Statistical Analysis Plan

Version B

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

Study Reference Number **S6051**

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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: 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>Planned Indication(s) for Use</td><td>Jetstream is intended to be used as adjunctive therapy for percutaneous intervention to remove atherosclerotic disease, debris, and thrombus from the SFA and/or PPA</td></tr>
<tr><td>Test Device</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</td></tr>
<tr><td>Control Device</td><td>NA</td></tr>
<tr><td>Device Sizes</td><td><u>Jetstream Atherectomy System</u>
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>1.6mm</td><td>145cm</td><td rowspan="2">7Fr</td><td rowspan="4">0.014inch</td></tr>
<tr><td>SC 1.85</td><td>1.85mm</td><td>145cm</td></tr>
<tr><td>XC 2.1/3.0</td><td>2.1mm(Blade Down)
3.0mm(Blade Up)</td><td>135cm</td><td rowspan="2">7Fr</td></tr>
<tr><td>XC 2.4/3.4</td><td>2.4mm(Blade Down)
3.4mm(Blade Up)</td><td>120cm</td></tr>
</table>
2. Jetstream Console</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</td><td>50 primary subjects will be enrolled in the J-SUPREME clinical trial.
In addition, at least one roll-in subjects per site is planned, so that a total of</td></tr>
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Subjects	approximately 60 subjects will be enrolled.
Planned Number of Investigational Sites / Countries	Up to 10 investigational sites in Japan may enroll subjects.
Primary Endpoint	The primary endpoint is the primary patency at 6 months post-procedure. Primary vessel patency, a binary endpoint, is defined as follows: - Bailout stenting or by-pass procedure during the index procedure is not needed (Procedural Success) - Duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤2.4 at the 6-month follow-up visit, in the absence of clinically-driven TLR and/or bypass of the target lesion and/or target limb major amputation through 6 months All Angio and DUS readings will be assessed by an independent core laboratory. Clinically-driven TLR, target lesion bypass and target limb major amputation will be adjudicated by an Independent Medical Reviewer (IMR).
Additional Endpoints	- Procedural success rate - 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, 6 months and 12 months post-index procedure, defined as all-cause death through 1 month, and/or target limb major amputation and/or TLR through 12 months - Primary Patency and Assisted Primary Patency at 1 month, 6 months and 12 months using different PSVRs - 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 6 months and

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	12 months post-index procedure - Rate of Primary and Secondary Sustained Clinical Improvement as assessed by changes in Rutherford Classification as compared to baseline at 6 months and 12 months post-index procedure - Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index as compared to baseline at 1 month. 6 months and 12 months post-index procedure
[redacted]	[redacted]
Follow-up Schedule	Subjects will be evaluated at 1, 6 and 12 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 6-month follow-up visit. - 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. - DUS at the 1-month, 6-month and 12-month 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 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. The trial will be considered complete (with regards to all follow-up) after all enrolled subjects have completed the 12-month follow-up visit, are discontinued prior to 6-month follow-up visit, have died, or the last 12-month follow-up visit window is closed. It is estimated that it will take approximately 2 years to complete this trial.

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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. Calcified lesions* with degree of stenosis ≥70% by visual angiographic assessment or occlusions, regardless of degree of calcification *Calcification needs to be in the segment 5mm proximal and 5mm distal to the stenotic lesion by visual estimate b. Guidewire must cross lesion(s) within the true lumen, without a sub-intimal course by physician's discretion based on visual estimate c. Vessel diameter ≥3.0 mm and ≤6.0 mm by visual estimate d. Total lesion length (or series of lesions) ≤150mm by visual estimate e. Target lesion located at least 3 cm above the inferior edge of the femur by visual estimate 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 drug-coated balloon <12 months prior to the procedure 4. Target lesion/vessel previously treated with any stent placement,

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	atherectomy, laser or other debulking devices prior to the procedure 5. Subjects who have undergone surgery or endovascular of the SFA/PPA in the target vessel to treat atherosclerotic disease within 3 months prior to the index procedure 6. Use of drug-coated devices, atherectomy, laser or other debulking devices other than the Jetstream System, CTO devices or cutting balloon, Angioscore or similar devices in the target limb SFA/PPA during the index procedure 7. History of major amputation in the target limb 8. Subjects who have lesions requiring treatment and planned the treatment with commercial devices in a contralateral limb within 30 days after the index procedure 9. Subjects who had lesions treated with commercial devices in a contralateral limb within 7 days prior to the index procedure (Note: If subject had treatment of contralateral limb 8 days or earlier prior to the index procedure, the procedure success needs to be confirmed by physician's discretion) 10. Life expectancy less than 24 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 11. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated 12. 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) 13. Subject has a history of coagulopathy or hypercoagulable bleeding disorder 14. Subject with untreatable hemorrhagic disease or platelet count $<80{,}000 mm^3$ or $>600{,}000 mm^3$ as baseline assessment. 15. Concomitant renal failure with a serum creatinine >2.0 mg/dL 16. Receiving dialysis or immunosuppressant therapy 17. History of myocardial infarction, or stroke/cerebrovascular accident (CVA) within 6 months prior to study enrollment

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	18. Unstable angina pectoris at the time of the enrollment 19. Pregnancy and/or breast feeding 20. 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.) 21. Septicemia at the time of enrollment 22. 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 23. Presence of aneurysm in the target vessel 24. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to the index procedure 25. Perforated vessel as evidenced by extravasation of contrast media prior to the index procedure
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	[redacted]

2 INTRODUCTION

This statistical plan addresses the planned analyses for the J-SUPREME trial 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. The primary analysis will be based on the data through 6 months post-procedure.

3 PRIMARY ENDPOINT ANALYSIS

The sample size justification for the primary analysis described in this section is aimed to properly control the type I error and preserve adequate statistical power when testing the primary hypotheses. Additional roll-in subjects (at least one roll-in case from each site) will be analyzed independently from the primary analysis.

3.1 Primary Effectiveness Endpoint

The primary endpoint is the primary patency at 6 months post-procedure.

Primary vessel patency, a binary endpoint, is defined as follows:

- Bailout stenting or by-pass procedure during the index procedure is not needed (Procedural Success)
- Duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4 at the 6-month follow-up visit, in the absence of clinically-driven TLR and/or bypass of the target lesion and/or target limb major amputation through 6 months
- All angiograms and DUS readings will be assessed by an independent core laboratory.

Clinically-driven TLR, target lesion bypass and target limb major amputation will be adjudicated by an Independent Medical Reviewer (IMR).

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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) and are enrolled in the study will be included in the ITT analysis population, regardless of whether the test device is activated. For PP analysis, only subjects who are activated with the test device will be included in the analysis population. In this study, those subjects enrolled after roll-in phase will be analyzed for endpoints.

[redacted]

4.2 Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria and signed the ICF will be eligible for enrollment in the study. Subjects are considered enrolled in the study when the guidewire successfully crosses the target lesion.

To control for inter-observer variability, data from independent core laboratories / an Independent Medical Reviewer (IMR) will be used for analysis. These include a core lab to assess angiograms and DUS readings, and IMR events using standard procedures.

[redacted]

4.4 Data Analyses

Baseline and outcome variables will be summarized using descriptive statistics. For continuous variables, the descriptive statistics will include mean, standard deviation, number of observations, minimum, and maximum). Some specific variables may also include median and confidence intervals (CI). For binary or categorical variables, the descriptive statistics will include percentage, numerator, denominator, and number of observations. Some variables may include confidence intervals as needed.

Data from the studies collected through 6 months will be submitted as the data set for Japanese market approval. Follow-up beyond 6 months will continue as planned in the most current version of the protocol.

5 ADDITIONAL DATA ANALYSES

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
- 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, 6 months and 12 months post-index procedure, defined as all-cause death through 1 month, and/or target limb major amputation and/or TLR through 12 months

- Primary Patency and Assisted Primary Patency at 1 month, 6 months and 12 months using different PSVRs
- 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 6 months and 12 months post-index procedure
- Rate of Primary and Secondary Sustained Clinical Improvement as assessed by changes in Rutherford Classification as compared to baseline at 6 months and 12 months post-index procedure
- Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index as compared to baseline at 1 month. 6 months and 12 months post-index procedure

5.2 Interim Analyses

No formal interim analyses are planned.

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5.4 Justification of Pooling

Not applicable.

5.5 Missing Data, Drop-Outs, and Protocol Deviations Handling

Boston Scientific employs strong oversight in order to minimize the loss of subjects throughout any trial follow-up by following actions but not limited to:

- A planned investigator / research coordinator meeting to ensure that site personnel are properly trained on the data that is required to be collected and the importance of planning for the follow-up visits.
- Clinical research associate closely monitors patient follow-up visits to be conducted within visit allowance.

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5.9 Duplex Ultrasound Analyses

DUS examinations will be performed at 1 month (0-37 days), 6 month (182±30 days) and 12 month (365±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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5.10 Follow-Up

All enrolled subjects who receive a treatment of Jetstream system will be evaluated prior to discharge from the index procedure and at 1 month, 6 months and 12 months after the index procedure.

Subjects who enrolled but a treatment was not performed will be considered enrolled and will be followed for safety through the 1-month follow-up visit only. Data for assessment of MAE will be collected for these subjects; other testing is not required.

Subjects requiring reintervention should be treated according to investigator's discretion and standard of care. These subjects should receive an approved, commercially available treatment (if appropriate).

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5.13 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. These safety parameters will be summarized using proportions based on the PP analysis set.

5.14 Analyses Software

All statistical analyses will be performed and validated by the independent CRO [redacted] using the Statistical Analysis Software (SAS), version 9.2 or later (Copyright © 2002-2010 by SAS Institute Inc., Cary, North Carolina 27513, USA. All rights reserved).

5.15 Changes to Planned Analyses

Any changes to the planned statistical analyses described above made prior to performing the analyses will be documented in an amended 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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