Post-Approval Study of the GORE® VIABAHN® Endoprosthesis for the Treatment of In-Stent Restenosis in the Superficial Femoral Artery

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Statistical Analysis Plan

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1 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of ISR 14-04 clinical study. This SAP summarizes the analyses that will be performed to determine the safety and effectiveness of the GORE® VIABAHN® Endoprosthesis for the treatment of in-stent restenosis in the superficial femoral artery. This SAP outlines tables, figures, and listings that are included in reports for the ISR 14-04 clinical study.

2 Study Design

2.1 Primary Objective

The primary objective of ISR 14-04 is to evaluate the post-market performance of GORE® VIABAHN® Endoprosthesis for the treatment of in-stent restenosis of the superficial femoral artery in a primarily U.S. population (at least 75% of patients being treated in the U.S.).

2.2 Design Summary

This study is a prospective, multicenter, non-randomized single-arm study to evaluate the post-market performance of the GORE® VIABAHN® Endoprosthesis for the treatment of in-stent restenosis in the superficial femoral artery.

A minimum of 15 Clinical Investigative Sites (referred to as “Sites” in the remainder of this document) in the U.S. and a maximum of 5 OUS Sites will participate in this study. A total of 108 Subjects (a minimum of 81 Subjects from the U.S. and a maximum of 27 OUS Subjects) will be enrolled in this study with a limit of 30 Subjects per U.S. Site. A minimum of 20 Subjects (out of the total 108 Subjects) will be enrolled with lesion lengths of 230-270mm. The anticipated accrual period is 24 months assuming an accrual rate is approximately 4.5 Subjects per month.

Patients are to be enrolled into the study provided all inclusion and no exclusion criteria are met as specified in Section 4. Subjects will be evaluated through hospital discharge and will be scheduled for follow-up visits at 30 days and at 12, 24, and 36 months post-treatment. Accounting for the expected period of enrollment, the total estimated duration of the study is 60 months.

2.3 Definitions

Ankle Brachial Index: The ankle systolic pressure in the study limb divided by the highest brachial systolic pressure in either arm.

Acute Procedural Success: Successful delivery of study device and complete coverage of the target lesion without a procedure- or device-related Serious Adverse Event prior to hospital discharge.

Major Amputation: Removal of the lower limb above the metatarsals in the study limb, resulting from a vascular event.

Patency: Blood flow through the study device.

Primary Patency: Patent blood flow through the study device, which requires either a PSVR measurement ≤ 2.5 or patent flow indicated by the Core Lab, and without repeat intervention.

Primary Assisted Patency: Blood flow through the study device regardless of repeat interventions to maintain patency prior to occlusion.

Secondary Patency: Blood flow through the study device regardless of repeat interventions to maintain or restore patency after occlusion.

Stent Integrity: Freedom from study device stent fracture which is clearly distinguishable on imaging from the previously implanted non-covered stent.

Target Lesion(s): Stenotic or occluded segment(s) within and adjacent to a previously implanted non-covered stent(s) (>30 days) in the superficial femoral artery. An adjacent lesion is an extension of the stenotic or occluded segment that is contiguous with that lesion within the previously implanted non-covered stent.

Target Lesion Revascularization (TLR): Repeat intervention within the study device and 5 mm proximal or distal to the edge of the study device to maintain or re-establish patency.

Toe Brachial Index: The toe systolic pressure in the study limb divided by the highest brachial systolic pressure in either arm.

2.4 Primary Endpoints

2.4.1 Primary Patency at 12 months Post-procedure

The primary effectiveness endpoint is Primary Patency at 12 months post-procedure. This will be estimated through 365 days along with a 95% confidence interval using Kaplan-Meier analysis. Equivalent analysis will be performed with regards to the primary patency partitioning the data by lesion length (< 230 mm and ≥ 230mm). All results will be compared to that obtained in the RELINE study.

2.4.2 Procedure or Device-related Serious Adverse Events Within 30 days of the Index Procedure

The primary safety endpoint is procedure- or device-related Serious Adverse Events within 30 days of the index procedure. The total number of events as well as the number of Subjects experiencing them will be tabulated along with a 95% confidence interval.

2.5 Secondary Endpoints

2.5.1 Acute Procedural Success

Acute Procedural Success is defined as successful delivery of the study device and complete coverage of the target lesion without a procedure- or device-related Serious Adverse Event prior to hospital discharge. This will be tabulated omitting all Subjects with unknown status.

2.5.2 Primary Patency

Primary patency is defined as patent blood flow through the study device, which requires either a PSVR measurement ≤ 2.5 or patent flow indicated by the Core Lab, without repeat intervention. Primary patency will be estimated at 30 days, 12, 24, and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

2.5.3 Primary Assisted Patency

Primary assisted patency is defined as blood flow through the study device regardless of repeat interventions to maintain patency prior to occlusion. Blood flow will require confirmation by the study Core Lab. Primary assisted patency will be estimated at 30 days, 12, 24 and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

2.5.4 Secondary Patency

Secondary patency is defined as blood flow through the study device regardless of repeat interventions to restore patency after occlusion. Blood flow will require confirmation by the study Core Lab. Secondary patency will be estimated at 30 days, 12, 24, and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

2.5.5 Freedom from Target Lesion(s) Revascularization (TLR)

Target Lesion Revascularization is defined as a repeat intervention within the study device and 5 mm proximal or distal to the edge of the study device to maintain or re-establish patency. Freedom from TLR will be estimated at 30

days, 12, 24, and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

2.5.6 Freedom from Major Amputation

Major Amputation is defined as removal of the study limb above the metatarsals, resulting from a vascular event. Freedom from major amputation will be estimated at 30 days, 12, 24, and 36 months along with a 95% confidence interval using Kaplan-Meier analysis.

2.5.7 Change in Ankle-Brachial Index (ABI)

Ankle Brachial Index is defined as the ankle systolic pressure in the study limb divided by the highest brachial systolic pressure in either arm. The minimum, maximum, median, mean, and standard error will be reported for the change in ABI relative to that measured pre-procedure at 30 days, 12, 24, and 36 months. All values measured within the defined window will be used in calculation.

2.5.8 Change in Rutherford Category

The change in Rutherford Category, measured relative to that obtained pre-procedure, will be assessed at 30 days, 12, 24, and 36 months. The minimum, maximum, median, mean, and standard error will be reported as well as the counts for each outcome. All values measured within the defined window will be used in calculation.

2.5.9 Stent Fracture

Device stent fractures will be assessed by the study Core Lab through x-ray images. A table of all stent fractures, which are clearly distinguishable from previously implanted stents, will be reported at 12, 24, and 36 months. All values measured within the defined window will be used in tabulation.

2.6 Additional Analysis

[redacted]

2.7 Sample Size

[redacted]

3 Study Treatment Arm

The GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface (US); GORE® VIABAHN® Endoprosthesis with PROPATEN Bioactive Surface (EU); and subsequently referred to as GORE® VIABAHN® Endoprosthesis throughout this document.

4 Study Data Collection

4.1 Data Collection Methods

This study will report clinical data using the Medidata Rave® Clinical Data Management System (CDMS) web-based application. The CDMS will be the database of record for the protocol and subject to regulatory inspections. All users will be trained to use the CDMS and will comply with study-specific guidelines / instructions as well as applicable regulatory requirements.

Subject data will be collected using protocol-specific case report forms (CRF). Site staff will enter data directly into the CRF for transmission to the Sponsor. The Sites will be notified of any significant amendments to the CRFs.

4.2 Data Clarification and Correction

Once entered, data will be evaluated to ensure 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.

4.3 CRF Completion Schedule

CRFs will be completed as soon as reasonably possible during or following each Subject visit.

5 Statistical Analyses

5.1 Timing of Analyses

Reports will be prepared when follow-up is complete for endpoints of the study (*e.g.,* 1-year, 2-year, and 3-year). Additional interim analyses and reports will be done in order to comply with regulatory reporting requirements. This will consist of, at a minimum, the physical characteristics of enrolled Subjects as well as tabulations of all interventions and adverse events. In addition, listings of all interventions and adverse events will be prepared.

Once all Subjects have either completed 36 months of follow-up or been withdrawn from the study, a formal statistical analysis will be performed to evaluate all study endpoints.

5.2 Analysis Populations

Both of the following populations will be used for analyses of primary and secondary endpoints.
(1) Intent to treat (ITT) – All patients assigned to the study treatment, regardless of whether or not they received it or have any protocol violations.

(2) Per protocol (PP) – A subset of the ITT population consisting of Subjects receiving the study device which meet all inclusion and exclusion criteria and without any major protocol violations.

5.3 Pooling of Data

Data from all study Sites will be pooled on a clinical basis, *i.e.,* 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

5.4.1 Primary Effectiveness - Primary Patency at 12 Months Post-procedure

Both the ITT and PP populations will be used with the following decision rules for calculating the primary patency at 12 Months post-procedure.

5.4.2 Primary Safety - Procedure or Device-related Serious Adverse Events Within 30 Days of the Index Procedure

Both the ITT and PP populations will be used with the following decision rules for calculating the serious adverse events within 30 days of the index procedure.

5.5 Secondary Endpoints

5.5.1 Acute Procedural Success

Both the ITT and PP populations will be used with the following decision rules for calculating the percentage of subjects experiencing the acute procedural success.

[redacted]

5.5.2 Primary Patency

Both the ITT and PP populations will be used with the following decision rules for calculating the primary patency through Kaplan-Meier time to event analysis.

[redacted]

5.5.3 Primary Assisted Patency

Both the ITT and PP populations will be used with the following decision rules for calculating the primary assisted patency through Kaplan-Meier time to event analysis.

[redacted]

5.5.4 Secondary Patency

Both the ITT and PP populations will be used with the following decision rules for calculating the secondary patency through Kaplan-Meier time to event analysis.

5.5.5 Freedom from Target Lesion(s) Revascularization (TLR)

Both the ITT and PP populations will be used with the following decision rules for calculating the secondary patency through Kaplan-Meier time to event analysis.

5.5.6 Freedom from Major Amputation

Both the ITT and PP populations will be used with the following decision rules for calculating the secondary patency through Kaplan-Meier time to event analysis.

5.5.7 Change in ABI

All subjects from both the ITT and PP populations which have their ABI measured at the corresponding visit, will be used for calculating the change in ABI statistics at each visit window. At each time point, the change in ABI values (post procedures measurement – pre-procedure measurement) will be tabled showing at least the minimum, maximum, median, mean, and standard error of the values obtained.

5.5.8 Change in Rutherford Category

All subjects from both the ITT and PP populations which have their Rutherford Category measured at the corresponding visit, will be used for calculating the change in Rutherford Category statistics at each visit window. At each time point, the change in Rutherford Category values (post procedures measurement – pre-procedure measurement) will be tabled showing the minimum, maximum, median, mean, and standard error as well as the counts for each outcome.

5.5.9 Stent Fractures

All subjects from both the ITT and PP populations which have x-ray images assessable by the study core lab will be used to create a table displaying the counts of each fracture type at 12, 24 and 36 months. All values measured within the defined window will be used in tabulation.

5.6 Additional Analysis

[redacted]

6 Analysis Specifications

[redacted]

6.2 Primary Endpoint

[redacted]

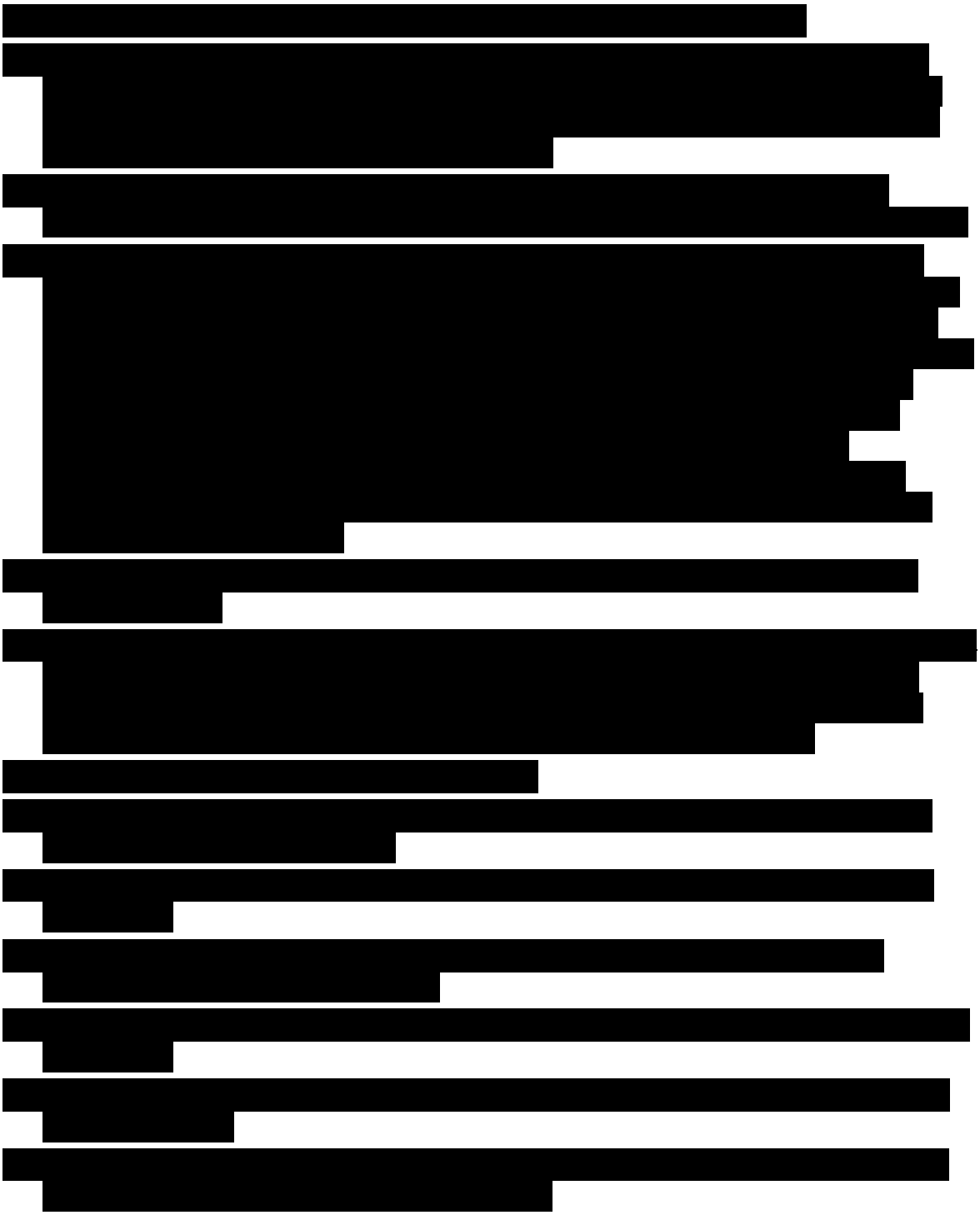
6.3 Verification Level for Statistical Output

[redacted]

7 Data Sets, Tables, Figures, and Listings

At a minimum, the following set of Tables, Figures, and Listings will be produced for the report. Unless specified, the populations for all tables are all of the “Enrolled Subjects”.

7.1 Analysis Tables



[redacted]

7.2 Analysis Listings

[redacted]

7.3 Analysis Figures

[redacted]

8 References

8.1 MD111325

Clinical Affairs Biostatistics Analysis Specifications and Programming Procedure

8.2 MD119211

Development, Approval, Management and Retention of a Statistical Analysis Plan