ARISE: Evaluation of the GORE® Ascending Stent Graft in the Treatment of DeBakey Type I/II Aortic Dissection (TBE 14-02)

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Protocol Number: TBE 14-02

Amendment 7

15 Sept 2020

W. L. Gore & Associates, Inc.
Medical Products Division

PROTOCOL SUMMARY

Study Title	ARISE: Evaluation of the GORE® Ascending Stent Graft in the Treatment of DeBakey Type I/II Aortic Dissection
Protocol Number	TBE 14-02
IDE or PMA Number	G140230
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division Telephone: 800-437-8181
Study Design	Prospective, multicenter, non-randomized, single arm study
Study Objective	Assess the feasibility of the treatment of DeBakey Type I/II aortic dissections with the GORE® Ascending Stent Graft

Study Endpoints	Primary Endpoint:
	• All-cause mortality at 30 days post-procedure
	
	Secondary Endpoints:
	• Successful dissection treatment (technical success), to include:
	  ○ Successful access to the aorta (transfemoral or retroperitoneal)
	  ○ Successful delivery of all required device components to the aorta and/or branch vessel
	  ○ Successful deployment of all required device components in their intended location
	  ○ Successful retrieval of device delivery system
	  ○ Exclusion of the primary entry tear of the aortic dissection based on completion angiography
	  ○ Patent Side Branch Component (if used as part of primary procedure) based on completion angiography
	• Major Adverse Cardiovascular and Cerebrovascular Event (MACCE) assessed through 30 days, 6 months, and 12 months
	• Individual MACCE components through 30 days, 6 months, and 12 months
	• Aorta related mortality
	• Device migration assessed through 1 month, 6 months, and 12 months
	• Endoleak assessed through 1 month, 6 months, and 12 months

Subject Population	Subjects with DeBakey Type I/II aortic dissection allowing for treatment with the GORE® Ascending Stent Graft, including: • Primary entry tear must be in the ascending aorta and ≥2cm distal to the most distal coronary artery ostia

	• Ascending aorta compatible with the GORE® Ascending Stent Graft including landing zone true lumen diameter between 27mm – 42mm and total aortic landing zone diameter ≤ 45 mm
Number of Subjects	Up to 30 subjects
Number of Sites	Up to 9 sites in the U.S.
Significant Inclusion Criteria	• DeBakey Type I/II aortic dissection compatible with the treatment requirements of the GORE® Ascending Stent Graft, including: ○ Primary entry tear must be in the ascending aorta and ≥2cm distal to the most distal coronary artery ostia ○ Ascending aorta compatible with the GORE® Ascending Stent Graft including landing zone true lumen diameter between 27mm – 42mm and total aortic landing zone diameter ≤ 45 mm • Able to undergo CT scan per protocol requirements to perform required case planning prior to endovascular procedure • High surgical risk, as determined by the implanting physician • An Informed Consent Form signed by subject or legally authorized representative
Significant Exclusion Criteria	• Planned aortic valve repair or replacement or coronary artery intervention within 30 days • Presence of mechanical heart valve in the aortic position • Primary entry tear location in the aortic arch or descending thoracic aorta with retrograde flow into the ascending aorta • Aortic insufficiency grade 3+ or 4+ • Life expectancy <12 months due to associated non-cardiac co-morbid conditions
Expected Time to Complete Enrollment	• Subject accrual: 2 years • Follow-up: 5 years from last subject enrollment • Total study duration: 7 years
Schedule of Events	• Screening: Surgical Risk Assessment, Spiral CTA of chest, abdomen and pelvis (Retrospective cardiac-gated CTA Scan optional), Physical Exam, Serum Creatinine, SF-36® Questionnaire, Transthoracic Echocardiogram and Modified Rankin Scale • Procedure: Endovascular procedure with post-treatment Angiogram and Transesophageal Echocardiogram • Post-procedure: Transthoracic or Transesophageal Echocardiogram ≤ 2 hours after procedure end time

	• Discharge: Physical Exam, Transthoracic Echocardiogram and Modified Rankin Scale • 1 month and 6 months post-treatment: Retrospective cardiac-gated CTA Scan with ≥10 cardiac phases of chest, Physical Exam, SF-36® Questionnaire, Transthoracic Echocardiogram and Modified Rankin Scale • Modified Rankin Scale also completed at 90 days for subjects suspected of experiencing a stroke event through 30 days • 12 month post-treatment: Retrospective cardiac gated CTA Scan of chest, SF-36® Questionnaire, Transthoracic Echocardiogram and Physical Exam • 24, 36, 48, and 60 months post treatment: Spiral CTA of chest (Cardiac Resolved CT Scan optional), Physical Exam, and SF-36® Questionnaire

Statistical Analysis Plan

ARISE: Evaluation of the GORE® Ascending Stent Graft in the Treatment of DeBakey Type I/II Aortic Dissection

Study Acronym/Protocol #: TBE 14-02

Table of Contents

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the evaluation of the GORE® Ascending Stent Graft in the treatment of DeBakey Type I/II aortic dissections (TBE 14-02).

2.0 Study Design Overview

2.1 Objectives

2.1.1 Primary Objective(s)

1. To assess the feasibility of treating DeBakey Type I/II aortic dissections with the GORE® Ascending Stent Graft
2. Refine patient selection for future clinical investigations
3. To estimate boundary conditions in DeBakey Type I/II aortic dissection patients which can be used for subsequent device development efforts including:
    - Aortic compliance
    - Cardiac and respiratory motion

2.2 Design Summary

This study is a prospective, multicenter, non-randomized single-arm study to assess the feasibility of the treatment of DeBakey Type I/II aortic dissections with the GORE® Ascending Stent Graft Device.

A maximum of 9 Clinical Investigative Sites (referred to as “Sites” in the remainder of this document) in the United States will participate in this study. A total of 30 patients will be enrolled in this study.

Patients may be enrolled into the study provided all inclusion and no exclusion criteria are met as specified in Section 4 of the study Protocol.

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint is all cause mortality through 30 days post-procedure.

2.3.2 Secondary Endpoints

Secondary endpoints include the following:

- Successful dissection treatment (technical success), to include:
    - Successful access to the aorta (transfemoral or retroperitoneal)
    - Successful delivery of all required device components to the aorta and/or branch vessel
    - Successful deployment of all required device components in their intended location

- Successful retrieval of device delivery system
- Exclusion of the primary entry tear of the aortic dissection based on completion angiography
- Patent Side Branch Component (if used as part of primary procedure) based on completion angiography

- Major Adverse Cardiovascular and Cerebrovascular Event (MACCE) assessed through 30 days, 6 months, and 12 months.
- Individual MACCE components through 30 days, 6 months, and 12 months.
- Aorta-related mortality
- Device migration assessed at 1 month, 6 months, and 12 months
- Endoleak assessed at 1 month, 6 months, and 12 months

2.3.3 Endpoint Definitions

[redacted]

[redacted]

2.4 Statistical Hypotheses

No formal statistical tests will be performed. Data will be presented descriptively with confidence intervals.

2.5 Sample Size Assumptions

[redacted]

2.6 Sample Size Calculations

[redacted]

3.0 Study Treatment Arms

3.1 Test Arm

The test arm are those Subjects enrolled in this study for the treatment of DeBakey Type I/II aortic dissections (see Section 4 of the study Protocol).

3.2 Control Arm

There is no control arm in this study.

4.0 Study Data Collection

4.1 Data Collected

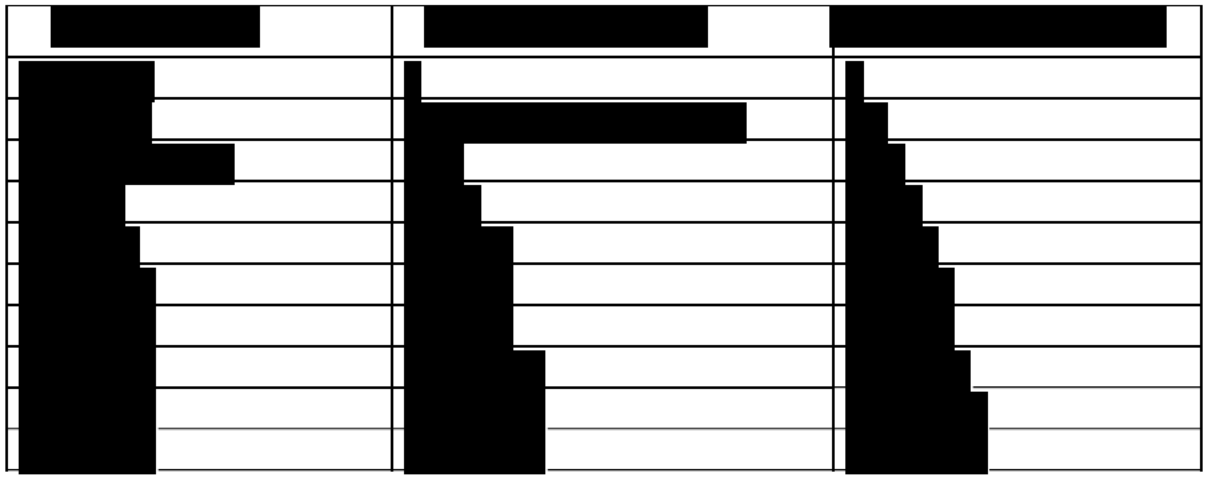
Data will be collected in Case Report Forms (CRFs) and include the following:

- Demographics
- Eligibility (Inclusion/Exclusion) Criteria
- Medical History
- Risk Assessment
- Subject Physical Evaluations and Vitals
- Modified Rankin Scale Assessments
- SF-36® Questionnaire
- Pre-Imaging Assessment
- Treatment Assessment
- Interval (Post) Imaging Assessments
- Device Accountability (Treatment and Post-Treatment)
- Planned Interventions
- Study Completion/Discontinuation/Compliance
- Adverse Events (AEs) and Treatments (including Reinterventions)
- Clinical Events Committee (CEC) Evaluations

4.2 Follow-up windows

[redacted]

[redacted]

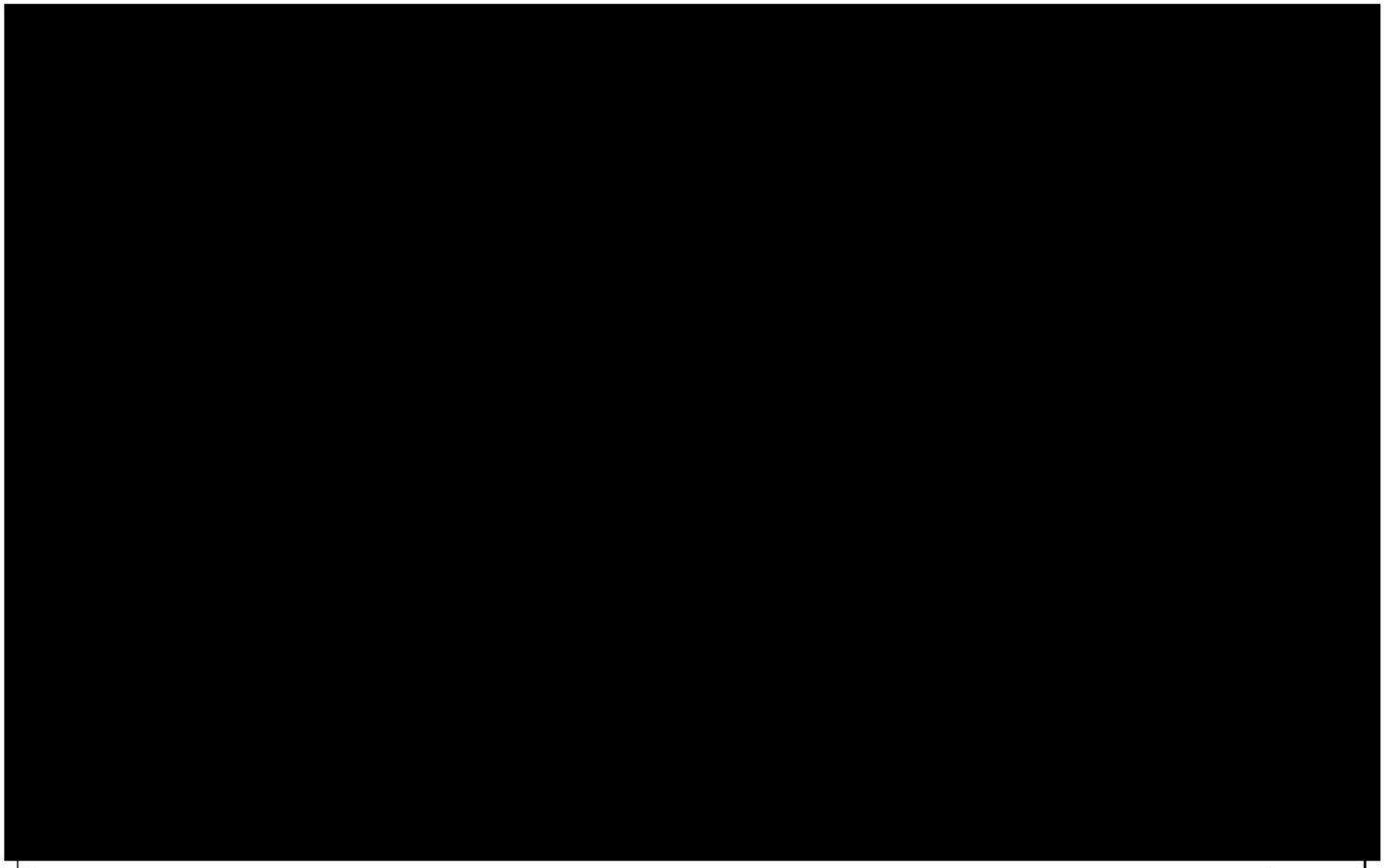


[redacted]

4.3 Schedule of Events

[redacted]

[redacted]



[redacted]

4.4 Data Safety Monitoring Board

See Section 9.3 of the study Protocol.

4.5 Clinical Events Committee

See Section 9.4 of the study Protocol.

4.6 Imaging

[redacted]

5.0 Statistical Analyses

5.1 Analysis Populations

All enrolled Subjects with an attempted initial procedure (have non-missing initial procedure date) will be included in analysis as follows:

- Primary Endpoint: all Subjects will be included; Subjects without known mortality status through 30-days will be considered failures for this (i.e. assumed dead for the primary endpoint analysis).
- Secondary Endpoint of technical success: all Subjects will be included; any Subject missing evaluation on this will be counted as a failure for this endpoint.
- Secondary Endpoint (MACCE, MACCE components, and aorta-related mortality): all Subjects will be included.
- Secondary Endpoints (device migration, endoleak): Subjects with known status (have had imaging done or endpoint event reported) at each follow-up window will be included; an endpoint event (endpoint failure) will be reported from a Site-reported adverse event. Subjects without imaging reported in a window but with an adverse event meeting the endpoint definition in a window will count as having an endpoint event for that window. Subjects without imaging reported in a window and with no endpoint event reported in window will not count towards the denominator for that window.

5.2 Timing of Analyses

Analysis of the study results will be ongoing throughout enrollment. Regular case review by the Data and Safety Monitoring Board (DSMB) and Sponsor will occur throughout enrollment.

DSMB data review will be instituted as follows:

- For the first four (4) Subjects, procedural reports will be provided to FDA and the DSMB Chairman within 5 working days of endovascular treatment and will include available procedural narratives, reports and any preliminary Adverse Events (AEs.
- Reporting Subject and device performance data to the DSMB following the endovascular treatment of every two (2) Subjects through patient 20 and every five (5) patients for patient 20-30, including the available 1 month follow-up visit data for preceding cohorts.

- Reports will include information on Subject baseline characteristics, deaths, and a summary of all serious adverse events such as paraplegia, paraparesis, stroke, and aortic rupture.
- Reports will also include observed device and/or procedure related adverse events such as deployment anomalies, branch lumen obstruction or occlusion, adverse events that result in secondary interventions for additional device implantation, and adverse events that result in conversion to open surgical repair.
- Reports provided to the DSMB will be submitted to the FDA as IDE supplements and a summary will be sent to each participating Site IRB.

The primary analysis will occur when enrollment is complete, and all available enrolled Subjects have completed the 1 month follow up assessment. A final DSMB review will be conducted when all enrolled Subjects have reached the 1 year follow-up window. Serial analyses of long-term results will occur during the follow-up period. No adjustments to the overall alpha level will be made since this is an exploratory study designed to evaluate basic feasibility.

5.3 Analyses Supporting Primary Objective(s)

Primary and secondary endpoint analyses will be summarized for main reporting efforts in order to support the study objective. Analysis populations will be as described in Section 5.1.

5.3.1 Primary Endpoint

[redacted]

5.3.2 Secondary Endpoint – Technical Success

[redacted] The individual components of technical success will also be summarized similarly. In addition, whether the primary technical success was assisted primary or secondary (see Endpoint Definitions Section 2.3.3) will also be summarized. All components of the technical success assessment and whether the technical success was assisted primary or secondary are asked in the treatment CRF.

5.3.3 Secondary Endpoint – MACCE

Kaplan Meier methodology will be used to estimate the overall MACCE event rate through the following specified time intervals: 30 days, 180 days (6 months), and 365 days (12 months). A Subject experiencing a MACCE event will have their time be equal to their earliest MACCE event onset; a Subject not experiencing a MACCE event will be censored at their last reported date of contact. This analysis will be performed for each MACCE component (see Endpoint Definitions Section 2.3.3) as well. Endpoint MACCE events will be death or CEC-adjudicated adverse events meeting the endpoint definitions (assessed on the CEC CRF). All possible adverse events that could meet the endpoint definition will be sent to the CEC for adjudication.

In addition to Kaplan Meier methodology, tables will be prepared with time intervals and the incident MACCE event rate will be reported in each time interval window. Denominators for the time windows will be the number of Subjects remaining in follow-up as of the beginning of the time interval window Time intervals for these tables will be as follows: 0 days, 1-30 days, 31-180 days, 181-365 days, 366-731, 732-1096, 1097-1461, 1462-1826.

5.3.4 Secondary Endpoint – Aorta-Related Mortality

The aorta-related mortality endpoint (see Endpoint Definitions Section 2.3.3) will be determined by CEC adjudication using a specific question asked on the CEC CRF.

For analysis of the aorta-related mortality endpoint, Kaplan Meier methodology will be used to estimate the aorta-related mortality rate through the following specified time intervals: 30 days, 180 days (6 months), and 365 days (12 months) and annually thereafter. Subjects without an aorta-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.

5.3.5 Secondary Endpoints – Device Migration and Endoleak

Tables (one for device migration and one for endoleak) will be prepared with time intervals and the incident event rate will be reported in each time interval window (using either the corresponding imaging date or adverse event onset date). Denominators for the time windows will be as specified in Section 5.1. An endpoint event (endpoint failure) will be reported from a Site-reported adverse event meeting the endpoint definitions. Time intervals for these tables will be the analysis windows shown in Table 1. In addition, endoleak rates will also be reported by endoleak type.

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 for each Subject. The denominator for each window will be calculated as the number of enrolled Subjects remaining in follow-up as of the beginning of the analysis window (Subjects must have an initial procedure date). At a minimum, separate summaries by AE relationship and severity will be prepared.

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

Selected AEs will be reviewed by the independent CEC and adjudicated with regard to device and/or procedure relationship and severity. Specific AEs of clinical interest in this Subject population will include, but are not limited to: death-related AEs, stroke, paraplegia/paraparesis, and MACCEs. Reported AEs which potentially meet the definition of AEs of clinical interest will be referred to the CEC for review and adjudication to the study Protocol's definitions provided for these events. The adjudicated opinion of the CEC will also be used in analysis and reporting of adverse event data.

5.4.1 Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the device or procedure. If the Site-reported primary relationship of the AE is any of the following it will be considered a (Site-reported) device and/or procedure related AE: related to device, related to procedure, or related to device and procedure.

Relationships include:

Related to device
The functioning or characteristics of the device caused or contributed to the AE.
Related to device and procedure
The device AND the endovascular procedure caused or significantly contributed to the AE.
Related to procedure
The endovascular procedure (and not the device) caused or significantly contributed to the AE.
Related to other procedure
Other procedure performed caused or significantly contributed to the AE.
Related to disease
Original (treated) disease caused or significantly contributed to the AE.
Not-related
An AE which cannot be attributed to the device or procedure.
Unknown relationship
The relationship of the AE to the device or procedure cannot be determined.

5.4.2 Adverse Event Classification

Each AE will be assessed by the Investigator to determine if it is serious or non-serious[3].

Serious Adverse Event
An SAE is an AE 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.

5.4.3 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 and the IRB, when applicable. The Investigator shall supply the Sponsor and IRB with any additional requested information. AE reporting for a Subject begins once the Subject is enrolled in the study through study completion/withdrawal.

The following information on each reported AE will be collected:

- AE Description
- AE Onset Date
- Primary Relationship
- Classification (Serious or Non-Serious)
- Action taken/Treatment required
- Outcome of Event
- Resolution Date

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

5.4.4 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 Additional Analyses

[redacted]

5.5.1 Sensitivity Analysis of Endpoint Results

[redacted]

5.5.2 Subgroup Analysis

[redacted]

5.5.3 Imaging Analysis

All imaging data will be Site-reported. The Sites will provide review of imaging data collected during the study at pre-treatment and follow-up.

[redacted]

[redacted]

[redacted]

5.5.4 Mortality

For analysis of all-cause mortality over time (i.e. at 1-year), 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.

5.5.5 Reintervention

The definition of a reintervention is outlined in the study Protocol. A reintervention procedure will be determined as occurring using CEC adjudication from a specific question asked on the CEC CRF. Planned interventions (entered into the Planned Intervention CRF) will not count as reinterventions.

[redacted]

5.5.6 Device Events

[redacted]

5.5.7 Site Data Pooling

Site data will be pooled based on clinical comparability, i.e., the study Sites followed a common protocol, the study was monitored to assure compliance with the protocol and applicable government regulations, and the data collection and handling procedures were the same across study Sites.

6.0 Interim Analyses and Safety Monitoring Analyses (if applicable)

Safety data will be periodically reviewed by the DSMB. A comprehensive summary of reported adverse events will be reviewed by the DSMB.

Analysis of the study results will be ongoing throughout enrollment. Serial analyses of long-term results will occur during the follow up period

7.0 Analysis Specifications

7.1 SAS Analysis Dataset Specifications

[redacted]

7.2 Statistical Output Specifications

[redacted]

7.3 Verification Level for Statistical Output

Levels of verification are defined in MD111325[4] and will be as follows for all regulatory output:

- All Analysis Datasets – Level I
- All Tables – Level I
- All Listings – Level II at a minimum

8.0 Data Sets, Tables, Figures, and Listings

At a minimum, the following set of Tables, Figures, and Listings will be produced.

8.1 Analysis Tables

8.2 Analysis Listings

8.3 Analysis Figures

9.0 References