Statistical Analysis Plan

Observational Registry Characterizing the Performance and Feature Use of the GORE® TAG® Conformable Thoracic Stent Graft featuring ACTIVE CONTROL System (TAG 15-03)

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the Observational Registry Characterizing the Performance and Feature Use of the GORE® TAG® Conformable Thoracic Stent Graft featuring ACTIVE CONTROL System. This SAP summarizes the analyses that will be performed to determine the safety and effectiveness of the GORE® TAG® Conformable Thoracic Stent Graft featuring ACTIVE CONTROL System (CTAG Device with ACTIVE CONTROL) when used for thoracic endovascular aortic repair. This SAP outlines tables, figures, and listings that are included in reports for the TAG 15-03 registry.

2.0 Study Design Overview

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the registry is to collect real-world clinical and device-specific outcomes of the CTAG Device with ACTIVE CONTROL in the treatment of aortic disease as part of routine clinical practice.

2.2 Design Summary

This registry is an observational, prospective, single-arm, post-market registry. A maximum of 20 clinical investigative sites (referred to as “sites” in the remainder of this document) in Europe will participate in this registry. Up to 125 patients, in total, will be enrolled in the registry. The anticipated accrual rate is approximately two patients per month per site for a total accrual period of approximately 12 – 18 months. The total estimated registry duration is 30 months. A maximum enrollment cap of forty (40) patients at any one site will be instituted to ensure that the registry is composed of multi-center data.

2.3 Study Endpoints

2.3.1 Primary Endpoints

2.3.1.1 Procedural technical success, [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.3.1.2 Treatment Success at the 30-day visit as defined as technical success and freedom from:

- [redacted]

2.3.2 Secondary Endpoints

2.3.2.1 Freedom from the following Major Adverse Events (MAEs) through 12 months, described individually at the 30-day and 12-month period. .

- [redacted]

2.3.2.2 Treatment Success at 12 months defined as technical success and freedom from:

- [redacted]

2.3.2.3 Freedom from the incidence of SAEs, other than MAEs, throughout the registry duration.

2.3.2.4 Measures of Pathology-Specific Remodeling:

[redacted]

Table 1: Event Definitions

Secondary Endpoints	**Lesion-related mortality**	All deaths during hospitalization for index endovascular procedure and within 30 days of the index endovascular procedure or secondary procedures due to the treated pathology, or the effectiveness of the endovascular repair (e.g., procedures to treat retrograde dissections, losses of patency, losses of device integrity, endoleaks, migrations, aortic expansions, aortic ruptures) and any deaths related to the treated pathology or endovascular graft (e.g., aneurysm rupture, retrograde dissection leading to fatal cardiac tamponade), unless evidence is available to demonstrate that the death is not lesion-related.
	Permanent Paraplegia	Paralysis secondary to spinal cord ischemia that is identified within 30 days of the index endovascular procedure and accompanied by a Spinal Cord Ischemia scale grade of "3" at the 30-day follow-up visit.
	Permanent Paraparesis	Partial paralysis secondary to spinal cord ischemia that is identified within 30 days of the index endovascular procedure and accompanied by a Spinal Cord Ischemia scale grade of "2" at the 30 day follow-up visit.
	Disabling Stroke	A stroke occurring within 30 days of the index endovascular procedure, combined with MRS ≥ 2 that is an increase from baseline of at least one grade at one month follow-up visit.
	Life-threatening Myocardial Infarction	Myocardial Infarction resulting in severe hemodynamic dysfunction necessitating resuscitation, cardiac arrest, or fatal outcome.
	New Onset Renal Failure Requiring Dialysis	New onset sustained renal failure identified within 30 days of the index endovascular procedure, combined with need / requirement for dialysis at the one month follow-up visit.
	Respiratory Failure*	Respiratory Failure resulting in prolonged intubation (>96 hours), tracheostomy, deterioration in pulmonary function, new onset O_2 dependence, or fatal outcome.
	Life-threatening Bowel Ischemia	Bowel Ischemia resulting in bowel resection or fatal outcome
	Serious Tissue Ischemia Secondary to a Thromboembolic Event	An ischemic event distal to the device implantation site caused by thromboembolic material and related to the device that is sufficiently debilitating to necessitate bypass, open surgical intervention, limb amputation or leading to death.
	Major Blood Loss	Estimated blood loss recorded during the endovascular procedure is >1000 mL

*Revised Standard - Standard described prolonged intubation as >48 hours. Adapted to compensate for the introduction and increasing use of branched and hybrid procedures in conjunction with a CTAG Device.

[redacted]

Table 2: Late Event Definitions

Late Secondary Endpoints	**Late Permanent Paraplegia**	Paraplegia secondary to spinal cord ischemia identified greater than 30 days after the index endovascular procedure combined with spinal cord ischemia scale grade = 3 at the subsequent visit.
	Late Permanent Paraparesis	Paraparesis secondary to spinal cord ischemia identified greater than 30 days after the index endovascular procedure, combined with spinal cord ischemia scale grade = 2 at the subsequent visit.
	Late Disabling Stroke	A stroke identified as having occurred greater than 30 days after the index endovascular procedure combined with MRS≥2 with an increase from baseline of at least one grade due to neurological deficits at the subsequent visit.
	Late New Onset Renal Failure Requiring Dialysis	New onset sustained renal failure identified greater than 30 days after the index endovascular procedure, combined with need / requirement for dialysis at the subsequent visit.

[redacted]

3.0 Study Treatment Arms

3.1 Test Arm

N/A

3.2 Control Arm

N/A

4.0 Study Data Collection

4.1 Study Data Collection Intervals and Windows

Patients' follow-up should be performed according to the site's standard of care, with a minimum of two follow-up visits, conducted at approximately 30 days and again at approximately 12 months following the initial procedure. For registry reporting, the follow-up visit windows are defined according to Table 3.

Table 3: Follow-Up Visit Windows

Follow-up Visit	Visit Window (days)
30 Days	15-59
Additional Routine Follow Up Visits	60-274
12 Months	275-455

Registry investigators may elect to employ a more intensive follow-up regimen that is part of their standard practice or tailored to the medical needs of his / her patient. Device evaluations conducted outside of the protocol-described follow-up visit windows are requested to be entered into the Electronic Data Capture (EDC) system. These interim evaluations may provide additional context to identified Adverse Events (AEs).

4.2 Clinical Events Committee

A Clinical Events Committee (CEC), who are independent of Gore and with relevant clinical expertise, will ensure consistent and accurate reporting for select AEs and all deaths. Candidate events for CEC adjudication will be identified using a systematic process for events that may contribute to a registry secondary endpoint, associated with death, or individually asked for adjudication by Gore.

Reported AEs which potentially meet a safety endpoint will be referred to the CEC for review and adjudication to the definitions provided for these events.

If there is a disagreement between the site and the CEC, the CEC adjudicated result will be reported.

4.3 Partial Dates

For some patients, full dates (day, month, and year) may not be known for all events. Rather than requiring full dates, this registry will allow partial dates to be entered. For analysis purposes, dates will be completed as to be the most conservative with regards to timing after the initial procedure date.

5.0 Statistical Analyses

5.1 Analysis Populations

All consecutive patients presenting with an indication for endovascular repair of the thoracic aorta, in accordance with applicable guidelines for endovascular interventions, are eligible for screening for participation in the registry.

Only patients who meet all of the inclusion criteria and none of the exclusion criteria may be enrolled. All patients enrolled with a non-missing initial procedure date will be eligible for inclusion in the analyses for primary and secondary objectives.

5.2 Timing of Analyses

The final analysis will be performed when all patients have completed their 12 month follow-up visit window or have been withdrawn from the registry. Analyses will be performed as needed for annual reports. Other interim analyses may be performed at the discretion of Gore.

5.3 Primary Endpoints

Procedural technical success [redacted]

Event status will be computed as follows:

[redacted]

Treatment Success at the 30-day visit

Event status will be computed as follows:

[redacted]

[redacted]

5.4 Secondary Endpoints

Freedom from the following Major Adverse Events (MAEs) through 12 months, described individually at the 30-day and 12-month period.

Event status will be computed as follows:

[redacted]

Treatment Success at 12 months

Event status will be computed as follows:

[redacted]

[redacted]

Freedom from the incidence of SAEs, other than MAEs, throughout the registry duration. This will be estimated through time-to-event analysis.

Event times will be computed as follows:

[redacted]

Measures of Pathology-Specific Remodeling:

[redacted]

Values measured within the 12 month follow-up window specified in Table 3 will be used in the calculations. If a patient has more than one measurement within the 12 month window, the last measurement will be used. Measurements outside the window will be excluded. Changes in dissection diameters may not be representative in the patients where the first post-implant CT scan is at the 30-day visit because most of the improvement likely occurs within the first 30 days. Dissection analyses will be performed with and without these patients.

5.5 Adverse Events

Adverse Events (AEs) are defined as any untoward medical occurrences in a patient whether device-related or not. For the purpose of this registry, all adverse events, regardless of seriousness or relationship, will be reported in accordance with applicable regulations, collected into the appropriate eCRF form, and documented in the patient's permanent medical record. The investigator at each site is ultimately responsible for reporting SAEs and device events to the sponsor.

The following information will be collected for each reportable event:

- Adverse Event Description
- Adverse Event Onset Date
- Relationship
- Classification
- Treatment
- Outcome
- Resolution Date

5.5.1 Adverse Events Classification

Each AE will be assessed by the investigator to determine if it is serious or non-serious, according to ISO 14155:2011. An SAE is defined as satisfying any of the following:

- led to death
- led to serious deterioration in the health of the patient 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

A planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered an SAE.

Any AE that does not meet the criteria for SAE is termed a non-serious adverse event.

5.5.2 Event Relationship

Each reported event will be assessed by the investigator for its primary suspected relationship, according to the following definitions:

- **Registry Device-related**

  The functioning or characteristics of the registry device caused or contributed to the event.
- **Registry Procedure-related**

  The procedure to implant the registry device (and not the registry device itself) caused or significantly contributed to the event.
- **Not-related**

An event which cannot be attributed to the registry device or procedure.

- **Unknown relationship**
  The relationship of the event to the registry device, procedure, or disease cannot be determined.

Event relationships initially reported as "Unknown" will need to be re-evaluated, when feasible, to foster a more definitive causality for event reporting and device attribution.

5.6 Poolability of Sites

Site data will be pooled based on clinical comparability. The registry sites will be monitored for compliance with registry protocol, including patient eligibility criteria, and will be audited for both compliance with the protocol and for data quality.

[redacted]

5.7 Handling of missing data

A worst-case analysis will be performed on the Treatment Success primary endpoint if patients are discontinued before the end of the 30-day visit window. These patients will be treated as treatment failures in this scenario.

5.8 Analysis of Primary Endpoints by Sex

The primary endpoint results will be examined by the subject's sex and tested for a difference in proportions using Fisher's Exact Test.

6.0 Interim Analyses and Safety Monitoring Analyses

The Clinical Events Committee (CEC) will periodically review select AEs and all deaths to ensure consistent and accurate reporting. The CEC will review and confirm identified events for causality and severity with an assessment on potential applicability to registry secondary endpoints. Analyses will be performed as needed for these review meetings.

7.0 Analysis Specifications

7.1 SAS Analysis Dataset Specifications

A specifications document is created for each analysis data set and contains, at a minimum:

- Variable Name
- Format
- Label
- Input Fields

7.2 Statistical Output Specifications

A specifications document is created for each statistical output (Table, Listing, or Figure) and contains, at a minimum:

- Title and footnote information
- Column headers
- General appearance of each cell (table, listing)
- If the spec includes a figure, either an example figure or a detailed description of the figure is included in this section
- Variables used in statistical output
- Change log section

7.3 Verification Level for Statistical Output

Define levels of verification (Level I, II, III per [redacted]) for statistical output.

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

8.0 Data Sets, Tables, Figures, and Listings

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

8.1 Analysis Tables

- Enrollment by Site
- Patient Demographics (Sex, Age)
- Patient Medical History (Transient Ischemic Attack, Carotid Disease, Coronary Artery Disease, Hypercholesterolemia, Hypertension, Congestive Heart Failure, Coronary Artery Bypass Graft, Chronic Obstructive Pulmonary Disease, Cigarette Smoking, Current Smoker, Diabetes Mellitus, Renal Insufficiency, Renal Dialysis, Peripheral Vascular Disease, Valvular Heart Disease, Cardiac Arrhythmia, Thromboembolic Event, Paraplegia, Paraparesis, Erectile Dysfunction, Cancer, Degenerative Connective Tissue Disease, AAA Repair, Ascending Aortic Arch Repair, Descending Aortic Arch Repair, Coarctation Repair, Type A Dissection Repair, Type B Dissection Repair, Traumatic Transection Repair, Penetrating Aortic Ulcer Repair, Other Aortic Repair, Stent Placement, ASA Risk Classification, NYHA Functional Classification,)
- Pathology
- Physical Exam (Height, Weight)
- Modified Rankin Scale
- Treatment (Procedure Time, Anesthesia Method, Adjunctive Technique, Access Success, Access Vessel, Endovascular Access Method, Blood Loss, Deployment Success, Unintentional Coverage of Major Aortic Branch Vessels, Aortic Device(s) Patent, Deployment System Successfully Removed)
- Hospitalization (Hospitalization Duration, Open Conversion Post Procedure, ICU Stay, ICU Hours)

- Devices Implanted (Number of Devices Implanted, Number of Devices Per Subject)
- Procedural Technical Success
- Procedural Technical Success by Sex
- Treatment Success
- Treatment Success by Sex
- Freedom from MAEs through 12 Months
- Treatment Success at 12 Months
- Kaplan-Meier of Freedom from SAEs
- Measures of Pathology-Specific Remodeling at 12 Months (Aneurysm/Isolated Lesion: Maximum Aortic Diameter; Dissection: Maximum Aortic Diameter, Minimum True Lumen Diameter, and Maximum False Lumen Diameter)
- Adverse Events by MedDRA SOC, HLT, PT and Follow-up Period
- Serious Adverse Events by MedDRA SOC, HLT, PT and Follow-up Period
- Completion/Discontinuation

8.2 Analysis Listings

- Deaths
- Conversions
- Major Adverse Events
- Serious Adverse Events

8.3 Analysis Figures

- Freedom from SAEs

9.0 References

9.1 [redacted] Clinical Affairs Biostatistics Analysis Specifications and Programming Procedure

9.2 [redacted] Development, Approval, Management and Retention of a Statistical Analysis Plan

9.3 Jordan WD, Rovin J, Moainie S, et al. Results of a prospective multicenter trial of CTAG thoracic endograft. Journal of Vascular Surgery 2015; 61(3):589-595.