“Real-World Data Collection of the GORE® when used as a Bridging Stent with Branched and Fenestrated Endografts in the Treatment of Aortic Aneurysms involving the Renal-Mesenteric Arteries”

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Real-World Data Collection of the GORE® [redacted] when used as a Bridging Stent with Branched and Fenestrated Endografts in the Treatment of Aortic Aneurysms involving the Renal-Mesenteric Arteries

Statistical Analysis Plan

Study Acronym / Protocol #: [redacted] 21-04

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the [redacted] 21-04 to confirm the clinical performance and safety of the GORE® [redacted] when used as a Bridging Stent with Branched and Fenestrated Endografts in the Treatment of Aortic Aneurysms involving the Renal-Mesenteric Arteries. This SAP summarizes the analyses that will be performed to confirm the safety and effectiveness of the GORE® [redacted] and outlines tables, figures, and listings that are included in reports for the [redacted] clinical study.

2.0 Study Design Overview

2.1 Objectives

Primary Objective(s)

The primary objective is to confirm the clinical performance of the GORE® [redacted] when used as a Bridging Stent with Branched and Fenestrated Endografts in the Treatment of Aortic Aneurysms Involving the Renal-Mesenteric Arteries.

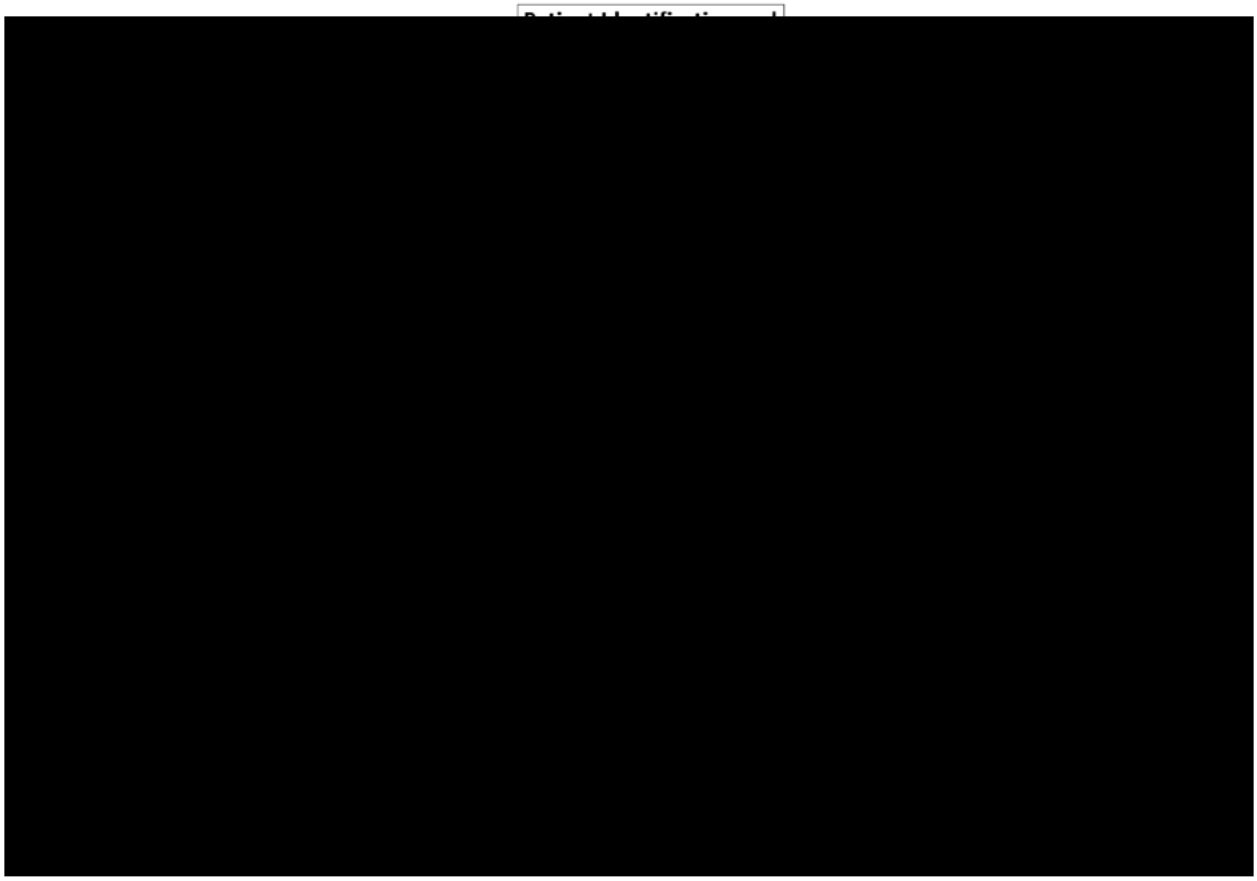
Secondary Objective(s)

The secondary objective is to confirm safety of the GORE® [redacted] when used as a Bridging Stent with Branched and Fenestrated Endografts in the Treatment of Aortic Aneurysms involving the Renal-Mesenteric Arteries.

Health Economic Data Analysis

A Health Economic analysis will be performed using clinical registry data. The objective of the Health Economic analysis is to understand the value of the treatment(s) studied during the period of the registry.

2.2 Design Summary



2.3 Study Endpoints

Primary Endpoint(s)

Primary Performance Outcome: Target vessel patency (patient level) at 12 months

Secondary Endpoint(s)

- Secondary performance outcomes:
- Reintervention (total and reintervention that can be attributed to branches originally treated with the [redacted] Stent Graft) at 12 months and annually through 5 years post-implant
- Target Vessel Technical Success
- Primary Technical Success (Total Endovascular Procedure)
- Target vessel instability at 12 months and annually through 5 years post-implant
- Target vessel patency, patient level, annually from 2-5 years post-implant (extended primary endpoint)
- Target vessel patency, vessel level analysis, annually from procedure to 5 years post-implant

Secondary safety outcomes

- Aneurysm-related mortality at 12 months and annually through 5 years post-implant
- MAEs at 30 days

Table 1. Protocol Definitions

Outcome	Definition per SVS reporting Standards
Technical Success Related Outcomes	
Target Vessel Technical Success	Successful catheterization and [redacted] Stent Graft placement in all intended target vessels. For this registry, technical success will be reported for the overall procedure and specifically for the vessels targeted for treatment with the [redacted] Stent Graft.
Primary Technical Success (Total Endovascular Procedure)	A modified technical success definition, requiring the following: 1. Successful side branch catheterization and placement of bridging stents with restoration and maintenance of flow in all intended target vessels 2. Patency dof all aortic modular stent graft components and intended side branch components 3. Absence of type I or type III endoleaks at completion angiography that extends beyond 30 days by confirmatory imaging (CTA, magnetic resonance angiography [MRA], or duplex ultrasound)
Vessel Patency Related Outcomes	
Primary Patency (Primary Endpoint)	Uninterrupted patency with no occlusion or procedure performed to maintain patency on the [redacted] Stent Graft or native target vessel. Interventions intended to treat endoleak or stent disconnection do not count as loss of primary patency.
Primary Assisted Patency	Endovascular intervention performed to maintain patency in the presence of a stenosis before occlusion
Secondary Patency	Endovascular restoration of patency after occlusion of the side branch, stent, or stent graft has already occurred. Conversion to bypass or inability to treat by endovascular means defines loss of secondary patency

Occlusion	Objective documentation by angiography, computed tomography, or ultrasound of complete stent occlusion with or without minimal flow into a targeted vessel
Stenosis	Objective documentation by angiography, computed tomography, or ultrasound of stenosis intra-stent or into a targeted vessel
Kink	Objective documentation by angiography, computed tomography, or ultrasound of kink in the stented or native segment of a targeted vessel
Other Outcomes	
Intraprocedural complications	Any vessel perforation, dissection, or occlusion during target vessel stenting
Reintervention	Any repeated vascular or nonvascular procedure related to the index procedure Reintervention will be adjudicated as major or minor based on the following Major: deployment of proximal or distal aortic or iliac extensions, removal of the device, use of thrombectomy or thrombolysis, and any major open surgical procedure. Minor: endovascular procedures (percutaneous transluminal angioplasty, atherectomy, stenting) without thrombectomy or thrombolysis, interventions to treat branch vessel stenosis, interventions to treat type II endoleak or branch-related endoleaks, and minor surgical revisions (patch angioplasty) of the access vessels. Each reintervention will be adjudicated as related to a [redacted] treated branch vessel component, related to a non-treated branch vessel component, or related to main body component(s), if possible.
Target vessel instability	Death or rupture related to side branch complication (e.g., endoleak) or reintervention to treat a branch-related complication, including endoleak, disconnection, kink, stenosis, occlusion, or rupture
Aneurysm-related mortality	Any death that occurs within the first 30 days or any death that results from aneurysm rupture, aorta-related complications (eg, infection, occlusion, dissection, hematoma), or a complication of a secondary intervention

Major Adverse Events (MAEs)	• All-cause mortality • Myocardial infarction (MI): MI resulting in severe hemodynamic dysfunction necessitating resuscitation, cardiac arrest, or fatal outcome. • Respiratory failure requiring prolonged (>24 hours from anticipated) mechanical ventilation or reintubation • Any renal function deterioration according to the RIFLE classification system. • Bowel ischemia requiring surgical resection or not resolving with medical therapy Permanent paraplegia (any grade 3 A-C spinal cord injury) in a patient who is no ambulatory. Any major stroke defined according to National Institutes of Health Stroke Scale (NIHSS) or equivalent.

2.4 Statistical Hypotheses

The registry is designed to statistically test the hypothesis that the Target Vessel Patency at 12 months (Primary Performance Endpoint) in both FEVAR and BEVAR populations of subjects is greater than 77%. The hypothesis will be tested separately in the two cohorts (FEVAR and BEVAR), using the subjects with imaging results available for the 12 months visit. The binomial exact test will be used with a one-sided 2.5% level of significance to test the null hypothesis.

The statistical hypothesis is specified as follows:

H0: P ≤77%

HA: P > 77%

Alpha= 0.025 (one-sided)

Whereas P is the probability of maintaining Target Vessel Patency at 12 months.

The ITT population will be used to perform this test.

[redacted]

2.5 Sample Size Assumptions

The assumptions used for the calculation of sample size in the registry included the anticipated performance of the [redacted] Stent Graft for the FEVAR and BEVAR procedures, the acceptance criteria determined from the literature and the derived Performance Goal (PG). [redacted]

[redacted]

2.6 Sample Size Calculations

[redacted]

3.0 Study Treatment Arms

3.1 Test Arm

Not Applicable for the observational registry

3.2 Control Arm(s)

Not Applicable for the observational registry

4.0 Study Data Collection

The validated Clinical Data Management System (CDMS) for this registry will be provided by Medrio. The sponsor keeps a separate Clinical Data Management Plan (CMMP) describing the procedures for verification, validation, and security of the CDMS. The CDMP will describe and document procedures regarding data management processes for this registry.

Once entered, data will be evaluated to confirm that it is complete, consistent, and logically sound. If changes to the data in the CDMS are required, all changes, reasons for changes, and persons making the changes will be captured in the CDMS's audit trail. Sponsor will perform periodic data reviews throughout the entire registry. Procedures and documentation for regular and ongoing data review are described in the Clinical Data Management Plan.

All registry data are targeted to be entered into the appropriate eCRF within 10 days of enrollment for the retrospective phase and within 10 days of collection for the prospective phase, however, data outside this window will not be considered a protocol deviation. Pre-Screening information will be recorded for all subjects and will only consist in inclusion /exclusion criteria evaluation, and enrollment information. All subsequent data entry will only occur after collection of inform consent to participate in the registry.

- Data Safety Monitoring Board (if applicable)
  Not applicable due to the observation study design
- Clinical Events Committee

An independent Clinical Events Committee (CEC) will review endpoint related clinical events during the registry to ensure the consistency of endpoints reported by the site. The [redacted] 21-04 CEC will be comprised of an interdisciplinary team of three members with pertinent expertise who are not directly involved in the conduct of the registry.

CEC will be managed by [redacted] to ensure the independency of the members from the sponsor. Sponsor will not take part of any CEC activities and may only deliver initial training to the CEC members on the protocol and registry device.

After review, the CEC will inform [redacted] whether or not additional data is required to evaluate any specific event, whether or not clarifications are needed.

Site may need to send anonymized source documentation to CRO related to the events that need to be adjudicated by CEC. This committee will operate under pre-specified procedures as outlined in its charter. The frequency of data review and other roles and responsibilities of the committee will be

- Site Enrollment Restrictions (if applicable)

  Up to 15 sites in Europe will be required to enroll a minimum of 220 patients that have had treatment with GORE® [redacted]® [redacted] when used as a Bridging Stent with Branched and Fenestrated Endografts in the Treatment of Aortic Aneurysms Involving the Renal-Mesenteric Arteries.

  Each site cannot contribute to more than 10% of the total patient for each cohort without sponsor approval, with a maximum of 20% of total enrollment for a single site.

- Core lab (if applicable)

  The Core Lab will perform assessments of imaging modalities according to objective process and standard procedures completed by trained and qualified personnel.

  Medical imagery will be transmitted to the Core Lab using the secure, web portal functionality of the [redacted] System. Imaging submitted through the portal will be stripped of personal health information and replaced with appropriate registry subject identifiers in automated, systemic fashion. Recipients will process received imaging according to their standard operating procedures or registry-specific processes. Completed assessments and measurements will be reported directly in the EDC system and this data is considered source data.

- Handling of missing dates
  All effort will be made to minimize the missing data, however, the data not available will be treated as missing in the study and the analysis will be conducted on the available data.

5.0 Statistical Analyses

Analysis Populations

- The registry population will consist of patients that have had treatment with GORE® [redacted]® [redacted] and that meet the registry eligibility criteria.

[redacted]

Timing of Analyses

The analysis to test the primary hypothesis will be conducted once all subjects have completed their 12 Month follow-up, data has been entered and cleaned in the EDC system. Subjects with a visit within 90 days of the annual time frames (i.e.., 275 – 455 for 12 Month visit) would be considered for analysis of the annual outcomes. In case of the multiple visits within the interval, the visit closest to and preceding the annual time point would be considered for the determination of the outcomes. [redacted] The subject follow-up will continue for five years, and the final analysis will be done once all subjects have completed five-year follow-up. [redacted] No interim analysis for the early termination of registry is planned due to the post marketing usage of the [redacted] Stent Graft and retrospective nature of the enrollment. In addition, once the primary analysis has been performed and hypothesis tested, further analyses may also be performed as needed for annual reports, presentations and publications based on interim data or at any other time at the discretion of Gore.

Analysis Populations

Intent-to-Treat (ITT) dataset will consist of all enrolled patients meeting the inclusion / exclusion criteria and treated at least one vessel with the [redacted] Stent Graft. A subset of the ITT dataset will be further identified of subjects with all vessels treated with [redacted] and another subset with all vessels treated with [redacted] only. ITT dataset will be used for the analysis of the primary and secondary endpoints. Similarly, per vessel analysis will be performed with all three datasets after identifying each vessel treated by [redacted] and also of the vessels treated without [redacted]

Pooling of Data

All sites in the registry will follow a common protocol and the data will be monitored to assure compliance. The data collection and handling procedures will be the same at all registry Sites. As such, there is no concern in pooling data from different sites together for analysis. [redacted]

Statistical Analysis of Primary Endpoint(s)

Analysis of the Primary Endpoint to test the hypothesis will be performed using binomial exact test using one-sided 2.5% level of significance.

All subjects with follow-up visit and imaging results available from 9 to 15 months will be included in the primary analysis. Subjects with the loss of Target Vessel Patency earlier than 15 months will also be included in such analysis and considered as failures regardless of the timing and availability of another visit between 9 to 15 months. [redacted]

Statistical Analysis of Secondary Endpoint(s)

[redacted]

6.0 Interim Analyses and Safety Monitoring Analyses (if applicable)

No interim analysis is planned for early termination of the registry due to the retrospective study design.

7.0 Analysis Specifications

7.1 [redacted]

8.0 [redacted]

9.0 References

[redacted] Clinical Affairs Definitions List

[redacted] Clinical Affairs Biostatistics Analysis Specifications and Programming Procedure

[redacted] Work Instructions for Analysis Data Set

[redacted] Analysis Data Set (ADS) Template

[redacted] Table Specification Template

[redacted] Listing Specification Template

10.0 Revision History

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]