse event must be recorded.

10.6 Recording Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the subject via eCRF. In addition, each subject in the study will be questioned about adverse events on the day of hospital discharge, and at thirty (30) days, six (6) months, twelve (12), eighteen (18) months, and twenty-four (24) month follow-ups after the index procedure. All required treatments and outcomes of the adverse event must be recorded.

10.7 Device Product Complaints, Failures, and Device Malfunctions

All study device/product complaints, failures, and malfunctions (with or without an associated adverse event), must be documented on the appropriate eCRFs, and reported to the Sponsor within 10 business days. Another study device may be used. If the study device is not implanted it must be retained at the site until the Sponsor provides directions on how to return the device for analysis.

A study device has malfunctioned if it meets the following definition: The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made on the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

A product complaint is defined as: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device.

If a device other than the study device (ENTERPRISE Investigational Device) malfunctioned, follow the manufacturer's instructions, and do not report as a product complaint on the eCRF and/or do not complete the study Device Malfunction eCRF.

10.8 Reporting of Adverse Events and Study Device Product Complaints and Device Malfunctions

As noted in the Table 6, a serious adverse event is to be reported immediately via eCRF but no later than 72 hours after knowledge of the event.

It is the responsibility of the investigators to inform their Institutional Review Board (IRB) of Adverse Events, Serious Adverse Events, Unanticipated Adverse Device Effects, and Device Malfunctions/Deviations as required by their IRB procedure and country law. The sponsor is responsible for sending information on the unanticipated adverse device effect to the regulatory authorities. In the instance of death a copy of the death certificate or other relevant documentation (autopsy report) should be provided. If an autopsy is performed, a copy of the autopsy report may be requested and sent to the regulatory authorities, if required.

If the ENTERPRISE device does not perform as expected, but is without any adverse event, the investigator must document on the appropriate eCRFs, and notify the Sponsor within 10 business days. If the study device is not implanted it must be retained at the site until the Sponsor provides instructions on the return process.

If a serious adverse event is related to the performance of the study device, the Sponsor must be notified immediately via eCRF immediately but no later than 72 hours after knowledge of the event. If the study device was not implanted it must be retained at the site until the Sponsor provides instructions on the return process.

Non-Serious adverse events are to be reported via eCRF within 10 days of learning of the event.

If a device other than the study investigational ENTERPRISE stent malfunctioned, follow the manufacturer's instructions, and do not report as a product complaint on the eCRF and/or do not complete the study Device Malfunction eCRF.

Table 6: Report requirements of adverse events, product complaint and device malfunctioning

Classification	Reporting time	Type of report
Death	Notify Sponsor as soon as possible but no later than 72 hours of learning of event. Notify IRB as required	eCRF
Unanticipated Adverse Device Effects (UADE)	Notify Sponsor as soon as possible but no later than 72 hours of learning of event. Notify IRB as required	eCRF
Serious Adverse Events (whether related to the performance of the study device or not)	Notify Sponsor as soon as possible but no later than 72 hours of learning of event. Notify IRB as required	eCRF
Non-serious Adverse Events	Notify Sponsor within 10 business days of learning of event. Notify IRB as required	eCRF
Study Device Product Complaint or Device Malfunction With or Without Adverse Event	Notify Sponsor within 10 business days of learning of event. Notify IRB as required	eCRF

10.8.1 Follow-up of Unresolved Adverse Events

All adverse events should be followed until they are resolved or the subject's participation in the study ends.

10.9 Medical Monitoring

10.9.1 Clinical Events Committee

An independent Clinical Events Committee (CEC) will review and adjudicate the relationship of AEs to the device, procedure and/or underlying disease. The CEC's determinations of relationship are those that will be used in the safety analysis.

10.9.2 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be responsible for monitoring the accumulated interim data as the study progresses to ensure patient safety. All safety review procedures will be established and agreed upon in the DSMB Charter prior to enrollment of the first subject.

Once the study begins, the DSMB will meet periodically to review safety data. The DSMB may request more frequent meetings if necessary to fulfill its charge.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Organizational Preparations

A site visit will be performed by the Sponsor or their designee prior to the start of the study to review the study protocol in detail and ensure the availability of appropriately trained personnel to conduct the study according to Good Clinical Practices (GCP) procedures. This protocol will be conducted under the principles described in the Declaration of Helsinki and the Code of Federal Regulations.

11.2 Training

In order to provide for safe use of the CODMAN ENTERPRISE® Vascular Reconstruction Device and Delivery System, the primary concern in operator selection for this study is adequate experience, commitment to safety, and consistency in adherence to the clinical protocol. Therefore, the investigators selected to participate will be neurointerventionalists who, by virtue of their experience and training, are accomplished in stent placement in intracranial arteries.

11.3 Case Report Forms

Electronic Case Report Forms (eCRFs) in an electronic data collection (EDC) system will be used to collect all subject data during the study.

Detailed description of the eCRF components and eCRF completion instructions are included in the Manual of Operations.

eCRFs must be fully completed for each subject and, signed electronically, in a timely manner so that they are available for review in the EDC system by Sponsor appointed monitors.

Data Reporting

The Principal Investigator, or an individual designated by him/her, is responsible for recording all data from the study on the eCRFs supplied by the Sponsor in the EDC system.

The Principal Investigator is required to electronically sign the eCRFs on the appropriate page(s) to verify that he/she has reviewed the entered data.

A Sponsor appointed monitor will verify completed eCRFs in the EDC system at regular intervals throughout the study. To this end, the Principal Investigator must permit inspection of the study files, and subject medical records by Sponsor appointed monitors and authorized government agencies.

ENTERPRISE device accountability and usage will be recorded on the Device Accountability Log which will be supplied to the investigator. Subject specific information will also be collected in the subject's eCRFs.

11.4 Monitoring and Source Data Verification

The purpose of monitoring the study is to verify that the rights and well-being of subjects are protected, that the reported study data are accurate, complete, and verifiable from source documents and that the conduct of the study is in compliance. Ongoing site monitoring will be conducted by the Sponsor or designees to ensure compliance to Good Clinical Practices, Code of Federal Regulations, the protocol and applicable laws and/or regulatory requirements.

The investigator and his/her staff will be expected to cooperate with the study responsible clinical research associate (CRA) (may also be referred to as Study Monitor) and to be available during at least a portion of the monitoring visits to answer questions and to provide any missing information.

Source data verification (SDV) is an essential element to ensure accuracy and credibility of the data and conclusions derived from clinical investigations. All electronic Case Report Forms will be reviewed for completeness and clarity by the Study Monitor. Entries on the eCRF are verified using the original documents of SDV such as subject files, informed consent forms signed by subjects, device accountability forms, and original recordings from automated instruments, X-ray films, laboratory notes, etc. whereby subject privacy is to be respected.

Missing or unclear data shall be supplied or clarified as necessary throughout the study. The Sponsor or designee may request further documentation such as physician and/or radiology suite procedure notes when adverse events are observed and reported.

Clinical site personnel will perform primary data collection based on source-documented hospital chart reviews.

11.5 Data Management

Clinical site personnel will enter data into electronic case report forms in the EDC system provided by the Sponsor for study data collection. The Sponsor or designee will be responsible for confirming the overall integrity of the data.

11.6 Securing Compliance

If it is discovered that an investigator is not complying with the signed agreement, the protocol, GCP requirements, the requirements of the Code of Federal Regulations or other applicable regulations, or any conditions of approval imposed by the reviewing IRB or regulatory authorities, Codman Neuro is required to promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. Codman Neuro will also require the investigator to dispose of or return the device, unless this action would jeopardize the rights, safety or welfare of a subject.

11.7 On-Site Audits

A trained and properly authorized employee of the Sponsor or designee, as well as regulatory authorities may request access to all study records, including source documents, for inspection and copying.

12 ETHICS AND REGULATORY CONSIDERATIONS

12.1 Institutional Review Board (IRB)

The protocol and informed consent must be submitted to the appropriate IRB and other requirements per country law, and written approval must be obtained and submitted to the Sponsor prior to enrolling any subjects.

The investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except when necessary to eliminate immediate hazards to human subjects.

The investigator must report to the IRB at least yearly on the progress of the investigation. A letter from the IRB should document continuing IRB review.

Notification to the IRB by the investigator within 3 months after completion, termination, or discontinuation of the study at the specific site must be documented.

Other investigator responsibilities to the IRB and sponsor include the following:

- During the conduct of the study, submit progress reports to the IRB as required.
- Report unexpected adverse device effects (UADE) that occur during the study to the IRB and Sponsor. A copy of the correspondence should be provided to the study monitor.
- As required, obtain approval from the IRB for protocol amendments and for revisions to the informed consent or subject recruitment advertisements. A copy of the correspondence should be provided to the study monitor.
- Notify the IRB and Sponsor of any protocol deviation to protect the life or physical well-being of a subject in an emergency within 24 hours but in no instance later than 5 days after the emergency occurred.
- Provide IRB with any other information it requests before or during the conduct of the study.
- Maintain a file of study-related information that includes all correspondence with the IRB.
- Notify IRB within 3 months after study completion, termination or discontinuation.
- Notify the Sponsor, within 24 hours, of withdrawal of approval by the reviewing IRB.

12.2 Informed Consent

Subject's informed consent must be obtained (and other locally required documents) and documented according to the principles of informed consent in the current version of the Declaration of Helsinki for Protection of Human Subjects.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator or designee. Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the study. Subject must be given ample time and opportunity to inquire about details of the study and all questions about the study should be answered to the satisfaction of the subject or the representative.

The subject must receive a copy of the signed and dated informed consent.

The consent form that is to be used must be approved by both the reviewing IRB and by the Sponsor.

In emergency cases, where it may not be possible to obtain the subject's written informed consent in order to save the life and well-being of the subject, the investigator must complete the following actions:

- If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the Sponsor and the reviewing IRB within 24 hours after the use occurs.
- For failure to obtain written informed consent prior to the subject's participation in the study, the investigator must document why informed consent was not obtained, obtain written concurrence by another licensed physician, and provide a brief description of the circumstances justifying the failure to obtain informed consent.

12.3 Confidentiality

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The Principal Investigator consents to visits by the staff of the Sponsor and its authorized representatives as well as regulatory authorities, which governs the conduct of clinical investigations in the EU/US.

12.4 Insurance

The Sponsor will take out liability insurance coverage concerning the device for every subject included in the study. This product liability insurance coverage is available to the investigator and to the subject.

13 RECORD KEEPING

13.1 Study Initiation

Before the study at a site can begin, the Sponsor must have all of the following required regulatory documents:

- IRB approval of the study protocol and informed consent
- Principal Investigator's C.V.
- Sub-investigator(s) C.V(s) , if applicable
- Principal Investigator's Financial Disclosure
- Sub-investigator(s) Financial Disclosure, if applicable
- Executed Clinical Research Agreement
- Statement of Investigator Agreement of Principal Investigator
- Statement of Investigator Agreement of Sub-Investigator, if applicable
- Name and address of Laboratory

- Laboratory certification (current)
- Laboratory normal values/reference ranges (current)

In addition to the documents required prior to the study, other documentation may be required during the course of the study.

13.2 Retention of Records

The investigator must retain the following essential study documents until the Sponsor authorizes disposal. Records that relate to each subject's identity (subject identification code) to his or her identity on the CRF's must be retained for a period of 2 years after the latter of the following two dates: the date on which the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a pre-market approval application. The following documentation must be available:

- Signed protocol and any amendments, and blank approved informed consent form
- Investigator Brochure and any revisions if applicable
- Signed Clinical Research Agreement between the Sponsor and investigator
- IRB approval and correspondence
- Study authorization from the Regulatory Authority for the initiation of the clinical study
- Relevant communications (e.g. letter, meeting notes, notes of telephone calls)
- Laboratory normals and certificates for any laboratory procedure or test included in the protocol
- Documentation of shipment of investigational devices and investigational device accountability at site
- Signed informed consent
- Signed, dated and completed CRF (copy), documentation of CRF corrections, and signature sheet of all persons authorized to make entries and/or corrections on CRFs
- Notification by investigator to the Sponsor and IRB of serious adverse events, if any
- Subject identification codes

The subject's medical record and other source documents must be kept for the maximum time permitted by the hospital, institution or private practice. The investigator should take measures to prevent accidental or premature destruction of records.

These documents serve to demonstrate investigator compliance with the standards of Good Clinical Practices, and with applicable regulatory requirements.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the names and address of the new custodian.

14 REPORTS

14.1 Investigators Final Report

Upon completion or termination of the study a final report will be prepared. This report will contain a critical evaluation of all data collected during the course of the investigation at each institution. The report must be signed by all participating investigators in the study and will be provided to the IRB as required by country specific law. Any modifications to this final report must be reviewed and approved by the Sponsor.

15 END OF STUDY

15.1 Planned End

The study will close when all subjects have completed the 24 month follow-up or have discontinued prematurely.

15.2 Premature End

The study may be discontinued or put on “hold” because of:

- New findings invalidate the earlier positive benefit-risk assessment.
- The time schedule (recruitment phase) cannot be met (e.g. more than doubling of recruitment time).
- The Sponsor decides to discontinue the study at any time.

15.3 Termination of Center by Sponsor

The Sponsor reserves the right to terminate an investigational site; this may include for any of the following reasons (but not be limited to):

- The center cannot comply with the requirements of the protocol
- Repeated failure to complete eCRFs in a timely manner
- Failure to report Serious Adverse Events within within 10 business days of knowledge
- Loss of or unaccounted for investigational device inventory
- Repeated protocol deviations/violations
- Investigator leaves the institution and no adequate replacement

15.4 Resumption of Terminated Studies

The Sponsor may not resume a terminated study without IRB and FDA/regulatory approval.

16 PUBLICATION

All submissions for publication will be sent to the Sponsor as outlined in the Clinical Research Agreement.

17 REFERENCES

Alg VS, Sofat R, Houlden H, Werring DJ. Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116 000 individuals. Neurology 2013; 80: 2154–65.

Atkinson JL, Sundt TM Jr, Houser OW, Whisnant JP. Angiographic frequency of anterior circulation intracranial aneurysms. J Neurosurg 1989; 70: 551–55.

Batjer HH, Adamson TE, Bowman GW. Sickle cell disease and aneurysmal subarachnoid hemorrhage. Surg Neurol 1991; 36: 145–49.

Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. Stroke 1986; 17: 831–35.

Broderick, T. Brott, T. Tomsick, R. Miller, and G. Huster, “Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage,” Journal of Neurosurgery, vol. 78, no. 2, pp. 188–191, 1993.

Broderick JP, Viscoli CM, Brott T, et al, and the Hemorrhagic Stroke Project Investigators. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. Stroke 2003; 34: 1375–81.

Bromberg JE, Rinkel GJ, Algra A, et al. Familial subarachnoid hemorrhage: distinctive features and patterns of inheritance. Ann Neurol 1995; 38: 929–34.

Bromberg JE, Rinkel GJ, Algra A, Limburg M, van Gijn J. Outcome in familial subarachnoid hemorrhage. Stroke 1995; 26: 961–63.

Brown RD Jr, Wiebers DO, Forbes GS. Unruptured intracranial aneurysms and arteriovenous malformations: frequency of intracranial hemorrhage and relationship of lesions. J Neurosurg 1990; 73: 859–63.

Burns, Huston 3rd, Layton, Piepgras, Brown Jr., “Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors,” Stroke, vol. 40, no. 2, pp. 406–411, 2009a.

Burns and Brown Jr., “Treatment of unruptured intracranial aneurysms: surgery, coiling, or nothing?” Current neurology and neuroscience reports, vol. 9, no. 1, pp. 6–12, 2009b.

Chapman AB, Rubinstein D, Hughes R, et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. N Engl J Med 1992; 327: 916–20.

Chason JL, Hindman WM. Berry aneurysms of the circle of Willis; results of a planned autopsy study. Neurology 1958; 8: 41–44.

Connolly HM, Huston J 3rd, Brown RD Jr, Warnes CA, Ammash NM, Tajik AJ. Intracranial aneurysms in patients with coarctation of the aorta: a prospective

magnetic resonance angiographic study of 100 patients. Mayo Clin Proc 2003; 78: 1491–99.
Edwards A, Taylor GW. Ehlers-Danlos syndrome with vertebral artery aneurysm. Proc R Soc Med 1969; 62: 734–35.

Fargen et al.; Long-term Results of Enterprise Stent-Assisted Coiling of Cerebral Aneurysms; Neurosurgery 71:239–244, 2012

Fiorella, F. C. Albuquerque, P. Han et al., “Preliminary experience using the neuroform stent for the treatment of cerebral aneurysms,” Neurosurgery, vol. 54, no. 1, pp. 6–16, 2004.

Fogelholm, J. Hernesniemi, and M. Vapalahti, “Impact of early surgery on outcome after aneurysmal subarachnoid hemorrhage. A population-based study,” Stroke, vol. 24, no. 11, pp. 1649–1654, 1993.

Foroud T, Koller DL, Lai D, et al, and the FIA Study Investigators. Genome-wide association study of intracranial aneurysms confirms role of Anril and SOX17 in disease risk. Stroke 2012; 43: 2846–52.

Gibbs GF, Huston J 3rd, Qian Q, et al. Follow-up of intracranial aneurysms in autosomal-dominant polycystic kidney disease. Kidney Int 2004; 65: 1621–27.

Gounis, M. J. de Leo 3rd, and A. K. Wakhloo, “Advances in interventional neuroradiology,” Stroke, vol. 41, no. 2, pp. e81–e87, 2010.

Guglielmi, F. Vinuela, J. Dion, and G. Duckwiler, “Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: preliminary clinical experience,” Journal of Neurosurgery, vol. 75, no. 1, pp. 8–14, 1991a.

Guglielmi, F. Vinuela, I. Sepetka, and V. Macellari, “Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: electrochemical basis, technique, and experimental results,” Journal of Neurosurgery, vol. 75, no. 1, pp. 1–7, 1991b.

Inagawa T, Hirano A. Autopsy study of unruptured incidental intracranial aneurysms. Surg Neurol 1990; 34: 361–65.

International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. N Engl J Med 1998; 339: 1725–33.

Johnston SC, Colford JM Jr, Gress DR. Oral contraceptives and the risk of subarachnoid hemorrhage: a meta-analysis. Neurology 1998; 51: 411–18.

Juvela S, Hillbom M, Numminen H, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. Stroke 1993; 24: 639–46.

Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: overall management results. J Neurosurg 1990; 73: 18–36.

Kissela BM, Sauerbeck L, Woo D, et al. Subarachnoid hemorrhage: a preventable disease with a heritable component. Stroke 2002; 33: 1321–26.
Kivisaari, M. Porras, J. O¨ hman, J. Siironen, K. Ishii, and J. Hernesniemi, “Routine cerebral angiography after surgery for saccular aneurysms: is it worth it?” Neurosurgery, vol. 55, no. 5, pp. 1015–1024, 2004.

Klatsky AL, Armstrong MA, Friedman GD. Alcohol use and subsequent cerebrovascular disease hospitalizations. Stroke 1989; 20: 741–46.

Knekt P, Reunanen A, Aho K, et al. Risk factors for subarachnoid hemorrhage in a longitudinal population study. J Clin Epidemiol 1991; 44: 933–39.

Lanterna, G. Tredici, B. D. Dimitrov et al., “Treatment of unruptured cerebral aneurysms by embolization with Guglielmi detachable coils: case-fatality, morbidity, and effectiveness in preventing bleeding—a systematic review of the literature,” Neurosurgery, vol. 55, no. 4, pp. 767–775, 2004.

Laskowitz and B. J. Kolls, “Neuroprotection in subarachnoid hemorrhage,” Stroke, vol. 41, supplement 10, pp. S79– S84, 2010.

Lee, M. Baytion, R. Sciacca, J. P.Mohr, and J. Pile-Spellman, “Aggregate analysis of the literature for unruptured intracranial aneurysm treatment,” American Journal of Neuroradiology, vol. 26, no. 8, pp. 1902–1908, 2005.

Li MH, Chen SW, Li YD, et al. Prevalence of unruptured cerebral aneurysms in Chinese adults aged 35 to 75 years: a cross-sectional study. Ann Intern Med 2013; 159: 514–21.

Longstreth WT Jr, Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. Stroke 1992; 23: 1242–49.

Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrhage and hormonal factors in women. A population-based case-control study. Ann Intern Med 1994; 121: 168–73.

Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group. Risks and benefits of screening for intracranial aneurysms in first-degree relatives of patients with sporadic subarachnoid hemorrhage. N Engl J Med 1999; 341: 1344–50.

Maher CO, Piepgras DG, Brown RD Jr, Friedman JA, Pollock BE. Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiectasia. Stroke 2001; 32: 877–82.

Mariani L, Bianchetti MG, Schroth G, Seiler RW. Cerebral aneurysms in patients with autosomal dominant polycystic kidney disease—to screen, to clip, to coil? Nephrol Dial Transplant 1999; 14: 2319–22.

Meyer FB, Sundt TM Jr, Fode NC, Morgan MK, Forbes GS, Mellinger JF. Cerebral aneurysms in childhood and adolescence. J Neurosurg 1989; 70: 420–25.

Mocco, K. V. Snyder, F. C. Albuquerque et al., “Treatment of intracranial aneurysms with the Enterprise stent: a multicenter registry,” Journal of Neurosurgery, vol. 110, no. 1, pp. 35–39, 2009.
Moret, C. Cognard, A. Weill, L. Castaings, and A. Rey, “Reconstruction technic in the treatment of wide-neck intracranial aneurysms. Long-term angiographic and clinical results. Apropos of 56 cases,” Journal of Neuroradiology, vol. 24, no. 1, pp. 30–44, 1997.

Moyle and A. B. Patel, “Intracranial aneurysms: endovascular treatment,” Mount Sinai Journal of Medicine, vol. 77, no. 3, pp. 279–285, 2010.

Müller TB, Sandvei MS, Kvistad KA, et al. Unruptured intracranial aneurysms in the Norwegian Nord-Trøndelag Health Study (HUNT): risk of rupture calculated from data in a population-based cohort study. Neurosurgery 2013; 73: 256–61.

Nagayama Y, Okamoto S, Konishi T, Suzuki H, Hamanaka H. Cerebral berry aneurysms and systemic lupus erythematosus. Neuroradiology 1991; 33: 466.

Naggara, P. M. White, F. Guilbert, D. Roy, A. Weill, and J. Raymond, “Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy,” Radiology, vol. 256, no. 3, pp. 887–897, 2010.

Nussbaum, M. T. Madison, M. E. Myers, and J. Goddard, “Microsurgical treatment of unruptured intracranial aneurysms. A consecutive surgical experience consisting of 450 aneurysms treated in the endovascular era,” Surgical Neurology, vol. 67, no. 5, pp. 457–464, 2007.

Palubinskas AJ, Perloff D, Newton TH. Fibromuscular hyperplasia, an arterial dysplasia of increasing clinical importance. Am J Roentgenol Radium Ther Nucl Med 1966; 98: 907–13.

Pierot, L. Spelle, X. Leclerc, C. Cognard, A. Bonafe, and J. Moret, “Endovascular treatment of unruptured intracranial aneurysms: comparison of safety of remodeling technique and standard treatment with coils,” Radiology, vol. 251, no. 3, pp. 846–855, 2009.

Raaymakers TW. Aneurysms in relatives of patients with subarachnoid hemorrhage: frequency and risk factors. MARS Study Group. Magnetic Resonance Angiography in Relatives of patients with Subarachnoid hemorrhage. Neurology 1999; 53: 982–88.

Rinne J, Hernesniemi J, Puranen M, Saari T. Multiple intracranial aneurysms in a defi ned population: prospective angiographic and clinical study. Neurosurgery 1994; 35: 803–08.

Schievink WI. Genetics of intracranial aneurysms. Neurosurgery 1997; 40: 651–62.

Schievink WI. Genetics and aneurysm formation. Neurosurg Clin N Am 1998; 9: 485–95.

Schievink WI. Marfan syndrome and intracranial aneurysms. Stroke 1999; 30: 2767–68.

Schievink WI, Riedinger M, Maya MM. Frequency of incidental intracranial aneurysms in neurofi bromatosis type 1. Am J Med Genet A 2005; 134A: 45–48.

Sedat, Y. Chau, L. Mondot, J. Vargas, J. Szapiro, and M. Lonjon, “Endovascular occlusion of intracranial wide-necked aneurysms with stenting (Neuroform) and coiling: mid-term and long-termresults,” Neuroradiology, vol. 51, no. 6, pp. 401–409, 2009.
Shapiro, J. Babb, T. Becske, and P. K. Nelson, “Safety and efficacy of adjunctive balloon remodeling during endovascular treatment of intracranial aneurysms: a literature review,” American Journal of Neuroradiology, vol. 29, no. 9, pp. 1777–1781, 2008.

Shiue I, Arima H, Hankey GJ, Anderson CS, and the ACROSS Group. Modifiable lifestyle behaviours account for most cases of subarachnoid hemorrhage: a population-based case-control study in Australasia. J Neurol Sci 2012; 313: 92–94.

Storrs BB, Humphreys RP, Hendrick EB, Hoff man HJ. Intracranial aneurysms in the pediatric age-group. Childs Brain 1982; 9: 358–61.

Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental fi ndings on brain MRI in the general population. N Engl J Med 2007; 357: 1821–28.

Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol 2011; 10: 626–36.

Wiebers DO, Torner JC, Meissner I. Impact of unruptured intracranial aneurysms on public health in the United States. Stroke 1992; 23: 1416–19.

Wiebers DO, Whisnant JP, Huston J 3rd, et al, and the International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 2003; 362: 103–10.

Winn HR, Jane JA Sr, Taylor J, Kaiser D, Britz GW. Prevalence of asymptomatic incidental aneurysms: review of 4568 arteriograms. Stroke 1983; 14: 121.

Yaşargil MG, Smith RD. Association of middle cerebral artery anomalies with saccular aneurysms and moyamoya disease. Surg Neurol 1976; 6: 39–43.

Yong-Zhong G, van Alphen HA. Pathogenesis and histopathology of saccular aneurysms: review of the literature. Neurol Res. 1990; 12:249–55.

Zacharia BE, Hickman ZL, Grobelny BT, et al. Epidemiology of aneurysmal subarachnoid hemorrhage. Neurosurg Clin N Am 2010; 21: 221–33.

19 APPENDICES

APPENDIX 1: STUDY DEFINTIONS

DEFINITIONS

ABRUPT CLOSURE

New reduced (TICI 0 or 1) flow at the target vessel during the index procedure as a result of a mechanical obstruction such as dissection or luminal thrombus. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, thrombus, or severe spasm.

ACUTE COMPLETE ANEURYSM OCCLUSION

The percentage of aneurysms in which a score of 1 (complete obliteration) is achieved on the Raymond Scale, without additional procedures for treatment of the aneurysm since the index procedure, as assessed immediately post-procedure.

ACUTE COMPLETE/PARTIAL ANEURYSM OCCLUSION

The percentage of aneurysms in which a score of 1 or 2 (complete obliteration or residual neck) is achieved on the Raymond Scale, without additional procedures for treatment of the aneurysm since the index procedure, as assessed immediately post-procedure.

ACUTE PERCENT ANEURYSM OCCLUSION

The percentage of aneurysms, without additional procedures for treatment of the aneurysm since the index procedure, as assessed by the Core Laboratory immediately post procedure, categorized as follows: 100%, ≥95-99%, ≥90-94%, and <90% occlusion.

ACUTE PROCEDURE SUCCESS

The percentage of aneurysms in which complete coverage across the aneurysm neck is achieved and for whom coil mass position is maintained within the sac with parent artery patency without additional procedures for treatment of the aneurysm since the index procedure, as assessed immediately post-treatment.

ACUTE THROMBOSIS

Angiographic evidence of thrombosis within the stent within 24 hours of stent deployment.

ADVERSE DEVICE EFFECT

A device-related Adverse Event

ADVERSE EVENT

Any untoward medical occurrence in a study subject, and which does not necessarily have a causal relationship with the product or treatment.; any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study devices, whether or not considered related to the devices. A preexisting condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period. Recanalization is not considered an adverse event since this is not an untoward medical occurrence to the subject, but rather an anticipated occurrence in the evolution of aneurysms.

ADVERSE EVENT OF SPECIAL INTEREST

Adverse events of Special Interest include:

- rupture > 24 hours post-treatment,
- major ipsilateral stroke > 1 month post-treatment,
- ipsilateral parenchymal hemorrhage > 1 month post-treatment, and/or
- device migration at the 6 month angiogram.

ANEURYSM DOME

Refers to the body of the aneurysm.

ANEURYSM NECK

Refers to the aperture or orifice of an aneurysm.

ANEURYSM SIZE

Aneurysm size (Meyers et al. 2010):

- small (≤ 5mm)
- medium (>5 to < 15mm)
- large (15 to < 25mm)

BARTHEL INDEX

Mahoney FI, Barthel D. “Functional evaluation: the Barthel Index.”
Maryland State Med Journal 1965;14:56-61. Used with permission.

Feeding
0 = unable
5 = needs help cutting, spreading butter, etc., or requires modified diet
10 = independent

Bathing
0 = dependent
5 = independent (or in shower)

Grooming
0 = needs to help with personal care
5 = independent face/hair/teeth/shaving (implements provided)

Dressing
0 = dependent
5 = needs help but can do about half unaided
10 = independent (including buttons, zips, laces, etc.)

Bowels
0 = incontinent (or needs to be given enemas)
5 = occasional accident
10 = continent

Bladder
0 = incontinent, or catheterized and unable to manage alone

5 = occasional accident
10 = continent

Toilet Use
0 = dependent
5 = needs some help, but can do something alone
10 = independent (on and off, dressing, wiping)

Transfers (bed to chair, and back)
0 = unable, no sitting balance
5 = major help (one or two people, physical), can sit
10 = minor help (verbal or physical)
15 = independent

Mobility (on level surfaces)
0 = immobile or < 50 yards
5 = wheelchair independent, including corners, > 50 yards
10 = walks with help of one person (verbal or physical) > 50 yards
15 = independent (but may use any aid; for example, stick) > 50 yards

Stairs
0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent

TOTAL (0–100):

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

BLEEDING

A loss of > 50cc of blood

BLEEDING COMPLICATION

Defined as a procedure-related hemorrhagic event that requires a transfusion and/or surgical intervention, a new hospitalization, or a lengthen hospital stay. These complications may include a hematoma requiring treatment (i.e., a hematoma > 5 cm in diameter occurring at the access site), or retroperitoneal bleeding.

CASE RERORT FORM (CRF)

A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each trial subject.

CEREBRAL ANEURYSM

An abnormal focal dilatation of a cerebral artery with attenuation of the vessel wall.

CEREBROVASCULAR ACCIDENT (CVA), symptomatic (of Neurological Deficit)

Greater than 30 days duration

Major: NIHSS ≥ 4, mRS ≥ 3
Minor: NIHSS < 4, mRS ≤ 2

CLINICAL COMPLICATION

A complication that results in an adverse event (i.e., there is a clinical/safety impact on the subject).

COILING PROCEDURE

Placement of one or more endovascular coil(s) used for embolizing an intracranial aneurysm.

COMPLETE ANEURYSM OCCLUSION

The percentage of aneurysms in which a score of 1 (complete obliteration) is achieved on the Raymond Scale on a post-procedure angiogram, without additional procedures for treatment of the aneurysm since the index procedure.

COMPLETE/PARTIAL ANEURYSM OCCLUSION

The percentage of aneurysms in which a score of 1 or 2 (complete obliteration or residual neck) is achieved on the Raymond Scale on a post-procedure angiogram, without additional procedures for treatment of the aneurysm since the index procedure.

DATE OF PRESENTATION

Refers to the date on which subject experienced signs or symptoms leading to medical evaluation and diagnosis of the cerebral aneurysm. Date of presentation may not be the same as the date of medical evaluation or diagnosis of the aneurysm but should be temporally related.

DEATH

Cardiac death. Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all

procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.

Vascular death. Death caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

Non-cardiovascular death. Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (eg, cancer, infection) should be classified as cardiac.

DE NOVO STENOSIS

An intracranial stenosis that has not been previously treated.

DEVICE MALFUNCTION

The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made on the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

DISSECTION

A flow-limiting tear or flap in the arterial wall requiring intervention to correct.

DYNA CT

An x-ray imaging software option which allows the reconstruction of 2-dimensional images acquired with an angiographic C-arm into 3-dimensional image format

DISTAL EMBOLIZATION

Defined as a new abrupt cut off or filling defect distal to the treated lesion.

ENROLLED, Subject

A subject is enrolled into the study at the time the study informed consent is signed.

EFFECTIVENESS

Reasonable assurance that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. [Tillman D-B, Director, Office of Device Evaluation, CDRH given at the ECRI Conference on Comparative Effectiveness of Health Interventions, October 2007. Fostering Comparative Effectiveness: An FDA Device Perspective]

EMERGENT PROCEDURE

Subjects requiring emergency intervention will not be responsive to any form of therapy except the procedure proposed. An emergency procedure is one in which there should be no delay providing intervention.

END OF PROCEDURE

The time the guiding catheter is removed from the subject.

ENTERED, Subject

Subjects will actually be "entered" in the study (if the intent is to proceed with stent deployment) at the time of the start of the index procedure as defined in this protocol (see definitions).

EVOLUTION OF ANEURYSM OCCLUSION

Stable = if the aneurysm is unchanged in size, configuration, and volumetric occlusion.

Improved = if progressive aneurysm occlusion or involution has occurred, using the 3 point category Raymond Scale.

Recanalized = if there is an increase in aneurysm filling resulting in a change in Raymond classification, using the 3 point category Raymond Scale.

Retreatment = defined as any additional treatment of the target aneurysm after the index procedure (retreatment includes staged procedures), and (regardless of whether retreatment is by surgery or endovascular treatment) due to recanalization, rupture or bleeding.

FEVER

Documented temperature > 38 degree C

FOCAL NEUROLOGICAL DEFICIT

Refers to signs including any peripheral, axial, and cranial nerve dysfunction.

GROIN HEMATOMA

An accumulation of blood at the puncture site requiring evacuation, transfusion, or extended hospital stay

HEADACHE

Subjective head pain often thunderclap in onset and classified as secondary in type attributed to subarachnoid hemorrhage

HEMMORHAGE

Acute loss of blood requiring transfusion

HUNT AND HESS SAH GRADING SCALE

Grade I Asymptomatic or mild headache
Grade 1a Fixed neurological deficit without meningeal or brain reaction
Grade II Moderate to severe headache, cranial nerve palsy, nuchal

rigidity
Grade III Lethargy, confusion, mild focal deficit
Grade IV Stupor, hemiparesis, early decerebrate posturing
Grade V Coma, decerebrate rigidity posturing, moribund appearance

HYDROCEPHALUS
A clinical entity in which a disturbance of cerebrospinal fluid circulation causes the accumulation of cerebrospinal fluid, resulting in progressive ventricular dilatation and increased intracranial pressure.

INDEX DATE
The treatment session during which the initial stenting of the aneurysm is attempted.

INDEX PROCEDURE
The treatment session during which stenting of the aneurysm is attempted will be referred to as the “index” procedure.

IN-SEGMENT MEASUREMENT
Defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.

IN-STENT MEASUREMENT
Defined as the measurements within the boundaries of the stent.

IN-STENT STENOSIS (PARENT VESSEL STENOSIS)
In-stent stenosis defined as greater than 50% narrowing of the vessel within the stent or within 10mm of either end of the stent.

MAJOR IPSILATERAL STROKE
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

MAJOR VASCULAR COMPLICATION
All pseudoaneurysms, vascular access site bleeding associated with a decrease in hemoglobin ≥ 5.0 g/dL as well as vascular events which require surgical repair or transfusion prior to discharge after procedure.

MODIFIED RANKIN SCALE
An instrument for the assessment of neurological status.

NEUROLOGICAL DETERIORATION
An increase from baseline NIHSS score of ≥ 4 points

PARENT VESSEL STENOSIS (IN-STENT STENOSIS)
In-stent stenosis defined as greater than 50% narrowing of the vessel within the stent or within 10mm of either end of the stent.

PERCENT ANEURYSM OCCLUSION

The percentage of aneurysms, without additional procedures for treatment of the aneurysm since the index procedure, as assessed by the Core Laboratory on a follow-up angiogram, categorized as follows: 100%, ≥95-99%, ≥90-94%, and <90% occlusion. Subjects who are retreated prior to the post-procedure follow-up visit will be included in the analysis and will be categorized as "Retreated."

POST-PROCEDURE

After the end of the index procedure (removal of the guiding catheter from the subject)

POST-TREATMENT

During the index procedure, it is the time period after treatment with the ENTERPRISE study device is completed and prior to the end of the index procedure (removal of the guiding catheter from the subject)

PRE-PROCEDURE

Prior to the start of the index procedure (access of the femoral artery)

PRE-TREATMENT

After start of the index procedure (access of the femoral artery) and prior to treatment with the ENTERPRISE study device

PROCEDURE SUCCESS

The percentage of aneurysms in which complete coverage across the aneurysm neck is achieved and for whom coil mass position is maintained within the sac with parent artery patency without additional procedures for treatment of the aneurysm since the index procedure, as assessed post-procedure.

PROCEDURAL SERIOUS ADVERSE EVENT

A SAE that occurs between the start of the procedure and within 24 hours of the baseline stenting procedure

PRODUCT COMPLAINT

Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device.

PROTOCOL DEVIATION

Action which deviates (varies) from the specified elements of a trial protocol including but not limited to non-adherence to inclusion/exclusion criteria; missed Subject visit or out-of-range visit interval; and, omitted or non-compliant tests or procedures required by the protocol. A protocol deviation may be intended or unintended; however, the result is the same as it compromises scientific integrity.

Observed Protocol Deviation:

Any protocol non-conformance identified by the Sponsor through monitoring visits, periodic reports, verbal communication or other trial-related mechanisms.

RAYMOND SCALE (3 POINT CATEGORY SCALE)

Classification of angiographic results:

- Class 1, complete obliteration;
- Class 2, residual neck; and
- Class 3, residual aneurysm.

Class 1 is defined as complete obliteration

Class 2 is defined as the persistence of any portion of the original defect of the arterial wall as seen on any single projection but without opacification of the aneurysmal sac.

Class 3 is defined as any opacification of the sac.

RECANALIZATION

An increase in aneurysm filling resulting in a change in (i.e., worsening of) the Raymond classification

REMNANT OPACIFICATION OR REMNANT RECANALIZATION

Describes an untreated component of the aneurysm in which there is no prosthetic material

RECANALIZATION RATE

The percentage of aneurysms in which recanalization is documented at any time up to and including the follow-up visit.

RETREATMENT

Retreatment will be defined as any additional treatment of the target aneurysm after the index procedure (retreatment includes staged procedures) and (regardless of whether retreatment is by surgery or endovascular treatment) due to recanalization, rupture or bleeding. The treatment session during which stenting of the aneurysm is attempted will be referred to as the “index” procedure.

RETREATMENT RATE

The percentage of target aneurysms that are retreated at any time up to and including the follow-up visit.

SEIZURE

A seizure refers to abnormal epileptiform neuronal discharge that results in focal or generalized alterations of sensation, motor function, behavior, or consciousness.

SERIOUS ADVERSE EVENT

Any significant adverse experience, including those that may be either life-threatening or involving permanent or long term injuries but excluding injuries that are non-life-threatening and/or that are temporary and reasonably reversible. A Serious Adverse Event includes any of the following events that may or may not be considered related to the device;

- Results in Death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

SOURCE DOCUMENTS

Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries, or evaluation checklists, dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the hospital, at the laboratories, and at technical departments involved in the clinical studies.

SPONSOR

Cerenovus

STAGED COILING PROCEDURE

A staged procedure is a procedure where entire treatment with the device (e.g. coils/stents) is completed over separate sessions.

START OF PROCEDURE

The time the femoral artery is accessed.

STENT MIGRATION

A change in placement of the stent from the initial placement at the end of the index procedure that is documented during a post-placement angiogram.

STENT MOVEMENT

A change in placement of the stent that occurs during the index procedure, or a retreatment procedure.

STROKE

Any sudden development of neurological deficits attributable to cerebral ischemia, infarction, or hemorrhage.

SUBACUTE CLOSURE

New reduced (TICI 0 or 1) flow at the target vessel observed as unintentional or persistent occurrence as a result of a mechanical obstruction, such as dissection or luminal thrombosis, occurring after completion of the index procedure but within 30 days of stent deployment.

SUBARACHNOID HEMORRHAGE (SAH)

Bleeding in the subarachnoid, intracerebral, intraventricular, or subdural spaces.

TARGET ANEURYSM

The target aneurysm must be an aneurysm that is a 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, and which is intended to be treated with the ENTERPRISE device.

TECHNICAL COMPLICATION

Study device-related technical complications

Study device-related technical complications refer to those events that are directly related to the performance of the ENTERPRISE stent.

Examples include, but are not limited to: failure to access the target site with the device, or failure of the device to deploy.

All study device-related technical complications will be reported on the eCRF.

Non-study device-related technical complications

Non-device-related technical complications refer to those events that are technical in nature, but are not directly related to the performance of the ENTERPRISE stent.

Examples include, but are not limited to: the required stent size for treatment is not available, or equipment failure occurs (other than the device) precluding continuation of the procedure.

All non-study device-related technical complications will be reported on the eCRF.

TICI Score

(Roth et al. Stroke, 2010)

Grade 0	No perfusion: No antegrade flow beyond the point of occlusion.
Grade 1	Penetration with minimal perfusion: The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
Grade 2:	Partial perfusion: The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, eg, the opposite cerebral artery or the arterial bed proximal to the obstruction.
Grade 2a	Only partial filling (~2/3) of the entire vascular territory is visualized
Grade 2b	Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.
Grade 3	Complete perfusion: Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction, and clearance of contrast material from the involved bed is as rapid

as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

TRANSIENT ISCHEMIC ATTACK (TIA) (of Neurological Deficit)

Resolution of new focal deficit within 24 hours. No CT or MRI evidence of infarction.

THROMBOSIS

In-stent thrombosis

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of study subjects

VASCULAR COMPLICATIONS

Vascular complication may include the following:

- Hematoma at access site > 4 cm
- Pseudoaneurysm
- Arteriovenous fistula
- Retroperitoneal bleed
- Peripheral ischemia/nerve injury
- Procedure related transfusion
- Vascular surgical repair