Statistical Analysis Plan

A Prospective, Multicenter, Single-arm Clinical Trial of Jetstream Atherectomy System for the Treatment of Japanese Patients with Symptomatic Occlusive Atherosclerotic Lesions in the Superficial Femoral and/ or Proximal Popliteal Arteries

J-SUPREME II

S2450

CONFIDENTIAL

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APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

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1 PROTOCOL SUMMARY

<table>
<tr><td colspan="2">J-SUPREME II: A Prospective, Multicenter, Single-arm Clinical Trial of Jetstream Atherectomy System for the Treatment of Japanese Patients with Symptomatic Occlusive Atherosclerotic Lesions in the Superficial Femoral and/ or Proximal Popliteal Arteries</td></tr>
<tr><td>Study Objective(s)</td><td>To evaluate the safety and effectiveness of the Boston Scientific (BSC) Jetstream Atherectomy System (Jetstream) for the treatment of Japanese patients with symptomatic occlusive atherosclerotic lesions in native superficial femoral artery (SFA) and/ or proximal popliteal arteries (PPA)</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Test Device and device Sizes</td><td>The Jetstream® Atherectomy System: A rotating, aspirating, expandable catheter system for active removal of atherosclerotic debris and thrombus in the SFA and/or PPA

Jetstream Atherectomy System

1. Jetstream Catheter
<table><tr><th>Model</th><th>Tip Diameter</th><th>Catheter Length</th><th>Min.Introducer Size</th><th>Max. Guidewire Diameter</th></tr><tr><td>SC 1.6</td><td>1.6 mm</td><td>145 cm</td><td rowspan="2">7 Fr</td><td rowspan="4">0.014 inch</td></tr><tr><td>SC 1.85</td><td>1.85 mm</td><td>145 cm</td></tr><tr><td>XC 2.1/3.0</td><td>2.1 mm (Blade Down)
3.0 mm (Blade Up)</td><td>135 cm</td><td rowspan="2">7 Fr</td></tr><tr><td>XC 2.4/3.4</td><td>2.4 mm (Blade Down)
3.4 mm (Blade Up)</td><td>120 cm</td></tr></table>
2. Jetstream Console</td></tr>
<tr><td>Control Device</td><td>NA</td></tr>
<tr><td>Study Design</td><td>A prospective, multicenter, single-arm trial evaluating the safety and efficacy of the Jetstream Atherectomy System in the treatment of symptomatic occlusive atherosclerotic lesions ≤150 mm in length located in the femoropopliteal arteries in subjects with symptoms classified as Rutherford categories 2-4.</td></tr>
<tr><td>Planned Number of Subjects</td><td>Thirty-one (31) subjects will be enrolled.</td></tr>
<tr><td>Planned Number of Investigational Sites/</td><td>About 5 investigational sites in Japan may enroll subjects.</td></tr>
</table>

Countries	
Primary Endpoint	The primary effective endpoint is the lesion success rate at the index procedure. Lesion success is defined as the case meets all criteria below: After dilatation with DCB: • Residual stenosis at the target lesion being ≤30% • No occurrence of Grade C or greater dissection (NHLBI) • No occurrence of clinically apparent perforation requiring treatments • No occurrence of any obstructive complication (e.g., recoil) demonstrating a marked decrease in the flow in the target vessel [redacted]
Additional Endpoints	• Procedural success rate (Bailout stenting or by-pass procedure during the index procedure is not needed) • Rate of distal emboli requiring additional treatment during the procedure or within 24 hours post-index procedure. • Reduction in lesion stenosis, that is, the difference between the percent stenosis prior to treatment with Jetstream and the percent stenosis following treatment with Jetstream (absolute mean percentage) • MAE rate at 1 month and 6 months post-index procedure, defined as all-cause death through 1 month, and/or target limb major amputation and/or TLR through 6 months • Clinically-driven TLR and Target Vessel Revascularization (TVR) Rate at each time point • Adverse Event rates at each time point • Distribution of Rutherford Class as compared to baseline at 1 month and 6 months post-index procedure • Rate of Primary and Secondary Sustained Clinical Improvement as assessed by changes in Rutherford Classification as compared to baseline at 1 month and 6 months post-index procedure • Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index as compared to baseline at 1 month and 6 months post-index procedure • Primary Patency and Assisted Primary Patency at 1 month and 6 months

	using peak systolic velocity ratio (PSVR) 2.4 • Primary Patency and Assisted Primary Patency at 1 month and 6 months using different PSVRs [redacted] • [redacted]
[redacted]	[redacted]
Follow-up Schedule	Subjects will be evaluated at 1 and 6 months post-index procedure. • Subjects who are enrolled but the Jetstream Atherectomy System is not used will be followed through the 1-month follow-up visit only. • Assessment of the primary endpoint will occur at the index procedure. • All follow-up visits will be conducted in the office/clinic. Planned protocol-required testing includes the following: • Angiography during the index procedure to assess procedural success and occurrence of emboli. • IVUS during the index procedure to assess lesion • DUS at the 1-month and 6-months follow-up visits to assess lesion and vessel patency
Study Duration	The trial will be considered complete (with regards to the primary endpoint) after all enrolled subjects have completed the index procedure, are discontinued prior to completion of the procedure or have died. The trial will be considered complete (with regards to all follow-up) after all enrolled subjects have completed the 6 month follow-up visit, are discontinued prior to 6 month follow-up visit, have died, or the last 6 month follow-up visit window is closed. It is estimated that it will take approximately 1 year to complete this trial.
[redacted]	[redacted]
Key Inclusion Criteria	1. ≥20 years of age 2. An acceptable candidate for percutaneous intervention and/or emergency surgery. 3. Willing and able to provide consent before any study specific test or procedure is performed, signs the consent form, and agrees to attend all required follow-up visits

	4. Chronic, symptomatic lower limb ischemia defined as Rutherford categories 2, 3 or 4 5. Stenotic, restenotic or occlusive lesion(s) located in the native SFA and/or PPA of which meet all of the following criteria*: a. Severely calcified lesions with degree of stenosis ≥70% by visual angiographic assessment [redacted] c. Guidewire must cross lesion(s) within the true lumen, without a sub-intimal course by physician's discretion based on visual estimate d. Vessel diameter ≥3.0 mm and ≤6.0 mm by visual estimate e. Total lesion length (or series of lesions) ≤150 mm by visual estimate f. Target lesion located at least 3 cm above the inferior edge of the femur by visual estimate [redacted] 6. Patent infrapopliteal and popliteal artery, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis by visual estimate) to the ankle or foot with no planned intervention
Key Exclusion Criteria	1. Target lesion must be one and decided by physician's discretion in the case that eligible lesions exist in both limbs 2. Target lesion/vessel with in-stent restenosis 3. Target lesion/vessel previously treated with any stent placement prior to the procedure 4. Use of atherectomy, laser or other debulking devices other than the Jetstream System, CTO devices or cutting balloon, Angioscore or similar devices, or ultra-high pressure balloon in the target limb SFA/PPA during the index procedure 5. History of major amputation in the target limb 6. Life expectancy less than 12 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the clinical trial, limit the subject's compliance with the follow-up requirements, or impact the scientific integrity of the clinical trial 7. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated 8. Known hypersensitivity/allergy to the investigational atherectomy system or protocol related therapies (e.g., nitinol, stainless steel or other stent materials, and antiplatelet or anticoagulant, thrombolytic medications) 9. Subject has a history of coagulopathy or hypercoagulable bleeding

	disorder 10 Subject with untreatable hemorrhagic disease or platelet count <80,000 mm^3 or >600,000 mm^3 as baseline assessment. 11. Being on peritoneal dialysis 12. History of myocardial infarction, or stroke/cerebrovascular accident (CVA) within 6 months prior to study enrollment 13. Unstable angina pectoris at the time of the enrollment 14. Pregnancy and/or breast feeding 15. Current participation in another investigational drug or device clinical study that has not completed the primary endpoint at the time of enrollment or that clinically interferes with the current study endpoints (Note: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies.) 16. Septicemia at the time of enrollment 17. Presence of other hemodynamically significant outflow lesions in the target limb requiring a planned surgical intervention or endovascular procedure within 30 days after the index procedure 18. Presence of aneurysm in the target vessel 19. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to the index procedure 20. Perforated vessel as evidenced by extravasation of contrast media prior to the index procedure
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2 INTRODUCTION

This statistical analysis plan addresses the planned analyses for the J-SUPREME II performance goal (PG) study based on the most current version of the protocol. All of the specified analyses may not be provided in reports to competent authorities but may be used for scientific presentations and/or manuscripts. For this PG Study, the primary analysis will be based on the data through 6 months post-procedure. If any additional analysis will be required, it will be specified in the CSR.

[redacted]

3.1 Primary Effectiveness Endpoint

The primary endpoint in this trial is the lesion success rate at the index procedure.

Lesion success is defined as the case meets all criteria below:

After dilatation with DCB:

- Residual stenosis at the target lesion being ≤30%
- No occurrence of Grade C or greater dissection (NHLBI)
- No occurrence of clinically apparent perforation requiring treatments

- No occurrence of any obstructive complication (e.g., recoil) demonstrating a marked decrease in the flow in the target vessel

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4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

The primary endpoints and additional endpoint / measurements will be analyzed on an Intent-To-Treat (ITT) and a Per-Protocol (PP) basis. All subjects who sign the written informed consent form (ICF) (see Section 19 of the protocol) and are enrolled in the trial (see also Section 9.1 of the protocol for the point of enrollment) will be included in the ITT analysis population, regardless of whether the test device is activated. [redacted]

[redacted]

4.2 Control of Systematic Error/Bias

[redacted]

[redacted]

In case if missing data is available in the primary / additional endpoints, the tipping point analysis will be done. In case missing data is available in the covariate variables, any suitable model based analyses may be applicable.

[redacted]

5 ADDITIONAL DATA ANALYSES

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, median, minimum and maximum) and discrete variables (percentage and count/sample, and the exact confidence intervals (CI), if specified).

[redacted]

5.1 Other Endpoints/Measurements

Other measurements not driven by statistical hypotheses are listed in the below. They will be presented by descriptive statistics.

- Procedural success rate (Bailout stenting or by-pass procedure during the index procedure is not needed)
- Rate of distal emboli requiring additional treatment during the procedure or within 24 hours post-index procedure.
- Reduction in lesion stenosis, that is, the difference between the percent stenosis prior to treatment with Jetstream and the percent stenosis following treatment with Jetstream (absolute mean percentage)

- MAE rate at 1 month and 6 months post-index procedure, defined as all-cause death through 1 month, and/or target limb major amputation and/or TLR through 6 months
- Clinically-driven TLR and Target Vessel Revascularization (TVR) Rate at each time point
- Adverse Event rates at each time point
- Distribution of Rutherford Class as compared to baseline at 1 month and 6 months post-index procedure
- Rate of Primary and Secondary Sustained Clinical Improvement as assessed by changes in Rutherford Classification as compared to baseline at 1 month and 6 months post-index procedure
- Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index as compared to baseline at 1 month and 6 months post-index procedure
- Primary Patency and Assisted Primary Patency at 1 month and 6 months using PSVR 2.4
- Primary Patency and Assisted Primary Patency at 1 month and 6 months using different PSVRs
- Presence or absence of an optimal size balloon crossing or not crossing through the target lesion
- Residual stenosis after dilatation with an optimal size balloon and DCB (Final residual stenosis if treatment with devices other than DCB is performed.)

5.2 Interim Analyses

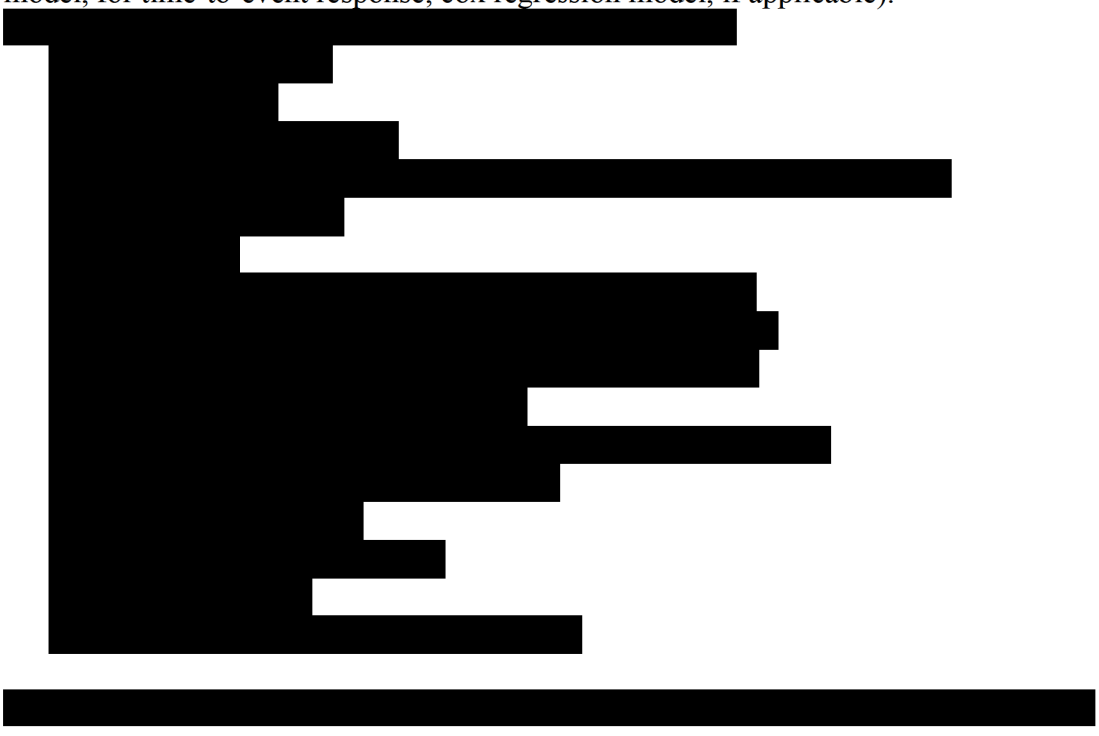
No formal interim analyses are planned.

5.4 Justification of Pooling

Not applicable.

5.5 Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary parameter (for example, for binary response, logistic regression model, for time-to-event response, cox regression model, if applicable).



5.6 Other Analyses

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be

performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis.

[redacted]

5.8 Duplex Ultrasound Analyses

DUS examinations will be performed at 1 month (0-37 days) and 6 month (182±30 days) post-index procedure. Only records obtained during the clinical visit window will be selected for analysis unless the Biostatistics representative(s) is informed otherwise. In the case where multiple examinations are performed during the visit window, the best interpretable record will be selected. Measurements from DUS examinations that occur after a TLR will not be excluded from selection, but rather, endpoint definitions will appropriately account for the presence or absence of a prior TLR

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[redacted]	[redacted]

5.11 Analysis of Site-Reported Serious and Non-Serious Adverse Events

Subject-level event rates will be calculated at various time points based on all events reported by the site regardless of whether or not they are ultimately adjudicated to be (or lead to) a MAE. [redacted]

5.12 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in a Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

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