# Statistical Analysis Plan

## Evaluation of the GORE® TAG® Thoracic Branch Endoprosthesis (TBE Device) in the Treatment of Lesions of the Aortic Arch and Descending Thoracic Aorta

**Study Acronym/Protocol #: SSB 11-02 Pivotal**

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# 1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the evaluation of the GORE® TAG® Thoracic Branch Endoprosthesis (TBE Device) in the treatment of lesions of the aortic arch and descending thoracic aorta.

# 2.0 Study Design Overview

This section consists of relevant elements from the study protocol, including (as applicable):

## 2.1 Objectives

### 2.1.1 Primary Objective(s)

The primary objective of the study is to determine whether the GORE® TAG® Thoracic Branch Endoprosthesis (TBE device) is safe and effective in treating thoracic aortic pathologies. Specifically, the objective will be to perform hypothesis-driven analysis of the device's safety and effectiveness in the treatment of aortic aneurysms requiring proximal device placement in Zone 0/1 & Zone 2 of the thoracic aorta, respectively. Due to the potential applicability of the TBE Device in additional pathologic presentations, enrollment of anatomically suitable non-aneurysm patients will also be allowed to provide additional clinical data to characterize performance in these applications.

## 2.2 Design Summary

This will be a non-randomized, multicenter, prospective study conducted at up to forty-five (45) Clinical Investigative Sites (referred to as "Sites" in the remainder of this document), with up to 40 sites in the U.S and up to 5 sites in Japan with the objective of determining whether the TBE device is safe and effective in treating lesions of the aortic arch and descending thoracic aorta. A minimum of 175 and up to a total of 465 Subjects will be enrolled across four independent study arms consisting of seven cohorts as described below. The anatomically suitable non-aneurysm cohorts will be referred to as the Non-Aneurysm Lesion (NAL) Cohorts.

The study will consist of seven cohorts described as follows:

- Zone 2, aneurysm patients (N=115, maximum)
  - Zone 2, aneurysm patients, Primary Enrollment (N=85)
  - Zone 2, aneurysm patients, Continued Access Enrollment (N=30, maximum)
- Zone 2, anatomically suitable non-aneurysm patients, descriptive analysis (N=200, maximum)
  - Dissection cohort (N=20 minimum)
  - Traumatic Transection cohort (N=10 minimum)
  - Other isolated lesion types cohort (No minimum)
- Zone 0/1, aneurysm patients, hypothesis driven (N=50, 0-10 Subjects from Japan) NOTE: due to removal of the 49/53mm device sizes from this trial, any Subjects enrolled with these device sizes will not be counted as part of this N=50 enrollment and replacement Subjects will be enrolled to keep N=50)
- Zone 0/1, anatomically suitable non-aneurysm patients, descriptive analysis (N=100, maximum)

- Dissection cohort (N=10 minimum)
- Other isolated lesion types cohort (No minimum)

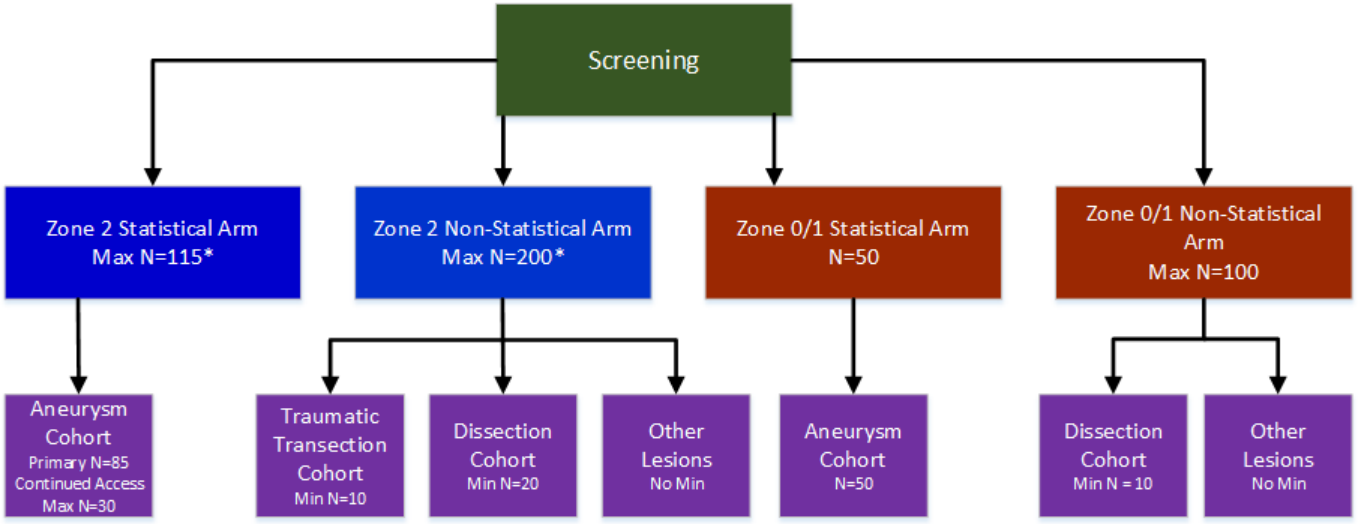
The Zone 2 aneurysm cohort will consist of 85 subjects accrued during the Primary Enrollment period along with a maximum of 30 subjects accrued during the Continued Access Enrollment period. Any Zone 2 training cases enrolled from Japan would not be included in PMA analysis, nor do they count towards enrollment minimums/maximums as shown above. However, once enrolled, the Japan Zone 2 training cases may be included for some analysis.

The maximum number of Subjects that may be enrolled at a single site is as follows:

- Zone 2, aneurysm patients, 17 Subjects
- Zone 0/1, aneurysm patients, 8 Subjects in US, 4 Subjects in Japan
- Zone 2 and Zone 0/1, anatomically suitable non-aneurysm patients, all cohorts, will not have a maximum per site as they are for descriptive analysis only

See **Figure 1** of a schematic representation of this study design.

**Figure 1**. Study Design Schematic




*Japan may contribute to the Zone 0/1 cohort. They will also conduct two training cases in Zone 2 Subjects which will not be included in the min and max for Zone 2 enrollment.

## 2.3 Study Outcomes

All outcomes (in addition to being described in two below subsections) are displayed in **Appendix A**. This table from the study protocol describes the responsible party for the determination and adjudication of each specific Primary Endpoint [redacted] In addition, there was a

third column added for this SAP to describe what Case Report Form (CRF) and question the study outcome will be determined from.

### 2.3.1 Primary Endpoint

The Primary Endpoints for the two hypothesis-driven study cohorts are described below. Definitions for these events are provided in the study protocol.

#### 2.3.1.1 Zone 2 Aneurysm Cohort

The Primary Endpoint for the Zone 2 aneurysm cohort will be a composite of the following events through 12 months (through day 546 unless otherwise specified in study protocol component definitions) following the index endovascular procedure:

- Device Technical Success
- Absence of the following:
  - Aortic rupture;
  - Lesion-related mortality;
  - Disabling stroke
  - Permanent paraplegia
  - Permanent paraparesis
  - New onset renal failure requiring permanent dialysis
  - Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system.

#### 2.3.1.2 Zone 0/1 Aneurysm Cohort

The Primary Endpoint for the Zone 0/1 aneurysm cohort will be Strategy Success.

Strategy Success (For planned staged procedures – landing zone optimization, transposition, and device placement – through one month following last planned procedure) and is defined as follows: a composite of the following events from the time of enrollment through one month following the index endovascular procedure (through day 59 unless otherwise specified in study protocol component definitions):

- Initiation of the index endovascular procedure following the debranching procedure
- Device technical success for the index endovascular procedure
- Absence of the following :
  - Aortic rupture
  - Lesion-related mortality
  - Disabling Stroke
  - Permanent paraplegia
  - Permanent paraparesis
  - New onset renal failure requiring permanent dialysis

- Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system.

[redacted]

[redacted]

## 2.4 Statistical Hypotheses

### 2.4.1 Performance Goal Derivation

#### 2.4.1.1 Zone 2 Aneurysm Cohort

Historical TAG/CTAG results (TAG 99-01, TAG 03-03, TAG 04-02, TAG 05-02, TAG 08-03) were re-analyzed to determine the Zone 2 aneurysm cohort performance goal for the Primary Endpoint (see study protocol for this data). Subjects treated for DTA aneurysms with proximal device placement in Zone 2

were identified in the historical TAG/CTAG studies. Using the data to the extent possible from historical TAG/CTAG Zone 2 aneurysm studies, the primary event rate through 12 months was calculated for these Subjects applying the Primary Endpoint definitions planned for the prospective Zone 2 aneurysm cohort. Subjects with one or more Primary Endpoint events through the 12 month window (i.e. through study day 546) were counted as failures (those with >1 event counted just once as failures). Subjects without an event through 12 months had to have imaging done within the 12 month time window in order to count as successes. The percentage of TAG/CTAG Subjects successful for the Primary Endpoint through 1 Year was 81%. The lower bound of the 95% confidence interval on this result is 71% (based on a combined sample size of 75 Subjects as displayed in the study protocol). However, this result did not include performance on device technical success (including patency and unanticipated additional procedure) at procedure (this was estimated to be 5-7%). Based on these results and the potential for these additional endpoint events, the performance goal was set at 64%.

#### 2.4.1.2 Zone 0/1 Aneurysm Cohort

A systematic literature review of hybrid repair literature was conducted (see study protocol for in-depth description of this literature review). Key results that were consistently identifiable from the review included perioperative death, neurological events and spinal cord ischemia, all of which are part of the Zone 0/1 Primary Endpoint. The results were individually summarized (i.e., a rate for each outcome was calculated across the identified literature) and then summed up; the estimated total percent of these events was 23.6%. Additional events included in the Primary Endpoint of the Zone 0/1 statistical arm are renal failure and the components of technical success. To account for these additional factors, an adjustment of 11% to the overall point estimate from the literature analysis was employed, increasing the anticipated point estimate from historical results to 34.6%. To account for potential variability in the new study population an additional margin of 5% was incorporated. This additional adjustment to the performance goal is justified given the potential for under-reporting of key events in literature and national databases. Due to this consideration, the study performance goal (success) for the proposed Zone 0/1 Primary Endpoint was set at 60%.

### 2.4.2 Zone 2 Aneurysm Cohort Hypothesis

The analysis of the Primary Endpoint for this cohort is intended to test the hypothesis that the success exceeds the performance goal of 64%. Using the performance goal of 64% with Primary Endpoint success through 12 months, the following hypothesis will be tested:

$H_O$: $P_{s2} \leq 0.64$

$H_A$: $P_{s2} > 0.64$

### 2.4.3 Zone 0/1 Aneurysm Cohort Hypothesis

The analysis of the Primary Endpoint for this cohort is intended to test the hypothesis that the success exceeds the performance goal of 60%. Using the performance goal of 60% with Primary Endpoint success through one month, the following hypothesis will be tested:

$H_O$: $P_{s01} \leq 0.60$

$H_A$: $P_{s01} > 0.60$

[redacted]

### 2.5.2 Zone 0/1 Aneurysm Cohort

[redacted]To meet the performance goal of 60%, a point estimate of > 74% Primary Endpoint success for 50 patients through one month is required. No attrition was accounted for.

[redacted]

Sample size calculations were determined using PASS 13 one-sided exact test for one proportion.

# 3.0 Study Treatment Arms

## 3.1 Test Arm

There are 4 arms (2 hypothesis-driven test arms) and seven study cohorts, described again as follows:

- Zone 2, aneurysm patients (N=115, maximum)
  - Zone 2, aneurysm patients, Primary Enrollment (N=85)
  - Zone 2, aneurysm patients, Continued Access Enrollment (N=30, maximum)
- Zone 2, anatomically suitable non-aneurysm patients, descriptive analysis (N=200, maximum)
  - Dissection cohort (N=20 minimum)
  - Traumatic Transection cohort (N=10 minimum)
  - Other isolated lesion types cohort (No minimum)
- Zone 0/1, aneurysm patients, hypothesis driven (N=50, 0-10 Subjects from Japan) NOTE: due to removal of the 49/53mm device sizes from this trial, any Subjects enrolled with these device sizes will not be counted as part of this N=50 enrollment and replacement Subjects will be enrolled to keep N=50.)
- Zone 0/1, anatomically suitable non-aneurysm patients, descriptive analysis (N=100, maximum)
  - Dissection cohort (N=10 minimum)
  - Other isolated lesion types cohort (No minimum).

A variety of pathologies can affect the thoracic aorta. These include aneurysms, dissections (including variants of dissection) and traumatic pathologies including transection. Aneurysm and dissection may affect any area of the thoracic aorta, including the ascending, arch or descending, whereas traumatic transections are typically located in the descending thoracic aorta (DTA). The study protocol has more detail about each of these pathologies and all lesion inclusion/exclusion criteria that are needed for possible study enrollment. However, at a minimum, the following are pathology inclusion criteria for the study cohorts (all must be a thoracic aortic pathology deemed to warrant surgical repair which requires proximal graft placement in Zone 0-2):

a) Aneurysms:
   i) Fusiform aneurysm (≥55 mm), or
   ii) Fusiform aneurysm (>2 times native aortic diameter), or
   iii) Saccular aneurysm (no diameter criteria)

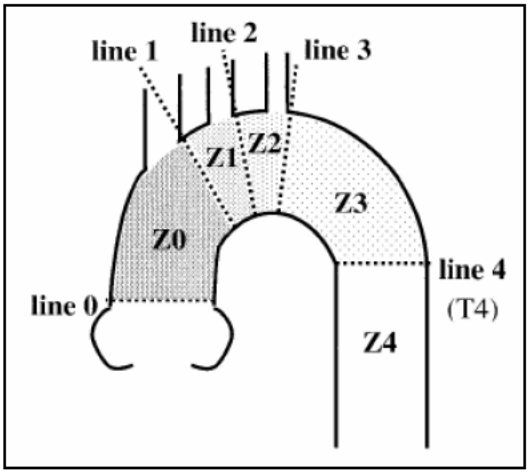
b) Non-aneurysms
   i) Intramural hematoma (no diameter criteria), or
   ii) Penetrating aortic ulcer (no diameter criteria), or
   iii) Traumatic aortic transection (no diameter criteria), or
   iv) Other isolated lesion with non-diseased proximal and distal landing zone, or

v) Type B aortic dissection requiring treatment for rupture or impending rupture, malperfusion syndrome, rapid expansion, uncontrollable pain, aneurysmal dilatation or prophylactic reasons, or

vi) Residual aortic dissection following surgical repair of Type A aortic dissection requiring treatment.

See **Figure 2** for a visual overview of the required placement of the proximal extent of the TBE device (to see the difference between Zone 0/1 and Zone 2 cases).

**Figure 2**. Anatomical Landing Zone Map for Thoracic Endovascular Stent Graft Placement[1]




## 4.0 Study Data Collection

This section contains information on data collected. Subject enrollment definition, withdrawal, and lost-to-follow-up details are explained in the study protocol.

### 4.1 Data Collected

Data will be collected in Case Report Forms (CRFs) and include the following:

- Cohort Enrollment Status
- Demographics
- Eligibility (Inclusion/Exclusion) Criteria
- Medical History
- Case Planning (form for each Zone and separately by Zone for dissection cases)
- Subject Physical Evaluations and Pressures
- Modified Rankin and Spinal Cord Ischemia Assessments
- Risk Assessments
- Trauma (Glasgow Coma and ISS) Assessments for Traumatic Transection Cases
- NIH Stroke Scale
- Pre-Imaging Site Assessment
- Pre-Imaging Corelab Assessment (separate forms for Aneurysm/Isolated Lesion and Dissection)

- Interval (Post) Imaging Assessments (Site, Corelab Aneurysm/Isolated Lesion, Corelab Dissection, Corelab Overall Device Events)
- Device Accountability (Pre and Post)
- Device Deficiencies
- Revascularization Procedure
- Initial Endovascular Procedure
- Missed Visits
- Adverse Events (AEs) and Treatments
- Safety Narratives
- CEC Adjudication
- Medications of Interest
- Study Completion/Discontinuation

## 4.2 Study Data Collection Intervals

**Table 1** and **Table 2** outline the required procedures at each follow-up visit for the respective study cohorts by Zone.

**Table 1: Zone 2 Subject Evaluations and Post-Treatment Follow-up Schedule**

| | Screening | Treatment | Discharge | 1 month | 6 months | 12 months | 24, 36, 48, and 60 months |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| Demographics and Medical History | X | | | | | | |
| Physical examination | X | | X | X | X | X | X |
| Modified Rankin Scale [a] | X | | X | X [b] | X | X | X |
| Spinal Cord Ischemia Scale [a] | X | | X | X | X | X | X |
| Brachial and Ankle Pressures (Optional) | X | | X [c] | X | X | X | X |
| Serum Creatinine Concentration | X | | | | | | |
| Spiral CTA (contrast) [d] | X[e] | | | X | X | X | X |
| Spiral CT (non-contrast) [d] | | | | X | | | |
| Angiogram at Completion of Procedure | | X | | | | | |
| NYHA Score, ASA Score | X | | | | | | |
| ISS Score, Glasgow Coma Score (Traumatic Transection Subjects only) | X | | | | | | |
| NIH Stroke Scale (NIHSS)[f] | X | | X | X | | | |

[a] If subject is unable to return to the site for a follow-up visit, they may be contacted by telephone to evaluate the Modified Rankin Scale and Spinal Cord Ischemia Scale

[b] For subjects suspected of having a stroke event within 30 days following the index endovascular procedure an additional MRS score should be completed at 90 days following the suspected stroke event but no greater than 120 days post index endovascular procedure.

[c] Within 48 hours of index endovascular procedure

[d] CTA of chest/abdomen/pelvis at Screening. CTA of chest at all follow-up visits, except for Dissection Subjects who must have a CTA of chest/abdomen/pelvis at all visits. Imaging Guidelines for CT are located in Protocol. MRA may be used in place of CTA during follow-up if the Subject is contraindicated for CTA.

[e] Screening CTA must be ≤ 90 days prior to enrollment

[f] NIH Stroke Scale should be performed for all subjects during Screening, Discharge and 1 Month visits. NIHSS should also be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of the index endovascular procedure until discharge. The scale should be performed as soon as possible after learning of the suspected event.

## Table 2: Zone 0/1 Subject Evaluations and Post-Treatment Follow-up Schedule

| | Screening | Treatment | | | Discharge | 1 month | 6 months | 12 months | 24, 36, 48, and 60 months |
|---|---|---|---|---|---|---|---|---|---|
| | | Phase 1 Procedure | Phase 1 Evaluation | Phase 2 Procedure | | | | | |
| Informed Consent | X | | | | | | | | |
| Demographics and Medical History | X | | | | | | | | |
| Physical Examination | X | | X [b] | | X | X | X | X | X |
| Modified Rankin Scale [c] | X | | X | | X | X [d] | X | X | X |
| Spinal Cord Ischemia Scale [c] | X | | X | | X | X | X | X | X |
| Brachial and Ankle Pressures (Optional) | X | | X | | X [e] | X | X | X | X |
| Serum Creatinine Concentration | X | | | | | | | | |
| Spiral CTA (contrast) [f] | X [g] | | | | | X | X | X | X |
| Spiral CT (non-contrast) [f] | | | | | | X | | | |
| Angiogram at Completion of Procedure | | | | X | | | | | |
| CTA of the Head/Neck [h] | X | | | | | | | | |
| NYHA Score, ASA Score | X | | | | | | | | |
| ISS Score, Glasgow Coma Score (Traumatic Transection Subjects only) | X | | | | | | | | |
| NIH Stroke Scale (NIHSS) [i] | X | | | | X | X | | | |

[a] Phase 1 Evaluation should be performed at least 24 hours after the revascularization procedure but within 30 days post treatment
[b] Subjects who are withdrawn prior to the Phase 2 Procedure should also have a Physical Exam at one month post Phase 1 procedure
[c] If subject is unable to return to the site for a follow-up visit, they may be contacted by telephone to evaluate the Modified Rankin Scale and Spinal Cord Ischemia Scale
[d] For subjects suspected of having a stroke event within 30 days following the index endovascular procedure an additional MRS score should be completed at 90 days following the suspected stroke event but no greater than 120 days post index endovascular procedure.
[e] Within 48 hours of index endovascular procedure
[f] CTA of chest/abdomen/pelvis at Screening. CTA of chest at all follow-up visits, except for Dissection Subjects who must have a CTA of chest/abdomen/pelvis at all visits. Imaging Guidelines for CT are located in Protocol. MRA may be used in place of CTA during follow-up if the Subject is contraindicated for CTA.
[g] Screening CTA must be ≤90 days prior to Phase 2 procedure.
[h] Screening CTA of Head/Neck must be ≤90 days prior to Phase 1 procedure. If CT of Head/Neck is not consistent with site's standard of care then radiological modality of evaluation is at investigator discretion (Ultrasound, MR, etc.) However, imaging of head/neck vasculature is required ≤90 days prior to Phase 1 procedure.
[i] NIH Stroke Scale should be performed for all subjects during Screening, Discharge and 1 Month visits. NIHSS should also be performed for any Subject suspected of having a stroke event that undergoes the treating site's stroke Protocol during the study interval from the initiation of the surgical revascularization procedure until discharge post-index endovascular procedure. The scale should be performed as soon as possible after learning of the suspected event.

### 4.3 Follow-Up Visit Windows

Follow-up visits will be scheduled at appointed times after the date of treatment. Follow-up visits should be scheduled within the ideal window when possible; however, any available data collected in the analysis windows will be summarized as occurring within the given window. Thus, a period during which each visit is allowed, i.e. window, is provided in **Table 3** (Zone 2) and **Table 4** (Zone 0/1).

**Table 3: Zone 2 Cohorts Schedule of Follow-up Visits and Time Periods**

| Follow-up Visit | Ideal Window (days) | Analysis Window (days) | Adverse Event Absolute Analysis Window (days) |
|---|---|---|---|
| Procedure | 0 | 0 | 0 |
| Post-Procedure | 1-14 | 1-14 | - |
| 1 Month | 23-44 | 15-59 | 1-30 |
| 6 Months | 150-210 | 60-242 | 31-182 |
| 12 Months | 275-455 | 243-546 | 183-365 |
| 24 Months | 640-820 | 547-911 | 366-731 |
| 36 Months | 1005-1185 | 912-1275 | 732-1096 |
| 48 Months | 1370-1550 | 1276-1640 | 1097-1461 |
| 60 Months | 1735-1915 | 1641-2006 | 1462-1826 |

**Table 4: Zone 0/1 Cohorts Schedule of Follow-up Visits and Time Periods**

| Follow-up Visit | Ideal Window (days) | Analysis Window (days) | Adverse Event Absolute Analysis Window (days) |
|---|---|---|---|
| Phase 1 Procedure: Great Vessel Revascularization | -7 up to -1 days before Phase 2 Procedure | -60 up to -1 days before Phase 2 Procedure | -60 up to -1 days before Phase 2 Procedure |
| Phase 1 Evaluation | -6 up to 0 days before Phase 2 Procedure* | -59 up to 0 days before Phase 2 Procedure* | -59 up to 0 days before Phase 2 Procedure* |
| Phase 2 Procedure: Index Endovascular Procedure | 0 | 0 | 0 |
| Post Procedure | 1-14 | 1-14 | - |
| 1 Month | 23-44 | 15-59 | 1-30 |
| 6 Months | 150-210 | 60-242 | 31-182 |
| 12 Months | 275-455 | 243-546 | 183-365 |
| 24 Months | 640-820 | 547-911 | 366-731 |
| 36 Months | 1005-1185 | 912-1275 | 732-1096 |
| 48 Months | 1370-1550 | 1276-1640 | 1097-1461 |
| 60 Months | 1735-1915 | 1641-2006 | 1462-1826 |

* Although Phase 1 Evaluation can occur on the same day as the Index Endovascular Procedure, the Phase 1 Evaluation must occur before the Index Endovascular Procedure

## 4.4 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review accumulating safety data on a regular basis and will advise the Sponsor regarding the continuing safety of study Subjects as well as the continuing validity and scientific merit of the study. The DSMB will be comprised of an interdisciplinary team of members with pertinent expertise in vascular or cardiothoracic surgery, as well as one biostatistician, who are not directly involved in the conduct of the study.

Based on the safety data, the DSMB will make recommendations to the Sponsor.

## 4.5 Clinical Events Committee

A Clinical Events Committee (CEC), consisting of appropriately trained Physicians with extensive relevant clinical experience, independent of the study, will adjudicate Primary Endpoint and Success Outcomes candidate events. The events to be adjudicated by CEC are detailed in **Appendix A**.

The CEC will also review Inclusion / Exclusion Deviations and adjudicate them as major or minor (see study protocol for these definitions).

### 4.6 Core Laboratory

All protocol required CTA imaging of the chest and/or chest, abdomen, and pelvis will be sent to the Core Lab via Medidata Medical Imaging (formerly known as Intelemage).

Analysis of pre-treatment and follow-up radiologic images will be conducted by an independent Core Lab (details in study protocol). At a minimum, the assessment will include:

- morphology of aortic lesion, adjacent aorta, and landing zones
- device status post-implant, including certain Success Outcomes as detailed in **Appendix A**.

## 5.0 Statistical Analyses

This section describes aspects of the statistical analysis which includes summarizing the analysis populations, analysis timing, and specifics on all planned analyses (Primary Endpoint analysis, [redacted]

### 5.1 Analysis Populations

5.1.1 Primary Endpoint

5.1.1.1 Zone 2 Aneurysm Cohort

The composite Primary Endpoint analysis population (to test the hypothesis) for the Zone 2 aneurysm cohort will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion) and is outlined as follows based on events described in **Section 2.3.1.1**:

1) Subjects with an event any time ≤ 546 days are a failure regardless of whether they had imaging in 12 month window
2) Subjects that don't have imaging in the 12 month window and don't have an event ≤ 546 days are excluded
3) Subjects with imaging in 12 month window and no event reported ≤ 546 days are successes
4) Subjects with >1 event just count once as failures

The rate (composite Primary Endpoint) within an analysis window (except for Procedure window) will use similar logic to that through 12 month window but will be window-dependent (i.e. 6 Month Primary Endpoint composite rate will be among those with an event in the 6 month window or had imaging in the 6 month window). All enrolled Subjects with no ‘major’ inclusion/exclusion criteria will be in the denominator in the Procedure window.

All hypothesis testing and Primary Analysis for the PMA will be based on Zone 2 Aneurysm Subjects accrued during the Primary Enrollment Period. Zone 2 Aneurysm Subjects accrued during Continued Access Enrollment will be analyzed separately for the PMA. Continued Access Enrollment Subjects may be pooled with the Primary Enrollment Subjects in subsequent reports and/or analysis.

#### 5.1.1.2 Zone 0/1 Aneurysm Cohort

The composite Primary Endpoint analysis population (to test the hypothesis) for the Zone 0/1 aneurysm cohort will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion) and is outlined as follows based on events as described in **Section 2.3.1.2**:

- Subjects with an event any time ≤ 59 days are a failure regardless of whether they had imaging in one month window
- Subjects that don't have imaging in the one month window and don't have an event ≤ 59 days are excluded
- Subjects with imaging in one month window and no event reported ≤ 59 days are successes
- Subjects with >1 event just count once as failures

The analysis population for the Zone 0/1 Aneurysm cohort will also exclude any Subjects treated with a 49/53mm device since those device sizes have been removed from this study. Any Subjects enrolled and treated with those device sizes will not be counted in the N=50 enrollment and replacement Subjects will be enrolled to keep N=50. The 49/53mm Subjects will be summarized separately and followed per the Protocol.

This analysis will also be repeated with 12 month results (following the same analysis population logic as that outlined for the Zone 2 aneurysm cohort in **Section 5.1.1.1**) with the exception that no hypothesis will be tested.

#### 5.1.1.3 NAL Cohorts

No hypotheses will be tested for any of the NAL cohorts. An NAL cohort will be summarized separately if there are at least 10 Subjects for a cohort. Else, NAL Subjects may be grouped by Zone (Zone 0/1, Zone 2) for analysis instead.

The Primary Endpoint analysis population for each of the five NAL cohorts will be among all enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion). In addition, the Primary Endpoint analysis population for each NAL cohort will follow Zone-similar logic to that written for the two hypothesis-driven aneurysm test arms (as described above in Section 5.1.1.1 (Zone 2) and Section 5.1.1.2 (Zone 0/1)).

However, additional analysis may be done with different analysis population criteria.

[redacted]

[redacted]

### 5.1.3 Additional Analyses

The analysis population for all other analyses (outlined in **Section 5.5**) for each of the cohorts will be among enrolled Subjects (excluding those with a CEC adjudicated 'major' inclusion/exclusion criteria violation or FDA mandated exclusion). Any additional analysis population details are outlined in the appropriate subsection of **Section 5.5**.

## 5.2 Timing of Analyses

Prior to primary analysis, the composite Primary Endpoint results [redacted] will not be analyzed (except as detailed below in **Section 5.2.2**) for the two hypothesis-driven test arms. Serial analyses of long-term results will occur during the follow-up period. A final analysis will be conducted once study follow-up is complete. In addition to the Primary Endpoint [redacted] at primary analysis time points, all other additional analyses (detailed in **Section 5.5**) will also be performed.

Details on primary analysis timing are provided in the below subsequent sections:

### 5.2.1 Zone 2 Aneurysm Cohort

Primary analysis timing will be dependent only on those Subjects enrolled during Primary Enrollment. The Primary Endpoint for the Zone 2 aneurysm cohort will be analyzed after all available Subjects meeting the analysis population criteria have completed the 12 month follow-up visit and have been in the study through 546 days. [redacted]

The subjects accrued during Continued Access Enrollment will be analyzed separately from the subjects accrued during Primary Enrollment at primary analysis. Depending on the timing of the primary analysis, continued access Subjects may not be analyzed at the time of primary analysis.

### 5.2.2 Zone 0/1 Aneurysm Cohort

The Primary Endpoint for the Zone 0/1 aneurysm cohort will be analyzed after all available Subjects meeting the analysis population criteria have completed the one month follow-up visit and have been in the study through 59 days. Subjects with suspected stroke Primary Endpoint events will need to have been in the study through 120 days before this Primary Endpoint analysis will be performed. This extra time is needed for these Subjects to allow for the Modified Rankin Scale to be assessed at any time during this period.

This analysis will also be repeated with 12 month results (following the same analysis population logic as that outlined for the Zone 2 aneurysm cohort in **Section 5.1.1.1**) with the exception that no hypothesis will be tested. [redacted]

### 5.2.3 NAL Cohorts

The Primary Endpoint for each of the NAL cohorts will be analyzed at the same time as the Zone-respective aneurysm cohort (i.e. Zone 2 NAL cohorts will have primary analysis conducted when the Zone 2 aneurysm cohort has primary analysis conducted). This analysis may be repeated for each of the NAL cohorts at later timepoint(s). This will possibly be conducted at different times for each of the NAL cohorts. [redacted] No hypotheses will be tested on the NAL cohorts.

## 5.3 Primary Endpoint Analysis

### 5.3.1 Zone 2 and Zone 0/1 Aneurysm Cohorts

The proportion of composite Primary Endpoint success (1 - composite Primary Endpoint failure) will be calculated for each hypothesis-driven cohort based on the details outlined for each Primary Endpoint component in **Appendix A**. One-sided Exact confidence intervals for binomial proportions (alpha=0.05) will be constructed to test each calculated composite proportion against the respective Primary Endpoint hypothesis. Each hypothesis-driven cohort tested must meet their respective Primary Endpoint analysis population criteria. The null hypothesis will be rejected if the lower bound of the 95% confidence interval estimating composite Primary Endpoint success exceeds the performance goal.

In addition, the Primary Endpoint data (composite and components) for each of these two cohorts will be summarized by statistics (count and percent).

In order to assess the impact of missing data on each of the composite Primary Endpoint hypothesis tests, sensitivity analyses will be performed and are outlined in **Section 5.5.1**.

[redacted]

### 5.3.2 NAL Cohorts

The Primary Endpoint data (composite and components) for the five cohorts meeting their respective Primary Endpoint analysis population criteria will be summarized by descriptive statistics (count and percent). No hypotheses will be tested.

[redacted]

## 5.5 Additional Analyses

Additional analyses will be performed as outlined below. [redacted]

[redacted]

[redacted]

### 5.5.3 Poolability of Sites

Site data will be pooled based on clinical comparability, i.e., the study Sites followed a common protocol, the study was monitored to ensure compliance with the protocol and applicable government regulations, and the data collection and handling procedures were the same at all study Sites. In order to justify pooling of Sites, a 2 x k analysis of the composite Primary Endpoint results (separately for the Zone 2 aneurysm and Zone 0/1 aneurysm cohorts) using a generalized Fisher's exact test will be performed, where k represents the number of site groups. Sites may be grouped together based on low enrollment with consideration given to the overall percent of enrollment combined. A 0.15 level of significance will be used for each test between site group and composite endpoint result. If the test is significant, composite Primary Endpoint results with 95% confidence intervals will be presented by Site group for each of the hypothesis-driven cohorts (Zone 2 aneurysm, Zone 0/1 aneurysm). [redacted]

### 5.5.4 Adverse Events

Adverse events (AEs) will be summarized for main reporting efforts. Adverse events are defined as any untoward medical occurrences in a Subject whether device-related or not. All AEs will be recorded on the appropriate CRF and documented in the Subject's permanent medical record. The Investigator at each Site is ultimately responsible for reporting all AEs to the Sponsor, as well as to the IRB, as applicable.

Adverse events will be summarized by incidence (i.e. a specific AE will not be counted more than once for a Subject within each window) in each analysis time window using MedDRA coded terminology. Analysis time windows will begin with the initial endovascular treatment window for all cohorts; AEs with onset prior to endovascular treatment (Zone 0/1 cohorts only) will be summarized separately. The denominator for each window will be calculated as the number of Subjects remaining in follow-up as of the beginning of the analysis window. At a minimum, separate summaries by severity (serious, non-serious) will be prepared. If summaries are prepared by relationship, the following categories will be considered as related to device/procedure: related to device, related to device and endovascular procedure, or related to endovascular procedure.

Partial dates (month and/or day unknown) for AE onset and AE resolution dates will be allowed for AE analysis time window determination. Exact imputation logic will be documented in the appropriate specifications document. In general, partial dates will be imputed to be most conservative with regard to timing after initial endovascular procedure date.

Candidate AEs for Primary Endpoint and Success Outcomes will be reviewed by the independent CEC and adjudicated (outlined in **Appendix A**).

#### 5.5.4.1 Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with aneurysm and non-aneurysm lesions of the aortic arch and DTA patients undergoing treatment with the TBE Device.

##### *5.5.4.1.1 Adverse Event Relationship*

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the device, surgical revascularization procedure, and/or endovascular procedure. It is permissible to assign multiple relationships for each reported AE.

**Related to Device**

The functioning or characteristics of the implanted device(s) caused or contributed to the Adverse Event. This is applicable to all components of the TBE Device (Aortic Component, Aortic Extender, Side Branch Component) as well as the CTAG Device.

**Related to Surgical Revascularization Procedure**

The surgical revascularization procedure (Zone 0/1 Subjects) (and not the device(s)) caused or significantly contributed to the Adverse Event.

**Related to Endovascular Procedure**

The endovascular procedure (and not the device(s)) caused or significantly contributed to the Adverse Event.

**Related to Device and Endovascular Procedure**

The endovascular procedure as well as the device(s) caused or significantly contributed to the Adverse Event.

**Unrelated to Devices and Procedures**

An Adverse Event which cannot be attributed to the device(s) or procedure(s).

**Unknown relationship**

The relationship of the Adverse Event to the device or procedure cannot be determined.

*5.5.4.1.2 Adverse Event Classification*

Each AE will be assessed by the Investigator to determine if it is serious or non-serious[2].

**Serious Adverse Event**

A Serious Adverse Event is an Adverse Event that

- led to death
- led to serious deterioration in the health of the Subject that either resulted in
  - a life threatening illness or injury, or
  - a permanent impairment of a body structure or body function, or

- inpatient or prolonged hospitalization, or
- medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function

- led to fetal distress, fetal death or a congenital abnormality or birth defect.

**Non-Serious Adverse Event**

Any event that does not meet the definition of serious will be classified as non-serious.

*5.5.4.1.3 Adverse Event Reporting and Coding*

AEs will be reported on the appropriate CRF and documented in the Subject's permanent medical record. The Investigator at each Site is ultimately responsible for reporting AEs to the Sponsor.

The following information on each reported Adverse Event will be collected:

- Adverse Event Name
- Adverse Event Onset Date
- Relationship
- Classification (Serious or Non-Serious)
- Treatment
- Outcome
- Resolution Date

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse Event submission guidelines:

- Adverse Event reporting begins once the patient is enrolled in the study. All Adverse Events should be reported from enrollment through study completion / discontinuation.
- Provide a diagnosis if possible. If unable to provide a diagnosis, report the symptoms as separate events. Adverse Events should be reported using the full name without abbreviations or narratives.
- Adverse Events with an outcome status of "Ongoing" should be assessed at each follow-up evaluation to determine if the event has resolved. Adverse Events ongoing at study completion / discontinuation should be left as "Ongoing" on the AE case report form.

*5.5.4.1.4 Subject Death*

Death is not an AE itself, but instead an outcome of an AE. Therefore, the cause of death, if known, should be the reported AE.

Any ongoing or unresolved AEs at the time of death will be indicated as ongoing/continuing on the CRF. Attempts should be made by the investigative Site to obtain death certificates, autopsy reports and device explants when at all possible.

5.5.4.2 Unanticipated Adverse Device Effects (UADEs)

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 protocol.

5.5.5 Core Laboratory Analysis

An independent Core Laboratory (Core Lab) will provide review of imaging data collected during the study at pre-treatment and follow-up.

Summaries of qualitative (yes/no, false lumen status categories) Core Lab imaging findings will be analyzed for each applicable analysis window. If there is more than one imaging finding for a Subject within a specific analysis window, the worst case finding will be used for summary in the window. The denominator for each window will be the number of Subjects with a non-missing Core Lab finding (such as either yes or no) in the given window.

Summaries of quantitative measurements will be calculated using the measurement obtained

[redacted]

Core Lab data will not be reconciled with Site-reported data.

5.5.6 Mortality

For additional analysis of all-cause mortality (in addition to Success Outcomes), Kaplan Meier methodology will be used. Subjects without death reported before the end of the time period of

interest will be censored at the Subject's last reported contact date or the end of the time period of interest, whichever date is earlier.

For additional analysis of lesion-related mortality (in addition to Primary Endpoint and Success Outcomes), Kaplan Meier methodology will be used. Subjects without a lesion-related death reported before the end of the time period of interest will be censored at the Subject's last reported contact date or the end of the time period of interest, whichever date is earlier.

### 5.5.7 Reinterventions

A Site-reported reintervention will be counted as occurring if the Site reports a 'yes' to the question "Was reintervention on the treated segment of the branch vessel or the aorta performed?" from the AE CRF. The incidence of Site-reported reinterventions will be summarized by analysis time window among those remaining in follow-up. In addition, the time to first Site-reported reintervention will be calculated using Kaplan Meier methodology. Subjects without a Site-reported reintervention reported before the end of the time period of interest will be censored at the Subject's last reported contact date or the end of the time period of interest, whichever date is earlier.

Unanticipated additional procedures related to the device, procedure, or withdrawal of the delivery system (meeting Primary Endpoint or Success Outcome criteria) will be summarized in the Primary Endpoint and Success Outcome tables and are not reconciled with Site-reported reinterventions as described above.

Initially treated Zone 2 cohort Subjects that have a reported reintervention involving Zone 0/1 treatment will remain in their original enrolled cohort for statistical analysis but narratives will be provided on these Subjects in submissions to the FDA (in all appropriate sections of the submitted report). In addition, the number and percent of these Subjects will be summarized.

### 5.5.8 Stroke and Paraparesis/Paraplegia

For additional analysis of these events (in addition to Primary Endpoint and Success Outcomes), all Subjects remaining in follow-up will be part of this analysis population. Event rates of each type of event will be displayed separately as well as an overall rate.

[redacted]

## 6.0 Interim Analyses and Safety Monitoring Analyses

There are no planned interim analyses of composite Primary Endpoint results for the two hypothesis-driven test arms.

However, safety data will be periodically reviewed by the DSMB (see **Section 4.4**). A comprehensive summary of reported adverse events will be reviewed by the DSMB on a regular and ongoing basis throughout the duration of the study. Safety data may be presented in various ways, such as serious adverse events vs. non-serious adverse events. In addition, adverse events resulting in mortality and/or in site-reported reinterventions may be presented separately.

Serial analyses of long-term results will occur during the follow up period.

## 7.0 Analysis Specifications

[redacted]

### 7.3 Verification Level for Statistical Output

All statistical output will be programmed per the Clinical Affairs Biostatistics Analysis SOP (MD111325)[3].

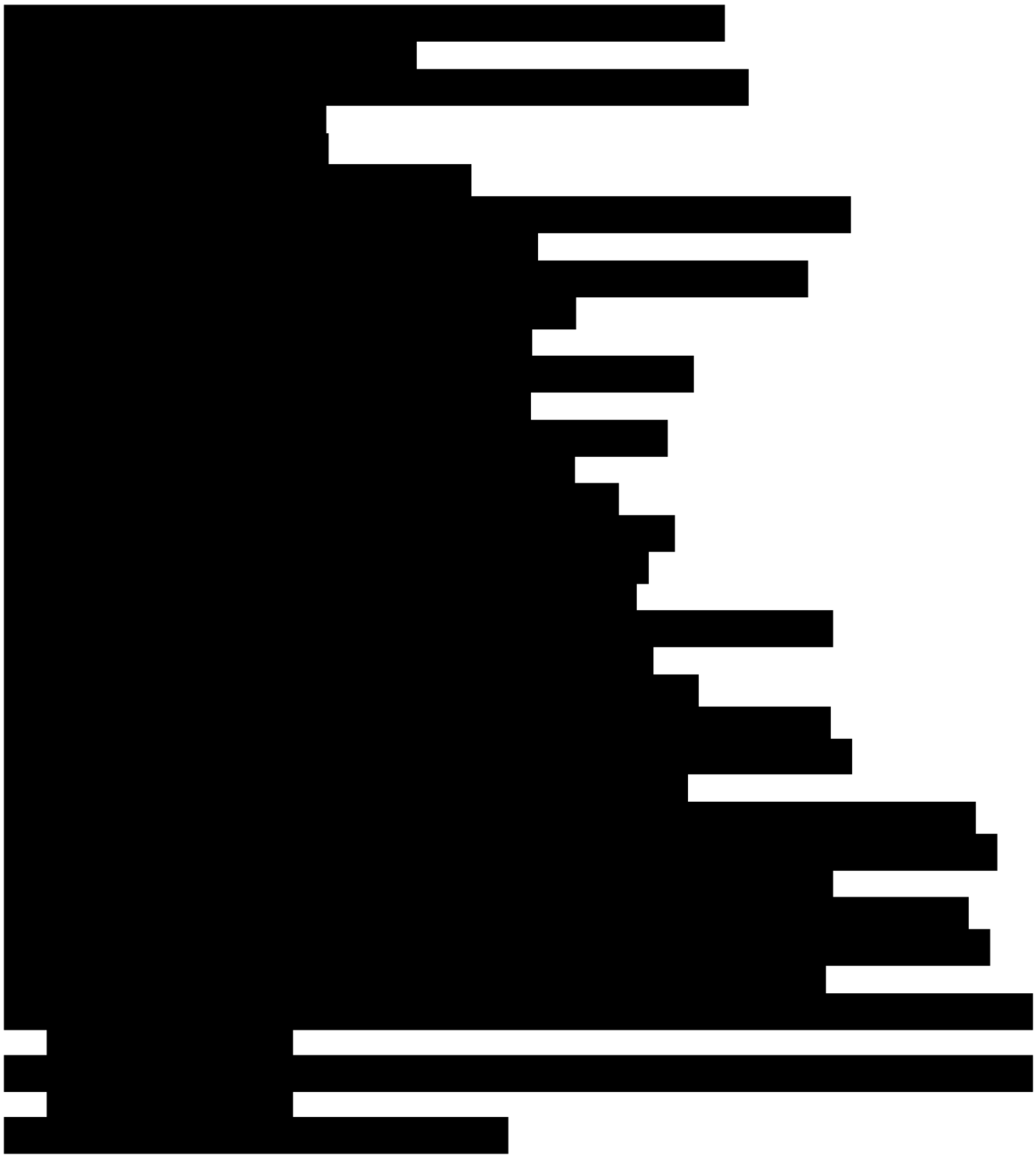
The verification level scheme for regulatory submissions is provided below:

- All Analysis Datasets – Level I
- All Tables – Level I
- All Listings – Level II

## 8.0 Data Sets, Tables, Figures, and Listings

This section includes a minimal list of planned statistical outputs for primary analysis, including tables, listings and figures. All output will be prepared by both study arms and cohort.

### 8.1 Analysis Tables



## **Appendix A**: Adjudication of Primary Endpoints and Success Outcomes

The table below describes the responsible party for the determination and adjudication of each specific Primary Endpoint and [redacted] The time periods for these endpoint/outcome determinations are described in **Section 2.3**. In addition, the third column explains what CRF, question (using permanent internal database short label), and question response will be used to determine endpoint/outcome failure.

| Key Outcome | Endpoint/Outcome Determination | Case Report Form, Question Short Label (Response Option Picked to Determine Endpoint / Outcome Failure) |
|---|---|---|
| **Device Technical Success for index endovascular procedure** | *Composite Event - Not Applicable* | |
| *Successful access and delivery* | • Site Investigator | • TX2, Question 'TX2 Access' (No) |
| *Patency of the graft* | • Site Investigator | • TX2, Question 'TX2 Patent' (No) |
| *Unanticipated additional procedure related to the device, procedure, or withdrawal of the delivery system* | • Site Investigator | • TX2, Question 'TX2 Unanticipated' (Yes) |
| **Aortic Rupture** | • Site Reported AE followed by CEC Adjudication Or Core Lab | • Event reported in AE form and CEC Adjudicated Question 'CEC Aortic Rupture' (Yes) or<br>• POSTCL-ANU, Question 'Post Lesion Rupture' (Yes – Within area of treatment) or<br>• POSTCL-DIS, Question 'Post Dis Rupture' (Yes – Within area of treatment) or<br>• Event reported in AE form and OMA Question 'OMA1 Aortic Rupture' (Yes) |
| **Lesion-related Mortality** | • Site Reported AE followed by CEC Adjudication | • Death reported (AE, Question 'AE Outcome' (Death)) and CEC Adjudicated Question 'CEC Lesion Related Mortality 2' (Yes) or<br>• Death reported (AE, Question 'AE Outcome' (Death)) and OMA Question 'OMA1 Lesion Related Mortality 2' (Yes) |
| **Disabling Stroke** | • Site Reported AE followed by CEC | • Event reported in AE form and CEC8 or CEC9 |

| Key Outcome | Endpoint/Outcome Determination | Case Report Form, Question Short Label (Response Option Picked to Determine Endpoint / Outcome Failure) |
|---|---|---|
| | Neurologist Review and adjudication | Question 'CEC Disabling' (Yes) |
| **Permanent Paraplegia** | • Site Reported AE followed by CEC Adjudication | • Event reported in AE form and CEC Adjudicated Question 'CEC Paraplegia' (Yes) |
| **Permanent Paraparesis** | • Site Reported AE followed by CEC Adjudication | • Event reported in AE form and CEC Adjudicated Question 'CEC Paraparesis' (Yes) |
| **Additional unanticipated post-procedural surgical or interventional procedure related to the device, procedure, or withdrawal of the delivery system** | • Site Reported AE with an unanticipated post-procedural surgical or interventional procedure followed by AE adjudication by CEC. | • Event reported in AE form where Site answers Question 'AE SAE Unanticipated' (Yes) and CEC Adjudicated Question 'CEC Reintervention' (Yes) or<br>• Event reported in AE form where Site answers Question 'AE SAE Unanticipated' (Yes) and OMA Question 'OMA1 Reintervention' (Yes) |
| **Initiation of the index endovascular procedure following the debranching procedure (Zone 0/1 cohorts only)** | • Site Reported Treatment Data | • PFU, Question 'PFU Continue' (No) |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

| Key Outcome | Endpoint/Outcome Determination | Case Report Form, Question Short Label (Response Option Picked to Determine Endpoint / Outcome Failure) |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

| Key Outcome | Endpoint/Outcome Determination | Case Report Form, Question Short Label (Response Option Picked to Determine Endpoint / Outcome Failure) |
|---|---|---|
| [redacted] | | |

| Key Outcome | Endpoint/Outcome Determination | Case Report Form, Question Short Label (Response Option Picked to Determine Endpoint / Outcome Failure) |
|---|---|---|
| | | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

| Key Outcome | Endpoint/Outcome Determination | Case Report Form, Question Short Label (Response Option Picked to Determine Endpoint / Outcome Failure) |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

[redacted]