COVER PAGE

Study Title: Retrospective Post-Market Clinical Follow-Up Study of [redacted] Vascular Graft in Peripheral Artery Disease, Aortic Aneurysms and Dialysis Access.

Document Date: 07 Jan 2022

NCT number: **NCT05124184**

Retrospective Post-Market Clinical Follow-Up Study of [redacted] Vascular Graft in Peripheral Artery Disease, Aortic Aneurysms and Dialysis Access.

Statistical Analysis Plan

Study Acronym / Protocol #: VGP 21-01

Table of Contents

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the VGP 21-01 to confirm the clinical performance and safety of [redacted] Vascular Graft throughout the device functional lifetime for each indication area. This SAP summarizes the analyses that will be performed to confirm the safety and effectiveness of the [redacted] Vascular Graft and outlines tables, figures, and listings that are included in reports for the VGP 21-01 clinical study.

2.0 Study Design Overview

2.1 Primary Objective(s)

The primary objective is to confirm the clinical performance and safety of [redacted] Vascular Grafts throughout the device functional lifetime for each indication area; peripheral artery disease (PAD), aortic aneurysms, and dialysis access. Cohorts including PAD, aortic aneurysm, and dialysis access represent applicable patient populations for these disease states. Appropriate sample sizes were calculated per cohort based on safety and performance acceptance criteria as part of the clinical evaluation process under European Medical Device Regulation (MDR). Statistical justifications were based on anticipated outcomes, and sample sizes were planned to estimate the same outcomes with determined level of accuracy.

2.2 Design Summary

This study utilizes a retrospective, multicenter, single-arm design. A single arm design was chosen as the registry is intended only to add to existing data and literature on the study populations and devices. A retrospective registry was determined to be an appropriate design for post-market clinical data collection based on consistency of device design, procedures, clinical results available in literature, and operative techniques. Up to 9 sites in Europe will be required to enroll 353 patients that have had treatment with [redacted] Vascular Grafts in the following indication areas:

- 144 patients in PAD Cohort
  - 72 Patients with any [redacted]
  - 72 Patients with [redacted]
- [redacted]65 patients in Aortic Aneurysm Cohort with [redacted]
- 144 patients in Dialysis Access Cohort
  - 72 patients implanted with any [redacted]
  - 72 Patients implanted with Patients with [redacted]

Each site is capped to enroll no more than 25% of the total patient for each cohort without sponsor approval, with a maximum of 50% of total enrollment for a single site. Subjects' medical records will be reviewed by the investigator and specific data will be collected retrospectively for up to 5 years of follow-up from the index procedure for subjects in the PAD and aortic aneurysm cohorts and up to 2 years for subjects in the dialysis access cohort.

2.3 Study Endpoints

2.4 Primary Endpoint(s)

- Peripheral Artery Disease Cohort

  Primary Safety Outcome: Device-related seroma or infection through 5 years

  Primary Performance Outcome: Secondary patency (revascularization) through 5 years

- Aortic Aneurysm Cohort

  Primary Safety Outcome: Survival through 5 years

  Primary Performance Outcome: Primary patency through 5 years

- Dialysis Access Cohort

  Primary Safety Outcome: Device-related infection through 2 years

  Primary Performance Outcome: Useable access circuit (reported as secondary patency) through 2 years

2.4.1 Secondary Endpoint(s)

- Peripheral Artery Disease Cohort
  Limb Salvage through 1 year
  Amputation-free survival through 1 year
  Device-related Adverse Events through 1 year
  Device-related infection requiring reoperation through 5 years
  Primary Patency through 1 year
- Dialysis Access Cohort
  Primary patency through 1 year
  Device-related adverse events through 1 year
- No secondary endpoints have been identified for the Aortic Aneurysm Cohort.

Table 1. Protocol Definitions

Outcome	Definition
Primary Patency	
Aortic Aneurysm / PAD Cohort	Patency of the study graft without additional or secondary surgical or endovascular procedures to maintain or restore flow to the graft. The only exceptions that do not disqualify the graft for primary patency are procedures performed for disease beyond the graft and its two anastomoses.
Dialysis Access Cohort	Interval following intervention until the next access thrombosis or repeated intervention.
Secondary Patency	
Aortic Aneurysm / PAD Cohort	Patency of the study graft with additional or secondary surgical or endovascular procedures to restore flow to the graft after occlusion or stenosis of the graft or its anastomoses

	The only exceptions that do not disqualify the graft for secondary patency are procedures performed for disease beyond the graft and its two anastomoses
Dialysis Access Cohort	Patency of the study graft from the time of access creation or placement until access abandonment
Limb Salvage	Freedom from an amputation above the level of the ankle of the index limb
Amputation Free survival	Freedom from an amputation above the level of the ankle of the index limb or all cause death
Device-related seroma or infection *PAD Cohort*	Clinical evidence of an infectious process in the direct vicinity of the access site or distal to the treated vascular site or seroma classified by the registry investigator as primarily related to the registry device
Device-related infection requiring reoperation *PAD Cohort*	Clinical evidence of an infectious process in the direct vicinity of the access site or distal to the treated vascular site classified by the registry investigator as primarily related to the registry device and required surgical intervention
Device-related infection *Dialysis Access Cohort*	Clinical evidence of an infectious process in the direct vicinity of the access site classified by the study investigator as primarily related to the study device
Survival	All Cause survival
Device-related Adverse Events	Any untoward medical occurrence classified by the registry investigator as primarily related to the registry device

2.5 Statistical Hypotheses

No formal statistical hypothesis is planned for testing in the study. Separate primary and secondary outcomes will be measured along with 95% confidence intervals for each cohort using Exact Binomial method. The analysis of the primary endpoint will be descriptive in nature.

2.6 Sample Size Assumptions

The sample size for the study is estimated using the desired width of the 95% confidence interval. It is assumed that for PAD and Dialysis cohorts, if the estimated percentage of the primary outcome is around 55%, the half-width of the confidence interval would be 12%. Similarly, for the Aortic Aneurysms, considering the primary outcome to be around 32%, the sample size of 65 subjects would allow the half-width of the confidence interval to be lower than 12%.

2.7 Sample Size Calculations

The sample is calculated assuming the Binomial Exact 95% confidence interval would be constructed for the primary outcomes using the above assumptions. The subjects for which the primary outcomes cannot be determined will be considered missing in the analysis. The sample size determined by cohort is as follows:

Table 2. Sample sizes

Cohort	Endpoint Used for Sample Size Calculation, Assumed Rate	Sample Size
PAD	≥ 56% Secondary patency (revascularization) at 5 years	72 Patients (per device)
Aortic Aneurysm	≥ 33% survival at 5 years	65 Patients
Dialysis Access	≥ 55% secondary patency through 2 years	72 Patients (per device)

3.0 Study Treatment Arms

Test Arm

Not applicable for registry

Control Arm(s)

Not applicable for registry

4.0 Study Data Collection

The chart reviews will be conducted by the investigator or a trained study coordinator at each site. Records from all patients who underwent treatment [redacted] Vascular Grafts for PAD, aortic aneurysms, or dialysis access will be identified for further screening according the inclusion and exclusion criteria. The subjects meeting all of the inclusion criteria and none of the exclusion criteria will be considered for data collection.

The following clinical routine data will be recorded in the registry database from the existing medical records of enrolled subjects.

- Subject information and Demographics (Age and sex)
- Medical History
- Index procedure information
- Discharge information
- Follow-up data, including (antiplatelet and anticoagulant therapy) and imaging reports (no imaging will be collected)
- Adverse events
- Device Deficiency
- Repeat Intervention
- Death or discontinuation

Repeat Interventions

Reinterventions may have been performed at the discretion of the investigator to treat AEs or maintain device performance. Any reinterventions performed will be documented on the appropriate CRF form. The components used as part of the reintervention, the date of the reintervention, procedural data and any AEs leading to reintervention will also be documented on the CRF form.

Follow Up

No on-site follow-up is required after the subject is included in the registry, as the registry consists of retrospective data collection only. Follow-up data will be collected from the information already present in the medical chart for at least 5 years from the index procedure for the PAD and aortic aneurysm cohort and at least to 2 years for the dialysis access cohort. This data should include any adverse events, repeat interventions, and records of office, telephone, or imaging visits. No imaging will be collected for this registry. In case the site recognized that the enrolled subject does not have data available regarding the last FU visit specified in the protocol, site should enter the next follow up data available (i.e. if a patient did not come in at year 5, but came in at year 6, year 6 data should be entered). If no follow up visit data is available, site staff should collect and document any past safety data (SAE, re-intervention, hospitalization, death, etc.) through the end of the follow up period specified for the cohort. If consent is waived, the site should contact relatives or general practitioner by phone to collect this data.

Subject Withdrawal from the Registry

Subjects who are alive at the time of their enrollment in the registry can withdraw from the registry without indicating any reasons at any time. No additional data will be collected and reported into the registry database after consent withdrawal. The sponsor may retain and continue to use any data collected before the withdrawal of consent, if not explicitly requested otherwise by the subject.

A replacement subject may be enrolled in the rare event that a subject decides to withdraw from the registry before all follow-up visits have been recorded in the EDC.

Subject Lost to Follow Up

No subject lost to follow up are expected in this registry. According to General Exclusion criterion #1, subjects with no follow-up after treatment should not be included in the registry. All subjects that complete at least one follow-up after treatment will be enrolled.

Subject Registry Completion

A subject has completed the registry when all expected follow-up visits have been completed and properly recorded in the EDC. Any subject who does not complete these requirements due to voluntary withdrawal, physician withdrawal, death, or any other reason will be considered a withdrawal.

Subject Discontinuation

Subjects will be discontinued from the registry in case of the explant of the device or, for subjects enrolled in the AV access cohort, renal transplantation.

Explant Procedures

Not applicable due to the retrospective data collection.

4.1 Clinical Event Committee

Not applicable due to the retrospective data collection.

5.0 Statistical Analyses

No formal statistical hypothesis is planned for testing in the study. Separate primary and secondary outcomes will be measured along with two-sided 95% confidence intervals separately for each cohort using Exact Binomial method.

i. Timing of Analyses

Separate analysis will be performed for each of the PAD, Aortic Aneurysms and Dialysis Access cohorts once all data has been entered and cleaned in the EDC. Analyses at any other time may be performed at the discretion of Gore. There are no planned interim analyses or guidelines for early termination due to the retrospective and exploratory nature of the study.

ii. Analysis Populations

This study consists of five different analyses populations, defined by indication/disease type and device used. Separate analysis will be performed for each patient population.

a. PAD patients treated with any [redacted]
b. PAD patients treated with [redacted]
c. Aortic Aneurysm patients treated with any [redacted]
d. Dialysis Access patients treated with any [redacted]
e. Dialysis Access patients treated with any [redacted]

iii. Pooling of Data

Clinical use is not expected to differ significantly between study sites. As such, there is no anticipated concern in pooling the data from different sites for analysis. However, separate analysis will be performed to show the consistency of safety and effectiveness by gender and age for the primary outcomes.

i) Statistical Analysis of Primary Endpoint(s)

Analysis for the primary endpoints will be presented with confidence intervals. Subjects with missing information on the primary outcomes will not be included in the analysis for the primary endpoint.

ii) Statistical Analysis of Secondary Endpoint(s)

Analysis for the secondary endpoints will be presented with confidence intervals. Subjects with missing information on these outcomes will not be included in the analysis.

6.0 Interim Analyses and Safety Monitoring Analyses (if applicable)

There are no planned interim analyses or conditions for early termination / registry stoppage due to retrospective study design.

7.0 Analysis Specifications

SAS Analysis Dataset Specifications

- A specifications document is created following the template defined in MD146539 Work Instructions for Analysis Data Set (ADS) and MD146540 Analysis Data Set (ADS) Template for each analysis data set with at least the following details:
- Variable name
- Format
- Label
- Input variables and derivation rules

Statistical Output Specifications

- A specifications document is created in accordance with the corresponding template that contains at least the following details:
- Title and footnote
- Column headers
- Row labels for tables
- Cell formats
- Datasets and variables used with derivation details
- Revision history

Verification Level for Statistical Output

- 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 list of the minimal planned statistical outputs, including tables, listings and figures which are to be created for the regulatory reports defined in the protocol. A different selection of tables, listings, and figures can be created for all other reporting efforts (Annual Reports etc.) as deemed necessary.

8.1 Analysis Tables

- Summary of Subject Demographics by cohort
- Summary of Medical History by cohort
- Summary of concomitant medication by cohort
- Summary of procedural details and assessments by cohort
- Summary of discharge details by cohort
- Summary of the devices used by cohort
- Summary of follow-up, subject availability by visit with counts and percentages.
- Kaplan-Meier estimate of the Device-related seroma or infection through 5 years in the PAD cohort
- Kaplan-Meier estimate of the Secondary Patency (revascularization) through 5 years in the PAD cohort
- Kaplan-Meier estimate of Survival through 5 years in the AA cohort
- Kaplan-Meier estimate of the Primary Patency through 5 years in the AA cohort
- Kaplan-Meier estimate of the Device-related infection through 2 years in the DA cohort
- Kaplan-Meier estimate of the Useable access circuit(reported as secondary patency) through 2 years in the DA cohort
- Kaplan-Meier estimate of the Limb Salvage through 1 year in the PAD cohort
- Kaplan-Meier estimate of the Amputation-free survival through 1 year in the PAD cohort
- Kaplan-Meier estimate of the Device-related Adverse Events through 1 year in the PAD cohort
- Kaplan-Meier estimate of the Device-related infection requiring reoperation through 5 year in the PAD cohort
- Kaplan-Meier estimate of the Primary Patency through 1 year in the PAD cohort

- Kaplan-Meier estimate of the Device-related Adverse Events through 1 year in the DA cohort
- Kaplan-Meier estimate of the Primary Patency through 1 year in the DA cohort
- Summary of the Device-related SAEs by cohort
- Summary of the Device-related death by cohort
- Summary of the procedure-related death by cohort
- Summary of the procedure-related SAE by cohort
- Summary of Repeat Interventions by cohort
- Summary of Freedom from Limb Salvage by cohort
- Summary of Device or Procedure Related Serious Adverse Events by cohort
- Summary of Adverse Events by MedDRA SOC, HLT, PT and Follow-up Interval (Number of Subjects, Number of Subjects with AEs, Number of AEs, at Procedure) by cohort
- Summary of Serious Adverse Events by MedDRA SOC, HLT, PT and Follow-up Interval (Number of Subjects, Number of Subjects with AEs, Number of AEs) by cohort
-

8.2 Analysis Listings

- Listing of Completion/Discontinuation Details
- Listing of Adverse Events
- Listing of Deaths

9.0 References

MD7929 Clinical Affairs Definitions List

MD111325 Clinical Affairs Biostatistics Analysis Specifications and Programming Procedure

MD146539 Work Instructions for Analysis Data Set

MD146540 Analysis Data Set (ADS) Template

MD146541 Table Specification Template

MD146542 Listing Specification Template