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Post-market study: Evaluation of the GORE® VIABAHN® Endoprosthesis for the treatment of Popliteal Artery Aneurysm

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Medical Products Division

Statistical Analysis Plan

Study Acronym/Protocol #: FPR 14-03/Protocol #1

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of FPR 14-03. This SAP summarizes the analyses that will be performed to determine the safety and effectiveness of the GORE® VIABAHN® Endoprosthesis when used for the treatment of subjects with Popliteal Artery Aneurysms. This SAP outlines tables, figures, and listings that are included in reports for the FPR 14-03 clinical study.

2.0 Study Design Overview

2.1 Objectives

2.1.1 Primary Objectives

The primary objectives of the GORE® VIABAHN® Endoprosthesis Popliteal Artery Aneurysm study are to document the safety and performance of the GORE® VIABAHN® Endoprosthesis for the treatment of PAAs at 12 months.

2.1.2 Secondary Objectives

The secondary objectives of the GORE® VIABAHN® Endoprosthesis Popliteal Artery Aneurysm study are to document long-term (through 36 months) safety and performance by evaluating freedom from limb loss, length of hospital stay after study procedure, length of study procedure, serious adverse events (SAEs), device or procedure related adverse events (AEs), technical success, primary patency, primary assisted patency, secondary patency and freedom repeat intervention. In addition, listings of device migration, endoleak, device fracture, and study limb amputation will be reported separately.

2.2 Design Summary

This is a retrospective, multicenter, non-randomized single-arm clinical study with a prospective follow-up to evaluate the safety and performance of the GORE® VIABAHN® Endoprosthesis for the treatment of patients with PAAs. All patients will have received the GORE® VIABAHN® Endoprosthesis for treatment of a PAA since September 15, 2012 (date at which reimbursement for the GORE®VIABAHN® device was received in France). Inclusion for all patients will be retrospective, follow-up visit(s) can be prospective.

A maximum of 10 Clinical Investigative Sites (referred to as “Sites” in the remainder of this document) in France will participate in this study. 50 patients with an adequate follow-up to assess primary endpoints will be enrolled. All patients will have received the GORE® VIABAHN® Endoprosthesis for treatment of a PAA since 15 September 2012 and meet all of the inclusion and none of the exclusion criteria as specified in Sections 4.2 and 4.3 of this protocol.

Data entry will be monitored and enrollment will be stopped when 50 subjects have data for the 12 months follow-up visit entered.

Patients with bilateral PAAs treated with GORE® VIABAHN® Endoprosthesis at different dates can be enrolled in the study. The first limb enrolled will be considered the study limb. Patients with both limbs treated within the same procedure will not be enrolled in the study.

Follow-up examinations through 12 months (+/- 3 months) post-implant will be collected for the primary endpoint analysis. This will include clinical assessment, imaging-based

evaluations, SAEs, device, and procedure related AEs. Patients will be further followed through 24 and 36 months post-procedure.

2.3 Study Endpoints

2.3.1 Primary Endpoints

2.3.1.1 Primary Patency at 12 Months

The primary performance endpoint for this trial is primary patency at 12 months. Primary patency is defined as blood flow without occlusion maintained through the device after implant without an intervention.

2.3.1.2 Primary Safety

The primary safety endpoint for this trial are serious adverse events and adverse events related to the study procedure or the study device at 12 months. An adverse event is any untoward medical occurrences, unintended disease or injury or any untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons related to the investigational medical device or procedure. For this study, only device or procedure related adverse events need to be reported. A serious adverse event is an adverse event that led to death or lead to serious deterioration in the health of the subject that resulted in a life threatening illness or injury, or a permanent impairment of a body structure of body function, or in-patient or prolonged hospitalization, or a medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function.

2.3.2 Secondary Endpoints

2.3.2.1 Technical Success

Technical success is defined as successful aneurysmal exclusion using the GORE® VIABAHN® Endoprosthesis at time of the procedure without Type I or III endoleaks that require post-procedure intervention within 30 days.

2.3.2.2 Freedom from limb loss on the study limb

Limb loss is defined as an amputation on the study limb above the metatarsals. Freedom from limb loss on the study limb at 12, 24, and 36 months after implant will be estimated by time-to-event analysis.

2.3.2.3 Freedom from repeat intervention

Re-intervention is defined as an endovascular or surgical procedure performed to treat a stenosis or occlusion within the study device(s) or within 5 mm of the proximal or distal edge of the device(s), treatment of endoleaks or other reasons. Freedom from repeat intervention at 12, 24, and 36 months after implant will be estimated by time-to-event analysis.

2.3.2.4 Length of procedural hospital stay

The length of hospital stay is defined as the number of days the subject remains in the hospital due to endovascular repair of a PAA with VIABAHN (“index procedure”).

2.3.2.5 Length of procedure

The length of the procedure is defined as the number of minutes the subject remains in the operating room or catheterization laboratory due to endovascular repair of a PAA. If no specific information is available the first and last angiographic timestamp can be used to capture the length of the procedure.

2.3.2.6 Serious adverse events and adverse events related to the study procedure or study device at 24 and 36 months

2.3.2.7 Primary patency at 24 and 36 months

Primary patency at 12, 24, and 36 months after implant will be estimated by time-to-event analysis.

2.3.2.8 Primary assisted patency

Primary assisted patency is defined as blood flow maintained through the device after implant regardless of re-interventions performed (without occlusion). Primary assisted patency at 12, 24, and 36 months after implant will be estimated by time-to-event analysis.

2.3.2.9 Secondary patency

Secondary patency is defined as blood flow through the device regardless of re-interventions performed (with or without occlusion) and freedom from surgical bypass. Secondary patency at 12, 24, and 36 months after implant will be estimated by time-to-event analysis.

[redacted]

2.5 Sample Size Assumptions

From 18 clinical studies evaluating the GORE® VIABAHN® Endoprosthesis for treatment of PAAs, the one year primary patency ranged from 79 to 100%. Previous literature on ePTFE surgical bypass has shown primary patency rates of 73-76% [Ravn, H., A. Wanhainen, and M. Bjorck, Surgical technique and long-term results after popliteal artery aneurysm repair: Results from 717 legs. J Vasc Surg, 2007. 46(2): p. 236-43] which is in-line with the expected endpoints presented above.

[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

Follow-up visits are scheduled for 12 months, 24 months, and 36 months after the procedure. The visits need to be done in a window of +/- 90 days in order to be documented as study visits. The visit windows are shown in Table 1.

Table 1: Schedule of Follow-up Visits and Time Periods

Follow-up Visit	Visit Window (days)
12 Months	275-455
24 Months	640-820
36 Months	1005-1185

5.0 Statistical Analyses

5.1 Timing of Analyses

An interim analyses of the primary endpoints and secondary endpoints (where possible) is planned for 12 month follow-up data after enrollment is completed. Complete analyses of the secondary endpoints will take place after the 36 month data for these patients are available. Patients that are lost to follow-up after their 12 month visit, will not be replaced, but any attempt will be made by the Investigator to document the reasons.

5.2 Analysis Populations

All enrolled Patients will be included in the analysis. Patients who have had bilateral PAAs treated with the GORE® VIABAHN® Endoprosthesis in both limbs will have only the data from the first limb collected in this study when the limbs were treated at different dates. Patients that had PAAs treated in both limbs on the same date will be excluded to avoid confounding issues with select endpoints.

5.3 Pooling of Data

Data from all study Sites will be pooled on a clinical basis. That is, the study Sites will follow a common protocol, the study will be monitored to assure compliance with the protocol and applicable government regulations, and the data collection and handling procedures will be the same at all study Sites.

5.4 Primary Endpoints

Performance will be evaluated by primary patency at 12 months of the GORE® VIABAHN® Endoprosthesis in the treatment of Popliteal Artery Aneurysms. A point estimate will be calculated requiring primary patency at the one year visit to be declared a success. Having loss of primary patency at day 365 will be tabulated as a failure. Primary patency is defined in section 3.3.1.

Safety of the GORE® VIABAHN® Endoprosthesis will be assessed through 12 months by evaluation of serious adverse events (SAEs) and adverse events related to the study procedure or the study device. Counts will be tabulated at 12 months.

5.5 Secondary Endpoints

Primary patency, which is defined as blood flow maintained through the device without an intervention. Blood flow should be determined at the follow-up visits, by either angiography or color-coded duplex sonography. In the event that duplex sonography is not obtained, blood flow will be assessed by clinician exam. Primary patency at 12, 24, & 36 months after implant will be estimated through time-to-event analysis.

Serious adverse events and adverse events relative to the study device and procedure will be obtained through 36 months for assessment of the device safety. Counts will be tabled at 24, & 36 months.

Length of hospital stay will be measured in calendar days. Length of hospital stay will be calculated omitting all patients with unknown endpoint status.

Length of procedure will be measured in minutes. Length of procedure will be calculated omitting all patients with unknown endpoint status.

Primary assisted patency at 12, 24, & 36 months after implant will be estimated through time-to-event analysis. Blood flow should be determined by angiography or color-coded duplex sonography. In the event that duplex sonography is not obtained, blood flow will be assessed by clinician exam.

Freedom from limb loss of the study limb at 12, 24, & 36 months after implant will be estimated through time-to-event analysis.

Freedom from repeat intervention at 12, 24, & 36 months after implant will be estimated through time-to-event analysis.

Secondary patency at 12, 24, & 36 months after implant will be estimated through time-to-event analysis. Blood flow should be determined by angiography or color-coded duplex sonography. In the event that duplex sonography is not obtained, blood flow will be assessed by clinician exam.

Technical Success is defined as successful aneurysmal exclusion using the GORE® VIABAHN® Endoprosthesis at time of the procedure without Type I and III endoleaks that require post-procedure intervention within 30 days. All subjects without known status for this endpoint will be omitted in calculating this statistic.

In addition, listings of the following events will be provided: endoleak, migration, fracture, and amputation.

5.6 Control of Bias

Bias will be controlled by strict adherence to patient eligibility criteria and to the study protocol. Sites will be monitored for compliance with study protocol, including subject eligibility criteria, and will be audited for both compliance with the protocol and for data quality.

5.7 Data Analysis

Analysis will be performed after all of the data has been obtained, entered, cleaned, and locked for the interim as well as the final analyses.

6.0 Interim Analyses and Safety Monitoring Analyses

An interim analyses of the primary endpoints and secondary endpoints (where possible) is planned for 12 month follow-up data after enrollment is completed. Due to the data being collected retrospectively, no safety monitoring analyses will be performed.

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

All analysis datasets and tables will be verified at Level I while all listings will be verified at Level II per MD111325 (Clinical Affairs Biostatistics Analysis Specifications and Programming Procedure) for statistical output.

8.0 Data Sets, Tables, Figures, and Listings

8.1 Analysis Tables

- Subject Demographics (Sex, Age)
- Subject Medical History (Smoking History, Diabetes Mellitus, Hypertension, Hyperlipidemia, Stroke, Coronary Artery Disease, Myocardial Infarction, Congestive Heart Failure, Deep Vein Thrombosis, Bilateral Popliteal Artery Aneurysm, History of Abdominal Aortic, Iliac, or SFA Aneurysm)
- Summary of Enrollment by Site (Number of Subjects Enrolled at Each Site)
- Summary of Pre-Procedure(Study Limb, Pre-Procedure Resting ABI, Runoff Vessels in Study Limb, Pedal Pulses Present in Study Limb, Aneurysm Diameter, Symptomatic Due to Aneurysm, Aneurysm Length, Mural Thrombus Present, Thrombus Diameter)
- Summary of Procedure (Length of Procedure Time, Successful Deployment, Post-deployment Dilation of Device(s) Performed, Additional Inflow/Outflow Procedures Performed, Additional Procedures Performed at Study Aneurysm Site, Post-procedure Resting ABI, Successful Aneurysmal Exclusion, Length of Hospital Stay)

- Summary of Device Use (Number of Devices Implanted, Length of Device Overlap, Device Diameter, Device Length)
- Medications (Aspirin, Clopidogrel, Prasugrel, Ticlopidine, Warfarin, Other)
- Primary Patency at 12 Months
- Primary Safety at 12 Months
- Kaplan-Meier Estimates of Primary Patency (Primary Patency by Time Post Treatment)
- Counts of Serious Adverse Events and Adverse Events Relative to the Study Device and Procedure at 24 and 36 Months After Procedure
- Kaplan-Meier Estimates of Primary Assisted Patency (Primary Assisted Patency by Time Post Treatment)
- Kaplan-Meier Estimates of Freedom From Limb Loss (Freedom From Limb Loss by Time Post Treatment)
- Kaplan-Meier Estimates of Freedom From Repeat Intervention (Freedom From Repeat Intervention by Time Post Treatment)
- Kaplan-Meier Estimates of Secondary Patency (Secondary Patency by Time Post Treatment)
- Technical Success at 30 Days
- Summary of All Adverse Events by MedDRA SOC, HLT, PT and Follow-up Interval
- Summary of Serious Adverse Events by MedDRA SOC, HLT, PT and Follow-up Interval
- Summary of Device and Procedure Related Adverse Events by MedDRA SOC, HLT, PT and Follow-up Interval
- Summary of Device and Procedure Related Serious Adverse Events by MedDRA SOC, HLT, PT and Follow-up Interval
- Summary of Subject Follow-Up (Subject Follow-Up by Interval)
- Subject Completion/Discontinuation (Completion/Discontinuation [Surgical bypass, Amputation above the metatarsal, Lost to follow-up, Death, Other])
- Repeat Interventions Summary (Days to First Intervention, Reason for Reintervention, Endoleak at Time of Intervention [Endoleak, Type], Type of Reintervention Performed, Successful Reintervention, ABI at Discharge)

8.2 Analysis Listings

- Listing of Device Fractures
- Listing of Deaths
- Listing of Study Completion/Discontinuation Data
- Listing of All Adverse Events
- Listing of Revision/Interventions
- Listing of All Endoleaks
- Listing of Device Migration
- Listing of Major Amputation on the Study Limb
- Listing of Minor Amputation on the Study Limb
- Listing of Reasons for Early Termination
- Listing of Additional Procedures
- Listing of Re-interventions
- Listing of Reasons for Non-inclusion in the Study
- Listing of Reasons for Exclusion from Analysis Population of Enrolled Patients

8.3 Analysis Figures

- Time to Loss of Primary Patency
- Time to Loss of Primary Assisted Patency
- Freedom From Limb Loss
- Freedom From Repeat Intervention
- Time to Loss of Secondary Patency

9.0 References

MD7929 Clinical Affairs Definitions List

MD111325 Clinical Affairs Biostatistics Analysis Specifications and Programming Procedure