Statistical Analysis Plan

Version AE

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/or proximal popliteal arteries in Chinese patients

JETSTREAM CHINA

Study Reference Number **S6050**

National Clinical Trial (NCT) Identified Number: NCT03455855

Date: April 8, 2021

CONFIDENTIAL

DO NOT COPY OR DISTRIBUTE WITHOUT WRITTEN PERMISSION

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:

Lead Biostatistician – [Sunil Babu Pilli J, Senior Biostatistician]	Date (dd-mmm-yyyy)
Clinical Project/Trial Manager – [Peng Lv, Sr. Project Manager]	Date (dd-mmm-yyyy)
Medical Director – [Qing Li, Medical Affair Manager]	Date (dd-mmm-yyyy)

Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
128DEC2017-Version AA	90702621 Rev/Ver AE	None	None	Original release
13MAY2020 Version AB	90702621 Rev/Ver AE	Page1 Approvals	Approvals initials been changed, and PM and Medical Director names added	SAP been transitioned to IQVIA Biostats
		Page 2 Revision History	Updated Revision History table	Updated as per the latest SAP version
		Page 14 Section 3.1.4	Removed Chi-square test from the section	Corrected from previous version
		Page 17 Section 4.1	Updated ITT population definitions	Updated as per the latest SAP version
		Page 18 Section 4.4	Updated all the Baseline parameters that need to analyze	Updated as per the latest SAP version
29JUL2020 Version AC	90702621 Rev/Ver AE	Page 15 Section 3.2.2	Updated text for the expected mean acute reduction.	Updated the endpoint hypothesis consideration
		Page 20 Section 5.5	Updated text based on sensitivity analysis for missing outcome data	
		Page 21 Section 5.6	Updated text for Univariate and multi-variate analysis	
19OCT2020 Version AD	90702621 Rev/Ver AE	Page1 Title page	Updated Protocol Number and SAP version	
		Page 8 Section 1	Updated Required Medication Therapy	As per latest Protocol version AC update
		Page 18 Section 4.2	Updated analysis set population wordings considered for analysis	As per Medical writer advice
		Page 18 Section 4.2	Enrollment subjects updated from 18 to 25 – 25% to 35% as per the latest protocol	As per latest Protocol version AC update

08APR2021 Version AE	90702621 Rev/Ver AE	Page 21 Section 5.2	Updated Interim Analysis	BSC study team internally decided to add an interim analysis to care about the subject's safety (6 and 12-months in the PE report).

TABLE OF CONTENTS

1 PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients
(JETSTREAM CHINA)</td></tr>
<tr><td>Objective(s)</td><td>To evaluate the safety and effectiveness of JETSTREAM™ Atherectomy System (Jetstream) for treating symptomatic Chinese patients with occlusive atherosclerotic lesions in native superficial femoral artery (SFA) and/ or proximal popliteal arteries (PPA)during percutaneous peripheral vascular intervention</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The Jetstream System is intended for use in atherectomy of the peripheral vasculature and to break apart and remove atherosclerotic disease, debris, and thrombus from the SFA and/or PPA</td></tr>
<tr><td>Test Device</td><td>Boston Scientific JETSTREAM™ Atherectomy System (Jetstream system), including Atherectomy Console (Jetstream Console) and Atherectomy Catheter (Jetstream Catheter)</td></tr>
<tr><td>Control Device</td><td>N/A</td></tr>
<tr><td>Device Sizes</td><td>The Jetstream System is a catheter based atherectomy device comprised of either a fixed Jetstream SC Catheter or an expandable Jetstream XC Catheter, Control Pod and PV Console.
1. Jetstream Console
2. Jetstream Catheter
<table>
<tr><th>Model</th><th>Catheter Length（cm）</th><th>Tip Diameter（mm）</th><th>Minimum Matched Introducer Size（F）</th><th>Maximal Matched Guidewire Diameter（inch）</th><th>Maximum Catheter Profile（mm）</th></tr>
<tr><td>Jetstream XC 2.1/3.0</td><td>135</td><td>2.1/3.0</td><td>7</td><td>0.014</td><td>2.5</td></tr>
<tr><td>Jetstream XC 2.4/3.4</td><td>120</td><td>2.4/3.4</td><td>7</td><td>0.014</td><td>2.45</td></tr>
<tr><td>Jetstream SC 1.6</td><td>145</td><td>1.6</td><td>7</td><td>0.014</td><td>2.33</td></tr>
<tr><td>Jetstream SC 1.85</td><td>145</td><td>1.85</td><td>7</td><td>0.014</td><td>2.33</td></tr>
</table></td></tr>
<tr><td>Study Design</td><td>This clinical study is a prospective, non-randomized, multicenter, single-arm study to demonstrate the acceptable safety and performance of the JETSTREAM™ Atherectomy System (Jetstream) used during percutaneous peripheral vascular intervention in patients with occlusive atherosclerotic lesions in the native SFA and/or PPA. It is intended that all patients with</td></tr>
</table>

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients (JETSTREAM CHINA**)**	
	qualifying lesions would be considered for enrollment and treated with the Jetstream System.
Planned Number of Subjects	Up to 72 subjects (including roll-in subjects) with symptomatic occlusive atherosclerotic lesions in the native SFA and/ or PPA will be enrolled. All eligible subjects will be treated with the Jetstream System.
Planned Number of Centers / Countries	Up to 6 clinical sites located in China are expected to participate in this study.
Primary Endpoint	**Primary Safety Endpoint:** Major Adverse Event (MAE), defined as all-cause death, target limb unplanned major amputation and/or target lesion revascularization (TLR), within 30 days post index procedure **Primary Effectiveness Endpoint:** Acute reduction of percent diameter stenosis (%DS) post atherectomy but prior to any adjunctive therapy, when compared to its baseline diameter stenosis (absolute mean percentage).
Additional Endpoints	• Procedural success, defined as ≤ 30% residual angiographic stenosis in 2 near-orthogonal projections by visual assessment, after successfully debulking the target lesion and adjunctive interventions (such as percutaneous transluminal angioplasty/stenting) without any MAE within 24 hours post index procedure • Primary vessel patency of the treated segment assessed by duplex ultrasound sonography (DUS) at 6 and 12 months post-procedure without TLR* • Clinical success rate (defined as improved Rutherford classification by at least +1 class compared to baseline) at 30 days, 6 and 12 months • Hemodynamic success rate (defined as positive change in Ankle-Brachial Index) at 30 days, 6 and 12 months • MAE rate 6 and 12 months post-index procedure • All-cause death at 30 days, 6 and 12 months • Clinically-driven TLR and TVR rate at 30 days, 6 and 12 months • Target limb major amputation at 30 days, 6 and 12 months • Rate of peri-procedural complications: ➢ Perforation at treated segment ➢ Abrupt closure at treated segment (including dissection and thrombosis) ➢ Significant dissection (types C – F) at treated segment

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients (JETSTREAM CHINA**)**	
	➢ Aneurysm at treated segment ➢ Distal embolization * *Vessel patency is defined as freedom from more than 50% stenosis based on DUS peak systolic velocity ratio comparing data within the treated segment to the proximal normal arterial segment. A systolic velocity ratio > 2.4 suggests > 50% stenosis.*
Method of Assigning Subjects to Treatment	Once a subject signs the Ethics Committee-approved Informed Consent Form, and has met all inclusion criteria and has no exclusion criteria, they are eligible to be enrolled in the clinical study. All eligible subjects will be considered to receive treatment with the Jetstream System. Enrollment occurs at the time of advancement of the Jetstream catheter into the introducer sheath.
Follow-up Schedule	Follow-up time points include: pre-discharge, 30 days, 6 and 12 months. All visits will be conducted in a clinic setting. Subjects who are enrolled but the Jetstream System is not used will be followed through the 30-day follow-up visit only.
Study Duration	The study will be considered complete after all subjects have completed the 12-month follow-up visit, are withdrawn from the trial (due to death or having been lost to follow-up) or their follow-up window (i.e., 30 days after a scheduled follow-up visit) has closed.
Required Medication Therapy	• If subjects have not already taken acetylsalicylic acid (ASA) (minimum 75 mg per day) and Clopidogrel (75 mg/day) or ticlopidine (200 mg/day) for at least 24 hours prior to the procedure, they will receive loading doses of 300 mg ASA and 300 mg Clopidogrel or 200 mg ticlopidine before the index procedure. • At the time of the procedure, subjects receive an intra-arterial bolus of heparin (usually 3000-5000 IU). • After the procedure, all subjects are recommended to be treated with ASA (minimum 75 mg per day) indefinitely, and with Clopidogrel (min 75 mg per day) or ticlopidine (200 mg) for 6 months. Note: a subject could be exempt of antiplatelet requirements if he/she requires Coumadin or other similar anti-coagulant due to known comorbidities and in the opinion of the investigator the combination of dual anti-platelet therapy (DAPT) and anticoagulation could pose an intolerable bleeding risk.
Key Inclusion Criteria	1. Subjects age 18 and older

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients (JETSTREAM CHINA**)**	
	2. Subject or the subject's legal representative is 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 3. Subject has documented chronic, symptomatic lower limb ischemia defined as Rutherford categories 2 - 4, and is eligible for percutaneous peripheral vascular intervention 4. Stenotic, restenotic or occlusive lesion(s) located in the native SFA and/or PPA, and meet all of following angiographic criteria by visual assessment: a. Atherosclerotic lesions with diameter stenosis ≥ 70% b. Guidewire must cross lesion(s) within the true lumen, without a sub-intimal course by physicians performed, based on visual estimate c. Minimum vessel diameter proximal to the lesion ≥ 3 mm and ≤ 6 mm d. Lesion length of single or multiple focal stenosis or chronic total occlusion (CTO) lesion can be up to 15 cm long e. Target lesion located at least 3 cm above the inferior edge of the femur 5. Patent infrapopliteal and popliteal artery, i.e., single distal runoff or better with at least one of three vessels patent (< 50% stenosis by visual assessment) to the ankle or foot with no planned intervention
Key Exclusion Criteria	1. Target lesion is located in the iliac artery or above the SFA 2. Target lesion stenosis < 70% 3. Target lesion is moderately to severely angulated (> 30°) or torturous at treatment segment 4. Target lesion/vessel previously treated with drug-coated balloon within 12 months prior to the index procedure 5. Target lesion/vessel previously treated with atherectomy, laser or other debulking devices prior to the index procedure 6. Target lesion/vessel with in-stent restenosis 7. Subjects who have undergone prior surgery or endovascular intervention of SFA/PPA in the target limb to treat atherosclerotic disease within 3 month prior to the index procedure 8. Use of drug-coated devices, or laser or any other debulking devices other than Jetstream System (such as CTO devices or cutting balloon) in the target limb during the index procedure 9. History of major amputation in the target limb

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients (JETSTREAM CHINA**)**	
	10. Documented life expectancy less than 12 months due to other medical co-morbid condition(s) 11. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated 12. Known history of coagulopathy or hypercoagulable bleeding disorder 13. Known hypersensitivity/allergy to the investigational devices or protocol related therapies (e.g., nitinol, stainless steel or other stent materials, and antiplatelet, anticoagulant, thrombolytic medications) 14. Platelet count < 80,000 mm^3 or > 600,000/ mm^3 or history of bleeding diathesis 15. Undergoing hemodialysis or concomitant renal failure with a serum creatinine > 2.0 mg/dL (176.8umol/L) 16. History of myocardial infarction (MI), stroke/cerebrovascular accident (CVA) or gastrointestinal bleeding within 6 months prior to the enrollment 17. Unstable angina pectoris at the time of enrollment. 18. History of severe trauma, fracture, major surgery or biopsy of a parenchymal organ within past 14 days 19. Pregnant, breast feeding, or plan to become pregnant in the next 12 months 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 outflow lesions in the target limb requiring intervention during the index procedure 23. Presence of other hemodynamically significant lesions in the target limb requiring intervention within 30 days of enrollment 24. Acute ischemia and/or acute thrombosis of the target lesion/vessel prior to the index procedure 25. Presence of aneurysm in the target vessel 26. Perforated vessel as evidenced by extravasation of contrast media prior to the enrollment
Multiple Interventions	• Contralateral Limb

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients (JETSTREAM CHINA**)**	
During Index Procedure	Iliac lesion(s) in the contralateral limb may be treated using the same access site during the index procedure under the following conditions: ➢ Treatment with a commercially available device occurs prior to the enrollment of the target SFA/PPA lesion, and ➢ Treatment of the iliac lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as < 30% residual stenosis by visual estimation) ➢ If the above criteria are not met, the subject may not be enrolled to the study but may be rescreened for eligibility after 30 days. • Target Limb Additional non-target inflow lesions (including iliac lesion and/or common femoral lesion proximal to the femoral bifurcation) in the target limb may be treated during the index procedure under the following conditions: ➢ Treatment with a non-drug-eluting commercially available device occurs prior to the enrollment of the target SFA/PPA lesion and ➢ Treatment of the iliac lesion is deemed an angiographic success without clinical sequelae (success is measured as < 30% residual stenosis by visual estimation) ➢ If the above criteria are not met, the subject may not be enrolled to the study but may be rescreened for eligibility after 30 days.
Statistical Methods	
Primary Safety Hypothesis	The primary safety hypothesis to be tested is that 30-day MAE-free rate in subjects treated with Jetstream System exceeds a PG of 88% at one-sided significance level of 2.5%.
Primary Safety Statistical Test Method	A normal approximation test will be used to assess the one-sided hypothesis of PG: H_0: Pt ≤ PG (not met) H_1: Pt > PG (met) Where Pt is the 30-day MAE-free rate for the subjects treated with Jetstream System and the PG is 88%.* *The PG of 88% was estimated on the basis of available literature and is consistent with those describing atherectomy outcomes.** ** ***Rocha-Singh et al. Performance Goals and Endpoint Assessments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients With Symptomatic Peripheral Arterial Disease. Catheterization and Cardiovascular Interventions 2007;69:910–919***

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients (JETSTREAM CHINA**)**	
Primary Effectiveness Hypothesis	The primary effectiveness hypothesis to be tested is that acute reduction of percent diameter stenosis (%DS) in subjects treated with Jetstream System exceeds 40%* within subject at one-sided significance level of 2.5%. *The expected mean acute reduction (i.e. %DSbefore Jetstream – %DSafter Jetstream) was 40%; the primary effectiveness hypothesis is to demonstrate there is a significant acute reduction (>0).
Primary Effectiveness Statistical Test Method	A paired t-test will be used to assess the one-sided hypothesis of reduction in %DS before and after subjects treated with Jetstream System. H_0: $\Delta t \leq 0$ (not met) H_1: $\Delta t > 0$ (met) where Δt is the averaged difference in acute reduction of %DS before and after the subjects treated with Jetstream System and the within-subject treatment effect is 40% with standard deviation of 18% derived by the Pathway PVD study, Jetstream Calcium study and JET Registry**. **The before-and-after atherectomy in the Pathway PVD shows 79.4%±17.7% and 35.0%±16.1% respectively. The before-and-after atherectomy in Jetstream Calcium study shows 86.9%±9.0% and 37.0%±13.0%. The before-and-after atherectomy in JET Registry shows 91.1%±9.8% and 44.4%±20%, and the acute reduction of %DS is 46.7%±20.5%.
Success Criteria for the PG Study	<u>Success Criteria for Primary Safety Endpoint</u> Jetstream System will be concluded as meeting PG for device safety if the one-sided lower 97.5% confidence bound on the observed 30-day MAE-free rate is greater than 88%. <u>Success Criteria for Primary Effectiveness Endpoint</u> Jetstream System will be concluded as meeting endpoint for device effectiveness if the one-sided lower 97.5% confidence bound on the difference between before and after atherectomy in %DS within subject is greater than zero. <u>Success Criteria for the Study</u> If the primary safety and the primary effectiveness endpoints are both met, the study will be considered a success and both device safety and effectiveness will be claimed.
Sample Size Parameters	The overall sample size is consist of the primary cohort and roll-in subjects. The sample size of primary cohort is driven by the primary safety endpoint.

Prospective, non-randomized, multicenter clinical study of the JETSTREAM™ Atherectomy System (Jetstream) in treatment of occlusive atherosclerotic lesions in the superficial femoral and/ or proximal popliteal arteries in Chinese patients (JETSTREAM CHINA**)**	
	• Power ≥ 90% • One-sided overall significance level = 2.5% (alpha) • PG for 30-day MAE-free rate = 88% • Expected 30-day MAE-free rate = 99% • Attrition rate = 15% (loss to follow-up at 30 days) • A minimum of 50 subjects to be evaluable at 30 days that will provide at least 99% power for the primary Safety endpoint • A sample size of 60 subjects to be enrolled in the primary cohort at baseline • With additional 2 roll-in subjects per site, the overall subjects to be enrolled are up to 72.
Core Lab	All angiographic and DUS readings will be assessed by independent core laboratories
Study Committee	A clinical event committee (CEC) will review and adjudication following pre-specified CEC events: • Death • Target limb major amputation • Target vessel revascularization (TVR) and target lesion revascularization (TLR) • Distal embolization requiring additional treatment • Perforation during index procedure that requires additional treatment

2 INTRODUCTION

This Statistical Analysis Plan (SAP) has been designed to document the planned analyses to be consistent with the objectives of the JETSTREAM China protocol. The specified analyses may be provided in reports to competent authorities and/or for scientific presentations and/or manuscripts. The primary analyses will be based on the single-arm procedure assessment (paired T-test) and 30-day post-procedure assessment for performance goal (PG).

Roll-in subjects will be analyzed separately for observational purpose.

3 PRIMARY ENDPOINTS ANALYSES

The sample size is justified by hypotheses parameters and driven by the 30-day primary safety endpoint to preserve adequate statistical testing power for either the primary effectiveness or the primary safety endpoints.

The primary effectiveness and safety hypotheses are planned for being tested after procedure and through 30 days, respectively at the pre-specified significance level of one-sided 2.5% each by the Bonferroni adjustment.

3.1 Primary Safety Endpoint

The 30-day MAE-free rate is selected to be assessed for the primary safety composite endpoint. The safety goal is designed to demonstrate that Jetstream meets the PG in terms of MAE-free rate through 30 days post-procedure.

3.1.1 Definition of MAE

Major Adverse Events (MAEs) defined as all causes of death, target limb unplanned major amputation, and/or target lesion revascularization (TLR) through 30 days

3.1.2 Safety Hypotheses

The primary safety hypothesis to be tested is that 30-day MAE-free rate in subjects treated with Jetstream meets the PG at a one-sided significance level of 2.5%.

The null hypothesis (H_0) states that the PG is not met as opposed to the alternative hypothesis (H_1) which states that the PG is met. The hypotheses inequalities are shown below:

H_0: Pt ≤ PG (not met)

H_1: Pt > PG (met)

where Pt is the 30-day MAE-free rate for the subjects treated with Jetstream System and the PG is 88%. The PG of 88% is estimated on the basis of available literature and is consistent with those described atherectomy outcomes

3.1.3 Safety Sample Size

The overall sample size is consist of the primary cohort and roll-in subjects. The primary cohort is driven by the primary safety endpoint. Approximately 72 subjects are planned to be enrolled in the single-arm study. The sample size justification is based on the following assumptions.

- Power ≥ 90%
- One-sided significance level (alpha) = 2.5%
- PG for 30-day MAE-free rate = 88%
- Expected 30-day MAE-free rate = 99%
- Attrition rate in 30 days = 15%
- N = 50 evaluable subjects are required at 30 days
- A maximum of N = 60 subjects to be enrolled in the primary cohort at baseline
- With additional 2 roll-in subjects per site, the overall subjects to be enrolled are approximately 72.

3.1.4 Safety Statistical Methods

A normal approximation test for comparing observed 30-day MAE-free rate with the PG will be used to assess the safety hypotheses for a minimum of 50 evaluable subjects.

3.1.5 Worst Case Assessment for Safety

The PG of 88% will only allow 1 subjects with 30-day MAE out of 50 subjects treated with Jetstream That is, the observed 30-day MAE-free rate in Jetstream will need to be at least 98% (49/50) in order to claim safety PG.

3.1.6 Additional Justification of Sample Size Parameters

The PG of 30-day MAE-free rate for Jetstream was based on the DEFINITIVE Ca++ study results (Roberts et. al. 2014), published by Catheterization and Cardiovascular Interventions. The 95% lower confidence limit 88.3% was reported.

The 30-day freedom from MAE rate was 93.1% (122/131) in DEFINITIVE Ca++ study with 95% exact confidence intervals: 87.4%, 96.8% estimated by SAS.

3.2 Primary Effectiveness Endpoint

The acute reduction of percent diameter stenosis (%DS) within a subject post atherectomy but prior to any adjunctive therapy is chosen to be assessed for the primary effectiveness endpoint. The goal is set to demonstrate that within a subject, the %DS in post treatment is smaller than the %DS in before-treatment by a pre-specified reduction during the procedure.

3.2.1 Definition of Acute Reduction

The acute reduction of %DS is defined to compare the post atherectomy but prior to any adjunctive therapy to its baseline diameter stenosis.

3.2.2 Effectiveness Hypotheses

The primary effectiveness hypothesis to be tested is that the acute reduction of %DS in subjects treated with Jetstream System exceeds 40%* within subject at a one-sided significance level of 2.5%.

The null hypothesis (H_0) states that there is no treatment effect before and after subjects treated with Jetstream System as opposed to the alternative hypothesis (H_1) which states that there is a treatment effect. The hypotheses inequalities are shown below:

H_0: $\Delta t \leq 0$ (not met)

H_1: $\Delta t > 0$ (met)

where Δt is the averaged difference in acute reduction of %DS before and after the subjects treated with Jetstream System and the within-subject treatment effect is 40% with standard deviation of 18% derived by the Pathway PVD study, Jetstream Calcium study and JET Registry.

*The expected mean acute reduction (i.e. %DSbefore Jetstream – %DSafter Jetstream) was 40%; the primary effectiveness hypothesis is to demonstrate there is a significant acute reduction (>0).

3.2.3 Effectiveness Sample Size and Power Analysis

The power analysis for the primary effectiveness endpoint is based on the following assumptions.

- One-sided significance level (alpha) = 2.5%
- Expected acute reduction of %DS = 40% with the standard deviation = 18%, within the range of historical data

The sample size is driven by the primary safety endpoint to provide at least 99% power to assess the primary effectiveness endpoint.

3.2.4 Effectiveness Statistical Methods

A paired t-test for the reduction in %DS before and after subjects treated with Jetstream System will be used to assess the effectiveness hypotheses for a minimum of 50 evaluable subjects.

3.2.5 Worst Case Assessment for Effectiveness

The mean and standard deviation of the reductions are based on each subject's change in %DS before and after atherectomy. If the standard deviation of 18% is observed, the acute reduction of %DS will be at least 6% to claim a success. Other scenarios are shown below.

Standard Deviation in Reduction (%DS)	Minimal Diff in Reduction (%DS)
8-10	3
11-14	4
15-17	5
18-21	6
22-24	7
25-28	8
29-31	9
32-35	10

3.2.6 Additional Justification of Sample Size Parameters

The expected acute reduction of %DS was based on the Pathway PVD study, Jetstream Calcium study, and JET Registry.

The before-and-after atherectomy in the Pathway PVD shows 79.4%±17.7% and 35.0%±16.1% respectively. The before-and-after atherectomy in Jetstream Calcium study shows 86.9%±9.0% and 37.0%±13.0%. The before-and-after atherectomy in JET Registry shows 91.1%±9.8% and 44.4%±20%, and the acute reduction of %DS is 46.7%±20.5%.

3.3 Success Criteria

The success criteria are defined hierarchically. The primary effectiveness hypothesis will be performed at only when the primary safety hypothesis is achieved.

3.3.1 Success Criteria for the Primary Safety Endpoint

Jetstream System will be concluded as meeting PG for device safety if the one-sided lower 97.5% confidence bound on the observed 30-day MAE-free rate is greater than 88%.

3.3.2 Success Criteria for the effectiveness Endpoint

Jetstream System will be concluded as meeting endpoint for device effectiveness if the one-sided lower 97.5% confidence bound on the difference between before and after atherectomy in %DS within subject is greater than zero.

3.3.3 Success Criteria for the Study

If the primary safety and the primary effectiveness endpoints are both met, the study will be considered a success and both device safety and effectiveness will be claimed. The success criteria is defined hierarchically. The primary effectiveness hypothesis will be performed at only when the primary safety hypothesis is achieved.

4 GENERAL STATISTICAL CONSIDERATION

4.1 Analysis Sets

The primary and pre-specified additional endpoints will be analyzed on an ITT basis and on a per-protocol basis. For the ITT analysis, all subjects who sign the written ICF and are enrolled in the study will be included in the analysis sample, regardless of whether the subject used the Jetstream System. For the per-protocol analysis, only enrolled subjects who are treated with the study device in the target lesion will be included in the analysis sample.

Data from per-protocol cohort and Roll-in cohort will be analyzed separately for observational purpose.

4.2 Control of Systematic Error/Bias

Selection of subjects will be made from the investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria that have signed the protocol-specific ICF will be eligible for enrollment in the trial. Consecutively eligible subjects should be enrolled into the study to minimize selection bias. In determining subject eligibility for the study, the investigator's assessment of imaging will be used. The effectiveness endpoint data obtained from the core laboratory and the safety adjudicated data from independent Clinical Event Committee (CEC) will be used for the primary analyses.

4.3 Enrollment for Each Investigative Site

The enrollment cap for each study site is 35% of total enrolled subjects. No study sites will be allowed to enroll more than 35% (N=25) of the total number of enrolled subjects to avoid treatment center bias and ensure homogeneous study results.

4.4 Baseline Data Analyses

Subject demographics, and clinical characteristics, site-reported and core lab reported lesion characteristics, procedure assessment, device information, and medication compliance will be summarized using descriptive statistics. The analysis level may be (but will not be limited to) by subject, lesion, procedure, or device.
For continuous and/or ordinal variables, the descriptive statistics will include mean, standard deviation, number evaluated, minimum and maximum. Some specific variables may also include additional statistics such as median and confidence intervals. For binary or categorical variables, the descriptive statistics will include percentage, numerator, denominator, and number evaluated. Some variables may include confidence intervals as needed.

At baseline demographics, medical history, cardiac history, Neurological history, peripheral vascular history and lesion characteristics like lesion type, lesion classification, Target lesion final outcome will be reported.

At procedure, procedure characteristics and study device used by Catheter model and tip diameter will be reported.

5 ADDITIONAL STATISTICAL ANALYSES

5.1 Secondary Endpoints Assessments

Secondary assessments may refer to (but not limited to) peri-procedural complications, clinical/procedural/hemodynamic success, safety/effectiveness endpoints, any type of AE rates at time points that data is collected (refer to the protocol section 7.2). All additional assessments are observational

- Procedural success, defined as ≤ 30% residual angiographic stenosis in 2 near-orthogonal projections by visual assessment, after successfully debulking the target lesion and adjunctive interventions (such as percutaneous transluminal angioplasty/stenting) without any MAE within 24 hours post index procedure
- Primary (vessel) patency of the treated segment assessed by duplex ultrasound sonography (DUS) at 6 and 12 months post-procedure without TLR
- Clinical success rate (defined as improved Rutherford classification by at least +1 class compared to baseline) at 30 days, 6 and 12 months
- Hemodynamic success rate (defined as positive change in Ankle-Brachial Index) at 30 days, 6 and 12 months
- MAE rate 6 and 12 months post-index procedure
- All-cause death at 30 days, 6 and 12 months
- Clinically-driven TLR and TVR rate at 30 days, 6 and 12 months
- Target limb major amputation at 30 days, 6 and 12 months
- Rate of peri-procedural complications:
    - Perforation at treated segment
    - Abrupt closure at treated segment (including dissection and thrombosis)
    - Significant dissection (types C – F) at treated segment
    - Aneurysm at treated segment
    - Distal embolization

Note that the vessel patency is defined as freedom from more than 50% stenosis based on DUS peak systolic velocity ratio (PSVR) comparing data within the treated segment to the proximal normal arterial segment. A systolic velocity ratio > 2.4 suggests > 50% stenosis.

No formal tests of hypotheses are proposed for secondary endpoints. Statistical comparisons may be performed for exploratory purposes. No formal inferences are planned on the additional assessments and therefore alpha-adjustments for multiple comparisons will not be used.

All additional assessments are observational.

For Primary endpoint report (30-Day) below Secondary Assessments will be performed:

- Procedural success.
- Clinical success rate at 30 Days.
- Hemodynamic success rate at 30 Days.
- All-cause death at 30 days.
- Clinically-driven TLR and TVR rate at 30 days.
- Clinically-driven TLR and TVR rate at 30 days.
- Target limb major amputation at 30 days.
- Rate of peri-procedural complications.

For 12-Month report below Secondary Assessments will be performed:

- Procedural success.
- Primary (vessel) patency of the treated segment assessed by duplex ultrasound sonography (DUS) at 6 and 12 months post-procedure without TLR
- Clinical success rate at 30 days, 6 and 12 months.
- Hemodynamic success rate at 30 days, 6 and 12 months.
- MAE rate 6 and 12 months post-index procedure.
- All-cause death at 30 days, 6 and 12 months.
- Clinically-driven TLR and TVR rate at 30 days, 6 and 12 months.
- Target limb major amputation at 30 days, 6 and 12 months.
- Rate of peri-procedural complications.

5.2 Interim Analyses

Primary Endpoint report should include all enrolled 72 subjects in 1 month data as the enrollment could not be completed as plan of all the subjects. The BSC study team internally decided to add an interim analysis to care about the subject's safety, not only include Primary Endpoint and show all data that includes 6 month and 12 month in the PE report.

5.3 Subgroup Analyses

Primary endpoints and/or additional assessments will be summarized by the following categories (but not limit to):

- Lesion location (distal, mid, proximal, ostial)
- Sex (male, female)
- Age (-64, 65-74, 75-)
- Lesion Characteristics (lesion length -50, 50-100, 100-150, 150- mm)
- Jetstream Catheter size (SC1.6, SC1.85, XC 2.1/3.0, XC 2.4/3.4)
- Diabetes (medically treated, non-medically treated)

All subgroup analyses are observational. No formal tests of hypotheses are proposed for subgroups and therefore alpha-adjustment for multiple comparisons will not be used.

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

Boston Scientific will employ robust oversight in order to minimize the loss of subjects throughout any trial follow-up. Additionally, the case report forms are easy-to-follow and maximize the data collection required at each follow-up visit without placing undue burden on the subject. Strategies that are planned to be utilized in the study include:

- 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.
- Tools in the site's Manual of Operations to assist with follow-up visit planning (e.g. follow-up wheels or similar tools).
- The use of trial newsletters to remind sites of upcoming visits and other project-related milestones to ensure data is being entered promptly and is complete.

5.5 Sensitivity Analysis for Missing Outcome Data

Sensitivity analyses for the primary effectiveness and/or safety endpoints assessment will be conducted to assess the impact of missing data on the result's robustness. In addition to the use of the worst-case analysis, the tipping point analysis will be performed as post-hoc analysis to consider all combinations of present/absent for all subjects with missing primary outcome.

The analysis finds a (tipping) point in this spectrum of assumptions, at which conclusions change from being favorable to the experimental treatment to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. The tipping point can be identified while the result is no longer statistically significant. This imputation analysis used a specified

sequence of shift parameters, which adjust the imputed values for observations in the active treatment group. The tipping point can be identified while the result is no longer statistically significant. A sample of SAS code for sensitivity analysis using the tipping-point method is provided below.

Multiple imputation often assumes that missing values are missing at random (MAR), and the following statements use the MI procedure to impute missing values under this assumption:

```
proc mi data=Mono2 seed=14823 out=outmi;
  class Trt;
  monotone reg;
  var Trt y0 y1;
run;
```

The following statements generate regression coefficients for each of the 25 imputed data sets:

```
ods select none;
proc reg data=outmi;
  model y1= Trt y0;
  by  Imputation;
  ods output parameterestimates=regparms;
run;
ods select all;
```

The following statements combine the 20 sets of regression coefficients:

```
proc mianalyze parms=regparms;
  modeleffects Trt;
run;
```

The "Parameter Estimates" table will be created which displays a combined estimate and standard error for the regression coefficient for Trt. The table displays a 95% confidence interval, which does not contain 0. The table also shows a t statistic of with the associated p-value 0.0011 for the test that the regression coefficient is equal to 0.

The conclusion is usually based on the MAR assumption.

5.6 Multivariable Analyses

Univariate and multivariable analyses will be performed as post-hoc analyses to assess the effect of potential predictors for the primary safety endpoint in a logistic regression model.

Clinically and/or statistical meaningful baseline covariates will be selected in the regression model.

For each outcome, predictors will be listed in ascending order of p-value. Univariate analyses will be performed. For the multivariable analyses, only coefficients in the final model, i.e., with p-values less than 0.1 will be listed.

No formal conclusion will be made by this secondary post-hoc analysis.

An appropriate regression model will be used to assess the effect of each individual covariate on study outcomes. Those variables found to be significant at the 0.1 level will be included in a multivariable regression model. The significance level thresholds will be set at 0.1.

For each outcome, predictors will be listed in ascending order of p-value. For the multivariate analyses, coefficients with p-values greater than 0.1 will not be listed.

5.7 Angiography

All subjects will undergo angiographic assessment during the index procedure per standard of care. Subjects requiring any subsequent revascularization procedure of the target vessel during the 12-month follow-up period will undergo angiographic assessment at the time of reintervention as standard of care.

Angiographic data and images collected during the index procedure and during any revascularization procedure of the target vessel during the follow-up period must be forwarded to the angiographic core laboratory for analysis. Angiograms performed at outside institutions should also be sent to the core laboratory. Angiograms will be centrally assessed by the core laboratory, for qualitative and quantitative analyses.

5.8 Duplex Ultrasound

Duplex Ultrasound (DUS) assessments will be performed at 6 months (182±30 days) and 12 months (365±30 days) post-index procedure. Only records obtained during the clinical visit window will be selected for analysis unless the Biostatistics personnel are informed otherwise. In the case where multiple examinations are performed during the visit window, the best interpretable record will be selected. Measurements from DUS assessments 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. Therefore a prior TLR may suggest a primary patency failure regardless of DUS result(s).

In the determination of >50% stenosis, a PSVR > 2.4 is used for the primary assessment. However a PSVR > 2.0 (e.g. alternative definition of vessel patency in SuperNOVA; BMS) and/or PSVR > 2.5 (e.g. definition of vessel patency in MAJESTIC; DES) and/or other clinical recommendation may be used in post-hoc analyses for publication purpose

The primary patency (binary rates) will be calculated based on the subjects who have adequate follow-up and/or have DUS assessments. The denominator will be based on number of subjects who reach the protocol-defined lower window and/or have events. The numerator will be based on number of subjects who finish the scheduled assessments (i.e. success or failure) within the protocol-defined upper window.

Follow-up Visit	Protocol Defined Lower[1] Window for Assessment	Protocol Defined Upper Window for Assessment
6 Months	152	212
12 Months	335	395

[1]Days for adequate follow-up

5.9 Time-To-Event Kaplan-Meier Analysis

The Kaplan-Meier product-limit method will be used to estimate event or event-free rates for time-to-event outcomes as post-hoc analyses.

5.9.1 Kaplan-Meier for Primary Patency

The Kaplan-Meier analysis is aimed to capture the first event for each subject. There are two ways to determine the first event, whichever comes first.

- Clinically-driven TLR date by CEC
- Ultrasound date to identify a subject not patent (i.e. PSVR>2.4)

5.9.2 Kaplan-Meier for MAE-Free

The Kaplan-Meier analysis will capture the first event for MAE-free composite endpoint and/or for selected individual components.

5.10 Time to CEC Adjudicated Events and Time to Adequate Follow-Up

The MAE binary rates (overall and individual components), as opposed to Kaplan-Meier rates, will be calculated based on the subjects who have adequate follow-up and/or have experienced any components of MAE.

The protocol-defined MAEs include:

- all causes of death
- target limb unplanned major amputation
- TLR

5.10.1 Event Rates Presented Using "Month" System

The denominator will be based on number of subjects who reach the protocol-defined lower window (i.e. adequate follow-up days) and/or subjects who experience the event. The numerator will be based on number of subjects-level events within the protocol-defined upper window. Subject-level events beyond the upper window will be counted as next visit.

Follow-up Visit	Protocol Defined Lower Window	Protocol Defined Upper Window
1 Month[1]	23	37
6 Months	152	212
12 Months	335	395

[1]All events with 1-month window will be collected. However for the primary safety endpoint, events up to 30 days post-procedure will be included.

5.10.2 Event Rates Presented Using Exact Days Cut-Off System

The denominator will be based on number of subjects who reach the protocol-defined lower window (i.e. adequate follow-up days) and/or subjects who experience the event. The numerator will be based on number of subjects-level events within the exact desired cut-off days. Subject-level events beyond the exact cut-off days will be counted as next cut-off days.

For the primary safety endpoints, the analysis will be performed with the exact days (i.e. events up to 30 days).

Follow-Up Cut-Off	Days for Adequate Follow-Up	Maximum Days to Event
30 Days[1]	23	30
182 Days	152	182
365 Days	335	365

[1]All events with 1-month window will be collected. However for the primary safety endpoint, events up to 30 days post-procedure will be included.

5.10.3 Missing Event Dates Considerations

All event rates will be calculated relative to the date of procedure (i.e. post-procedure).

When calculating rates of adverse events with missing event date (i.e. mm/dd/yyyy), the ideal is to work with safety and/or data management representatives to query sites for missing data. However missing and partial missing dates may be handled as using the worst case scenario as follows:

Partial Date Description	Action Taken
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

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

Subject-level event rates will be calculated at various time points (e.g. exact days) 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 descriptive statistics.

5.12 Technical and Procedural Successes

Technical success is defined as delivery and deployment of the assigned study stent to the target lesion to achieve residual angiographic stenosis no greater than 30% assessed visually.

Procedural success is defined as technical success with no MAEs noted within 24 hours of the index procedure. The procedural success is included in the protocol-defined additional assessments.

5.13 Primary and Secondary Sustained Clinical Improvements

The rates of primary and secondary sustained clinical improvements are to assess the changes in Rutherford classification from baseline at 1 month, 6 months, 12 months, 24 months, and 60 months.

The primary sustained clinical improvement is defined as an improvement in Rutherford classification of one or more categories as compared to baseline without the need for repeat TLR.

The secondary sustained clinical improvement (i.e. clinical success) is defined as an improvement in Rutherford classification of one or more categories as compared to baseline including those subjects with repeat TLR. The clinical success at 1 month, 6 months, and 12 months are included in the protocol-defined additional assessments.

The clinical deterioration is defined as downgrade in Rutherford classification of one or more categories as compared to baseline.

5.14 Hemodynamic Improvement

The rate of hemodynamic improvement is to assess the changes in ABI from baseline at 1 month, 6 months, and 12 months. The definition of improvement is to observe either the ABI measurement ≥ 0.9 or the change from baseline ≥ 0.1.

There are two scenarios for hemodynamic improvement shown below.

Subject #1's baseline ABI= 0.95 and 12-month ABI= 1.0. The subject #1 shows 12-month improvement due to 12-month observed ABI= 1.0.

Subject #2's baseline ABI= 0.6 and 12-month ABI= 0.8. The subject is 12-month improvement due to the ABI increase of 0.2 (i.e. 0.8 – 0.6) regardless of 12-month ABI measurement of 0.8 (i.e. <0.1).

Note that the ABI deterioration is defined as observing 0.1 or more in ABI decrease from baseline.

5.15 Analyses Software

All statistical analyses will be performed and validated by the independent CRO (e.g. IQVIA in Bangalore) 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). BSC will review statistical reports.

5.16 Changes to Planned Analyses

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

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. Statistical analyses and validation will be done by an independent CRO.

7 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by the independent CRO.

7.1 Derivation for Primary Patency

The primary patency is based on PSVR measurement derived from the core laboratory data provided by Vascular Ultrasound Core Lab (i.e. VASCORE), clinically driven TLR determined by CEC form, and bypass surgery determined in the text field by AE form.

A subject's 12-month primary patency is derived as patent (i.e. "YES") only if:

- VASCORE form: a subject's 12-month DUS assessment is done and PSVR ≤ 2.4; and
- CEC form: no clinically-driven TLR prior to 12-month DUS visit. Note that if there is one clinically-driven TLR and the event date is later than (>) 12-month DUS visit, the subject's primary patency will remain "YES"; and
- AE form: no bypass surgery is identified prior to 12-month DUS visit. Note that if there is one surgery and the surgery date is later than (>) 12-month DUS visit, the subject's primary patency will remain "YES".

7.2 Derivation for Assisted Primary Patency

The assisted primary patency is based on PSVR measurement derived from VASCORE form only. A subject's 12-month assisted primary patency is derived as "YES" only if the subject's 12-month DUS visit is within 12-month window and PSVR ≤ 2.4.

7.3 SAS Codes for Chi-Square Test

The confidence intervals and the p-value for the chi-square test can be produced by the following SAS code.

```
proc freq data=;
    tables xx/binomial(p=) alpha=;
run;
```

For example, the worst case scenario in the PG testing of the primary safety hypotheses is used for the exercise. A dummy frequency table is coded as below.

```
%let total=50; %let yes=49; %let no=&total.-&yes.;
data dsn1;
    yn=1; wgt=&yes.; output;
    yn=0; wgt=&no.; output;
run;
```

A list of SAS codes for Binomial and Chi-Square method is used for PG=88% and 95% confidence limits.

```
proc freq data=dsn1 order=data;
   tables yn/ binomial(p=0.88) alpha=.05;
   weight wgt;
run;
```

The SAS output for the worst case scenario is presented below.

Binomial Proportion	
yn = 1	
Proportion	0.9800
ASE	0.0198
95% Lower Conf Limit	0.9412
95% Upper Conf Limit	1.0000
Exact Conf Limits	
95% Lower Conf Limit	0.8935
95% Upper Conf Limit	0.9995

Test of H0: Proportion = 0.88	
ASE under H0	0.0460
Z	2.1760
One-sided Pr > Z	0.0148
Two-sided Pr > |Z|	0.0296

Sample Size = 50

7.4 SAS Codes for Paired T-Test

The confidence intervals and paired t-test p-value can be produced by the following SAS code.

```
proc ttest data=;
 paired post*prior;
run;
```