# 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)

## CLINICAL PROTOCOL

(S6050)

National Clinical Trial (NCT) Identified Number: NCT03455855

**Sponsored By**

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**Date: October 21, 2021**

# Contact Information

| Role | Contact |
|---|---|
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| **Investigational Sites** | A list of investigational sites is maintained and provided in the Manual Of Operations. |
| **Vendors/Labs** | A list of other institutions involved in the trial is maintained and provided in the Manual Of Operations. |

**Original Release:** July 13, 2017

**Current Version:** October 21, 2021

**Revision History**

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| AA | July 13, 2017 | 90702637 Rev./Ver. AH | None | None | Original release |
| AB | August 25, 2017 | 90702637 Rev./Ver. AH | Page 9 in Protocol Synopsis "Key Exclusion Criteria" (#22) and Page 36 Section 9.3 "Exclusion Criteria" (#22) | Add an additional exclusion criterion (#22) "Presence of outflow lesions in the target limb requiring intervention during the index procedure" | To clearly exclude the candidates with outflow lesions requiring treatment during the index procedure in order to minimize interference in safety endpoints |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | Header;<br>Title Page | Protocol version was updated from "AB" to "AC";<br>Protocol release date was updated from "Aug 25, 2017" to "Jun 30, 2020"; Protocol template version was updated from "AH" to "AL". | Protocol / Protocol template update |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | Contact Information | Clinical contact was changed from "Jian Wen" to "Jing Zhou", and update the contact information accordingly. | Adjust the clinical trial manager |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | Protocol Synopsis – Key Exclusion Criteria;<br>9.3 Exclusion Criteria | In the eighth criteria, remove restrictions on the use of drug-coated devices | Adjust based on the new clinical evidence on drug-coated devices especially DCB and the current clinical practice, to achieve optimal target lesion treatment. |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | Protocol Synopsis – Multiple Interventions During Index Procedure; | Remove the restriction on the use of drug-eluting devices during the treatment of non-target inflow lesions in the target limb | Adjust based on the new clinical evidence on drug-coated devices especially DCB and the current clinical practice, |

**Revision History**

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| | | | 8.3.2 Target limb | | to achieve optimal target lesion treatment. |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | Protocol Synopsis – Primary Effectiveness Hypothesis;<br>12.1.2.1 Effectiveness Hypothesis; | Add the below note in the primary effectiveness hypothesis:<br>"*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). See Statistical Analysis Plan for detail." | Primary effectiveness hypothesis and primary effectiveness statistical test method are not match |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | 8.2.2 Target Lesion;<br>8.5 Treatment;<br>11.6.1 Treatment of target lesion | Delete "no treatment of drug-eluting device (balloon or stent) in the index lesion is allowed during the index procedure."<br>Remove the restrictions on the use of drug-eluting devices following Jetstream system during the index procedure. | Adjust based on the new clinical evidence on drug-coated devices especially DCB and the current clinical practice, to achieve optimal target lesion treatment. |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | 10 Subject Accountability | Add two sections:<br>"10.4 Lost to Follow-up" and "10.5 End-of-Study Definition" | To be consistent with the newest version of BSC global protocol template |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | 12.3.1 Analysis Sets | Provide the definition for ITT and PPS. Also, specify that the primary and pre-specified additional endpoints will be analyzed on an ITT basis and on a pre-protocol basis. | To be consistent with the requirements of medical device GCP |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | 10.3 Control of Enrollment;<br>12.3.3 Number of Subjects per | Change the number of subjects per investigator site from "25% of the total number (N=18)" to | Increase enrollment flexibility to enable potentially enrolled centers to enroll more |

**Revision History**

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| | | | Investigator Site | "35% of the total number (N=25)". | patients to accelerate enrollment |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | 12.3 General Statistical Methods | Add the section of 12.3.8 Sensitivity Analysis | To be consistent with the requirements of medical device GCP |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | 20.6 Reporting to Regulatory Authorities / IRBs /ECs /Investigators | Add the following contents:<br>"Investigator and investigational site are responsible for reporting all SAEs and device deficiencies that could lead to SAEs to IRBs/ECs, local Food and Drug Administration within 24 hours of investigator becoming aware of the event." | To be consistent with the newest version of BSC global protocol template |
| AC | June 30, 2020 | 90702637 Rev./Ver. AL | 26.2 Definitions | Modify the definition of technical success | The definition of technical success in the definition table and in the section of 7.2 are not matched |
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | Header;<br>Title Page | Protocol version was updated from "AC" to "AD";<br>Protocol release date was updated from "June 30, 2020" to "October 21, 2021"; Protocol template version was updated from "AL" to "AP"; NCT Number was added. | Protocol/Protocol template update |
| AD | October 21, 2021October 21, 2021 | 90702637 Rev./Ver. AP | Contact Information | Clinical contact was changed from "Jing Zhou" to "Peng Lv"; Author changed from "Yanfei Yang" to "Haotian Zhang" and update the contact information accordingly. | Adjust the clinical trial manager and author information. |

**Revision History**

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | 6 Study Objectives and Endpoints | Combine Section 6 "Study Objectives" and Section 7 "Study Endpoints" to comply with the updated Protocol Template. Adjust the Section number accordingly. | Adjust Section name and number according to the updated Protocol Template. |
| AD | October 21, 2021October 21, 2021 | 90702637 Rev./Ver. AP | Protocol Synopsis – Planned Number of Subjects;<br>Protocol Synopsis – Sample Size Parameters;<br>7.1 Scale and Duration<br>8.1 Study Population and Eligibility<br>9.3 Enrollment Controls<br>11.1.1 Primary Safety Endpoint | Change the estimated sample size from "up to 72 subjects" to "approximately 80 subjects", Roll-in subject number from "12 subjects" to "20 subjects" | Considering the additional sites, the planned number of roll-in subjects and overall subjects is modified. |
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | Protocol Synopsis – Planned Number of Centers / Countries;<br>7.1 Scale and Duration | Change the planned site number from "up to 6 clinical sites" to "approximately 10 clinical sites" | Increase clinical site to accelerate enrollment |
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | Protocol Synopsis – Required Medication Therapy<br>10.5 Required concomitant Therapy | Change the term "After the procedure, all subjects will 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" to "Subjects shall receive DAPT during a period of at least 6 months | Modify the required concomitant medication according to the updated antithrombotic therapies in low extremity artery disease to provide optimal antithrombotic treatment. |

**Revision History**

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| | | | | post the index procedure, if tolerated. After 6 months of DAPT post procedure, all subjects are suggested to be treated with ASA (minimum 75 mg/d) indefinitely. For subjects who are intolerant to aspirin, alternative antiplatelet medications according to investigator's discretion, such as 300mg of clopidogrel.*"*<br>Change term "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" to "The risk of bleeding may be increased in the subjects who need anticoagulation in addition to DAPT. If needed, oral warfarin and low-dose rivaroxaban (2.5mg twice per day) can be used, but no other new generation of oral anticoagulants, such as apixaban or dabigatran is allowed. subjects receiving anticoagulant therapy should not receive additional antiplatelet therapy if, in the opinion of the investigator, this could present an intolerable bleeding risk." | |
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | 7.1 *Scale and Duration* | Modify the estimated enrollment duration from "8 months" to "4 years" | Modify the estimated enrollment duration against the actual situation. |

**Revision History**

| Revision Number | Release Date | Template number and version | Section | Change | Reason for Change |
|---|---|---|---|---|---|
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | 11.3.3 Number of Subjects per Investigator Site | Change the number of subjects per investigator site from "35% of the total number (N=25)" to "35% of the total number (N=28)". | Increase the number of subjects per site according to the updated subject's amount. |
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | 11.3.6 Interim Analyses | Change the term "No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility" to "Steering Committee can make the decision to conduct the interim analyses accordingly (such as the process seriously delayed due to epidemic)." | Modify interim analysis information against the actual situation. |
| AD | October 21, 2021 | 90702637 Rev./Ver. AP | 23 Study Registration and Results | Added "Study Registration" and "Clinical Investigation Report" sections according to the protocol template update. | Update the related sections per protocol template. |

## 2. 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<br>(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.<br>1. Jetstream Console<br>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** | Approximately 80 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** | Approximately 10 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<br><br>**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<br>• Primary vessel patency of the treated segment assessed by duplex ultrasound sonography (DUS) at 6 and 12 months post-procedure without TLR*<br>• Clinical success rate (defined as improved Rutherford classification by at least +1 class compared to baseline) at 30 days, 6 and 12 months<br>• Hemodynamic success rate (defined as positive change in Ankle-Brachial Index) at 30 days, 6 and 12 months<br>• MAE rate 6 and 12 months post-index procedure<br>• All-cause death at 30 days, 6 and 12 months<br>• Clinically-driven TLR and TVR rate at 30 days, 6 and 12 months<br>• Target limb major amputation at 30 days, 6 and 12 months<br>• Rate of peri-procedural complications:<br>➢ Perforation at treated segment<br>➢ Abrupt closure at treated segment (including dissection and thrombosis) |

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|---|---|
| | ➢ Significant dissection (types C – F) at treated segment<br>➢ Aneurysm at treated segment<br>➢ Distal embolization<br><br>* *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.<br>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 before the index procedure.<br>• At the time of the procedure, subjects receive an intra-arterial bolus of heparin (usually 3000-5000 IU).<br>• Subjects shall receive DAPT during a period of at least 6 months post the index procedure, if tolerated.<br>• After6 months of DAPT post procedure, all subjects are suggested to be treated with ASA (minimum 75 mg/d) indefinitely. For subjects who are intolerant to aspirin, alternative antiplatelet medications according to investigator's discretion, such as 300mg of clopidogrel.<br>Note: The risk of bleeding may be increased in the subjects who need anticoagulation in addition to DAPT. If needed, oral warfarin and low-dose rivaroxaban (2.5mg twice per day) can be used, but no other new generation of oral anticoagulants, such as apixaban or dabigatran is allowed. subjects |

| **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**)** | |
|---|---|
| | receiving anticoagulant therapy **should not** receive additional antiplatelet therapy if, in the opinion of the investigator, this could present an intolerable bleeding risk. |
| **Key Inclusion Criteria** | 1. Subjects age 18 and older<br>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<br>3. Subject has documented chronic, symptomatic lower limb ischemia defined as Rutherford categories 2 - 4, and is eligible for percutaneous peripheral vascular intervention<br>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:<br>a. Atherosclerotic lesions with diameter stenosis ≥ 70%<br>b. Guidewire must cross lesion(s) within the true lumen, without a sub-intimal course by physicians performed, based on visual estimate<br>c. Minimum vessel diameter proximal to the lesion ≥ 3 mm and ≤ 6 mm<br>d. Lesion length of single or multiple focal stenosis or chronic total occlusion (CTO) lesion can be up to 15 cm long<br>e. Target lesion located at least 3 cm above the inferior edge of the femur<br>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<br>2. Target lesion stenosis < 70%<br>3. Target lesion is moderately to severely angulated (> 30° ) or torturous at treatment segment<br>4. Target lesion/vessel previously treated with drug-coated balloon within 12 months prior to the index procedure<br>5. Target lesion/vessel previously treated with atherectomy, laser or other debulking devices prior to the index procedure |

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|---|---|
| | 6. Target lesion/vessel with in-stent restenosis<br>7. Subjects who have undergone prior surgery or endovascular intervention of SFA/PPA in the target limb to treat atherosclerotic disease within 3 months prior to the index procedure<br>8. Use of 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<br>9. History of major amputation in the target limb<br>10. Documented life expectancy less than 12 months due to other medical co-morbid condition(s)<br>11. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated<br>12. Known history of coagulopathy or hypercoagulable bleeding disorder<br>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)<br>14. Platelet count < 80,000 $mm^3$ or > 600,000/ $mm^3$ or history of bleeding diathesis<br>15. Undergoing hemodialysis or concomitant renal failure with a serum creatinine > 2.0 mg/dL (176.8umol/L)<br>16. History of myocardial infarction (MI), stroke/cerebrovascular accident (CVA) or gastrointestinal bleeding within 6 months prior to the enrollment<br>17. Unstable angina pectoris at the time of enrollment.<br>18. History of severe trauma, fracture, major surgery or biopsy of a parenchymal organ within past 14 days<br>19. Pregnant, breast feeding, or plan to become pregnant in the next 12 months<br>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) |

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| | 21. Septicemia at the time of enrollment<br>22. Presence of outflow lesions in the target limb requiring intervention during the index procedure<br>23. Presence of other hemodynamically significant lesions in the target limb requiring intervention within 30 days of enrollment<br>24. Acute ischemia and/or acute thrombosis of the target lesion/vessel prior to the index procedure<br>25. Presence of aneurysm in the target vessel<br>26. Perforated vessel as evidenced by extravasation of contrast media prior to the enrollment |
| **Multiple Interventions During Index Procedure** | • Contralateral Limb<br>Iliac lesion(s) in the contralateral limb may be treated using the same access site during the index procedure under the following conditions:<br>➢ Treatment with a commercially available device occurs prior to the enrollment of the target SFA/PPA lesion, and<br>➢ Treatment of the iliac lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as < 30% residual stenosis by visual estimation)<br>➢ 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.<br>• Target Limb<br>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:<br>➢ Treatment with a commercially available device occurs prior to the enrollment of the target SFA/PPA lesion and<br>➢ Treatment of the iliac lesion is deemed an angiographic success without clinical sequelae (success is measured as < 30% residual stenosis by visual estimation) |

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|---|---|
| | ➢ 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:<br>$H_0$: Pt ≤ PG (not met)<br>$H_1$: Pt > PG (met)<br>Where Pt is the 30-day MAE-free rate for the subjects treated with Jetstream System and the PG is 88%.*<br>*The PG of 88% was estimated on the basis of available literature and is consistent with those describing atherectomy outcomes. **<br>** ***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*** |
| **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%.<br>*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). See Statistical Analysis Plan for detail. |
| **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.<br>$H_0$: Δt ≤ 0 (not met)<br>$H_1$: Δt > 0 (met)<br>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**. |

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| | **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** | Success Criteria for Primary Safety Endpoint<br>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%.<br>Success Criteria for Primary Effectiveness Endpoint<br>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.<br>Success Criteria for the Study<br>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.<br>• Power ≥ 90%<br>• One-sided overall significance level = 2.5% (alpha)<br>• PG for 30-day MAE-free rate = 88%<br>• Expected 30-day MAE-free rate = 99%<br>• Attrition rate = 15% (loss to follow-up at 30 days)<br>• A minimum of 50 subjects to be evaluable at 30 days that will provide at least 99% power for the primary safety endpoint<br>• A sample size of 60 subjects to be enrolled in the primary cohort at baseline<br>With additional 2 roll-in subjects per site, the overall subjects to be enrolled are approximately 80. |

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| **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:<br>• Death<br>• Target limb major amputation<br>• Target vessel revascularization (TVR) and target lesion revascularization (TLR)<br>• Distal embolization requiring additional treatment<br>• Perforation during index procedure that requires additional treatment |

# 3. Table of Contents

## 3.1. *Table of Figures*



## 3.2. *Table of Tables*

# 4. Introduction

## 4.1. Background of development

Peripheral arterial disease (PAD) is a common disease characterized by atherosclerotic stenosis and occlusion in peripheral arteries. Its prevalence is in the range of 3 – 10% with increasing with age (about 15 – 20% in people of age over 70-year old).[1-3] It most affects lower extremities vessels causing claudication, about 5% of the patients eventually develop critical limb ischemia (CLI) with a poor prognosis – amputation in 30% and death in 25% of those with CLI at 1 year.[4, 5]

Previous studies show that the prevalence of lower extremity artery disease (LEAD) in China is 2.1 – 27.5% in general population.[6] But as one of the most rapidly aging nations (the age of > 65-year old was 9% of its population in 2011, expecting double by 2020), the prevalence will increase remarkably in the near future.

The femoropopliteal artery is the most commonly involved site in patients with PAD.[7] Endovascular therapy, percutaneous transluminal angioplasty (PTA) with optional bailout stenting is currently recommended for the majority of symptomatic patients by ACCF/AHA and TASC II.[5, 8] For calcified lesions, treatment with PTA may not provide sufficient revascularization and stenting is often required.[9] However, inadequate stent expansion is more likely to occur in such calcified lesions and there is a concern that the risk of in-stent restenosis and thrombotic events may be increased. In order to improve the clinical outcomes, novel technologies of debulking of the extensive atheromatous burden has emerged with promising clinical outcomes of atherectomy of femoro-popliteal lesions. [9 - 12]

JETSTREAM™Atherectomy System (Jetstream) is one of these atherectomy systems, and was approved under 510(K) for the Pathway PV System, a first- generation model, in July 2008, and later in April 2013, for the current model. Jetstream Atherectomy System was also granted a CE mark in September 2013 and is currently marketed in the United States, Europe, Austria, and other regions.

## 4.2. Clinical Study Summary

### 4.2.1. Pathway PVD clinical study

The Pathway PVD clinical study was a prospective, multicenter, single arm study conducted using the Pathway PV System, a first-generation model of Jetstream, in which a total of 172 subjects were enrolled at 9 investigational sites in Germany, Austria, and Belgium.[10]

The primary safety endpoint was the freedom from major adverse events (MAE) including clinically driven target lesion revascularization (TLR), any death, target vessel revascularization (TVR), myocardial infarction (MI), and index limb amputation at 30 days post procedure. The primary effectiveness endpoint was a reduction in mean percent stenosis, with and without adjunctive therapy.

The secondary endpoints included: (1) MAE at 6 months, (2) absence of death or amputation as a result of the Pathway PV System during the follow-up period, (3) clinical success defined as ≥ 1 clinical category improvement of Rutherford scale (or equivalent) from baseline at 6 and 12 months; (4) hemodynamic success defined as a > 0.1 improvement in the ABI during the period from baseline to 30 days post procedure and no deterioration > 0.15 from the maximum early post procedure level at 6 and 12 months. Target lesions had reference vessel diameters ranging from 3 – 5 mm (visual estimation), total lesion lengths (alone or series of lesions) up to 10 cm for the femoropopliteal arteries as well as up to 3 cm for the tibial or peroneal arteries (Rutherford categories 1–5 or equivalent).

The 30-day freedom from MAE was 99% (170/172), with 2 amputations planned prior to the intervention being performed (Table 4.2-1). No procedure or device related amputations occurred.

**Table 4.2-1：Major Adverse Events at 30 Days and 6 Months**

| | **30 Days (n=172)** | **6 Months (n=162)** |
|---|---|---|
| MAE | 2 (1.1%) | 31 (19%) |
| TVR | 0 (0%) | 4 (2.5%) |
| Death*<br>Sudden Cardiac Arrest (probable) | 0 (0%) | 1 (0.6%) |
| Amputation | 2 (1.1%) | 2 (1.2%) |
| TLR | 0 (0%) | 25 (15%) |
| Non-Q wave MI | 0 (0%) | 1 (0.6%) |

At the 6-month follow-up, 31 subjects had at least 1 MAE. The freedom from serious adverse device effects (SADEs) and TLR at 6 months post-procedure, was 85% with a 95% lower confidence interval of 78%.[13]

Success in crossing and debulking the target lesion was achieved in 99% (208/210) of the cases. Thirty-three percent of the cases were atherectomy procedures alone, while in 59% of the lesions, adjunctive low-pressure angioplasty was also employed. Stenting was indicated in 7% of the subjects. Mean diameter stenosis was reduced from 79.4% ± 17.7% at baseline to 35.0% ± 16.1% after atherectomy. After adjunctive therapy, the diameter stenosis was further reduced to 21.4% ± 10.5%. Interventional success, defined as residual stenosis ≤ 30% by visual estimation, was achieved in 209/210 (99%) lesions.

Clinical success was achieved in 68% (91/133) at 6 months and 70% (75/107) at 12 months, based on improvement in Rutherford classification. Hemodynamic success was achieved in 52% (63/121) subjects at 6 months and in 52% (51/98) at 12 months.

Primary and secondary duplex-documented patency rates at 12 months were 61.8% (76/123 lesions) and 81.3% (100/123 lesions), respectively. Clinically driven TLR rates were 15% (25/172) at 6 months and 26% (42/162) at 12 months, while TVR rates (including TLR) were 17% (29/172) and 30% (49/162), at 6 and 12 months respectively.

Additional evaluation of the Pathway PVD Trial dataset was completed by Sixt et al,[13] the focus of which was to evaluate the changes in Quality of Life (QOL) following atherectomy. The primary endpoint was evaluation of the QOL using the 5-point Walking Impairment Questionnaire (WIQ) scale. The primary safety endpoint was freedom from MAE, including clinically driven TLR, any death, TVR, MI, and index limb amputation at 30 days post-procedure, previously reported by Zeller et al.[10] Secondary endpoints were also previously reported. The subject cohort improved from baseline by an average of 0.94 points in the WIQ at 30-days post procedure, 0.78 points at the 6 month follow-up and 1.07 points at the 12 month follow-up. When comparing subjects with and without restenosis, a significant improvement in the WIQ was observed at 6 months, but not at the 12-month follow-up. Twenty-five (25) procedure-related serious adverse events were reported in the 158 subjects at the 6 month follow-up. These events included 18 (11%) TLR, 1 (0.6%) TVR, 3 (1.9%) emboli, 1 (0.6%) dissection, 1 (0.6%) abrupt closure, and 1 (0.6%) re-intervention in the target limb. All were treated without permanent injury, amputation, or death. An additional serious adverse event was noted at 4 days post-procedure where one participant experienced a cerebral infarct and was treated with drug therapy. The overall conclusion is that the Jetstream Atherectomy device for infrainguinal treatment of atherostenotic lesions significantly improved the quality of life, as evaluated by the 5 point WIQ. Additionally, the clinical data and analyses support the Jetstream device as safe and effective.

Additional analysis of data from the Pathway PVD Trial was completed by Sixt et al,[14] the goal of which was to determine whether the Jetstream Atherectomy system produced different outcomes in subjects with and without type 2 diabetes mellitus (DM). For the 172 subjects enrolled in the Pathway PVD Trial, 80 subjects were in the DM group and 92 were in the non-DM group. Lesion characteristics did not differ between the two groups, although the DM group had significantly higher body weight ($p<0.001$) and body mass index ($p<0.001$). Procedure related adverse events were documented in 49% (39/80) of the DM group and 43% (40/92) of the non-DM group. At the 30 day follow-up, the MAE rate for the DM group was 2.5% (2/80) and 0% (0/92) in the non-DM group. At the 6 and 12 month follow-ups, MAE rates were 13.8% (11/80) and 25% (20/80) in the DM group compared to 21.7% (20/92) and 31.5% (29/92) in the non-DM group, respectively. The 12 month TLR rate was 20% (16/80) in the DM group and 28% (26/92) in the non-DM group. During the study period 1 (1.3%) DM subject died, due to probable sudden cardiac arrest, at approximately 50 days post-procedure and 1 (1.1%) non-DM subject died due to non-Q wave MI, at 5 months post-procedure. The latter death was noted previously as occurring after the 6-month dataset was analyzed. Other assessments (ABI, Rutherford Class, Walking Impairment) did not differ between the DM and non-DM groups. The overall conclusion was that the Jetstream Atherectomy system in complex infrainguinal arteries provides comparable and acceptable outcomes in DM and non-DM patients.

In summary, conclusions from the Pathway PVD Trial support that the Jetstream Atherectomy System is safe and effective for treating obstructive lesions with a maximum lesion length of 10 cm in infrainguinal arteries with a reference vessel diameter of 3 mm to 5 mm.

### 4.2.2. Jetstream Calcium Study

The Jetstream Calcium Study was a prospective, single-arm, multicenter study to evaluate the Jetstream Atherectomy System for severely calcified femoral-popliteal artery lesions, i.e., subjects with claudication and lesions with superficial calcium > 90° and > 5 mm in length as determined by intravascular ultrasound (IVUS). The 2.1 mm catheter was used in this study without distal protection. This study enrolled 26 subjects with eligible lesions in the SFA, popliteal artery, and tibial artery.[15]

The primary effectiveness endpoint was calcium removal and luminal gain measured by comparing pre-intervention to post-atherectomy intravascular ultrasound (IVUS) images. Secondary endpoints included (1) Major adverse events (MAE), defined as death, myocardial infarction, amputation, and target lesion or vessel revascularization up to 30 days; (2) adjunctive therapy use; and (3) residual diameter stenosis.

The visually assessed angiographic diameter stenosis improved from 89±9% pre-treatment to 37±13% post atherectomy and finally to 10±6% post adjunctive treatment. After matching pre- and post atherectomy IVUS segments, the treated segment median length measured 36 mm. The segment of superficial calcium with calcium reduction measured 13mm in median length, or 37% of the entire treated segment. The IVUS findings from pre to post atherectomy at the lesion level showed that the minimum lumen area increased from 5.1±2.8mm$^2$ to 8.3±2.6 mm$^2$ ($p<0.0001$) and area stenosis decreased from 64±17% to 41±18% ($p<0.0001$). By comparing pre- and post-atherectomy IVUS images, the slice with maximum calcium reduction was identified; the lumen area in these slices increased from 6.6±3.7mm$^2$ to 10.0±3.6mm$^2$ ($p=0.0001$). The decrease in calcium area, measured as 2.8±1.6mm$^2$, was responsible for 86±23% of the lumen area increase (Table 4.2-2).

**Table 4.2-2: Intravascular Ultrasound Findings – 26 Lesions**

| | | Pre-treatment | Post-atherectomy | p-value |
|---|---|---|---|---|
| **Proximal reference lumen area (mm$^2$)** | | 14.6±5.1 | 14.5±5.2 | 0.91 |
| **Distal reference lumen area (mm$^2$)** | | 14.8±6.2 | 14.7±5.9 | 0.97 |
| **Minimum lumen area site** | Lumen area(mm$^2$) | 5.1±2.8 | 8.3±2.6 | <0.0001 |
| | Minimum lumen diameter(mm) | 2.0±0.4 | 2.8±0.4 | <0.0001 |
| | Lumen symmetry index | 0.70±0.13 | 0.76±0.14 | 0.11 |
| | Area stenosis (%) | 64±17 | 41±18 | <0.0001 |
| **Maximum calcium ablation site** | Lumen area(mm$^2$) | 6.6±3.7 | 10.0±3.6 | 0.001 |
| | Minimum lumen diameter(mm) | 2.3±0.5 | 3.0±0.5 | <0.0001 |
| | Lumen symmetry index | 0.70±0.14 | 0.70±0.14 | 0.26 |
| | Area stenosis (%) | 53±23 | 29±22 | 0.0005 |
| | Maximum superficial calcium (°) | 151±70 | 146±71 | 0.83 |
| | Decrease of calcium area(mm2) | NA | 2.8±1.6 | NA |
| | Calcium reduction (%) | NA | 86±22 | NA |

| | | | | |
|---|---|---|---|---|
| **Surface Shape of calcium** | Convex | 58% (15) | 27% (7) | 0.02 |
| | Concave | 42% (11) | 73% (19) | |
| **Irregularity of superficial calcium** | Irregular | 54% (14) | 39% (10) | 0.27 |
| | Smooth | 46% (12) | 61% (16) | |
| | Reverberation | 31% (8) | 39% (10) | 0.58 |
| | Maximum arc of Reverberation (˚) | 23±20 | 65±40 | 0.006 |
| **Values are mean ± standard deviation or (n).** | | | | |

The Jetstream system removed and modified moderate to severe superficial calcium to achieve significant lumen gain, and as shown in Table 4.2-3 adjunctive balloon angioplasty after calcium modification showed further lumen increase without major complications. No major adverse events occurred up to 30 days post procedure.

**Table 4.2-3: Intravascular Ultrasound Findings - 11 Lesions with Adjunctive Balloon**

| | | (1) Pre-treatment | (2) Post-atherectomy | (3) Post-balloon | p-value | |
|---|---|---|---|---|---|---|
| | | | | | 1 vs. 2 | 2 vs. 3 |
| **Proximal reference lumen area ($mm^2$)** | | 15.1 | 14.6 | 17.7 | 0.15 | 0.013 |
| **Distal reference lumen area ($mm^2$)** | | 16.1 | 16.4 | 18.5 | 0.55 | 0.083 |
| **Minimum lumen area site** | Lumen area($mm^2$) | 4.4 | 7.1 | 11.9 | <0.001 | <0.001 |
| | Minimum lumen diameter(mm) | 2.0 | 2.7 | 3.4 | <0.001 | <0.001 |
| | Lumen symmetry index | 0.74 | 0.81 | 0.76 | 0.13 | 0.33 |
| | Area stenosis (%) | 70.9 | 51.8 | 34.2 | <0.001 | <0.001 |
| **Maximum calcium ablation site** | Lumen area($mm^2$) | 6.3 | 9.3 | 13.3 | <0.001 | <0.001 |
| | Minimum lumen diameter(mm) | 2.3 | 3.0 | 3.6 | <0.001 | <0.001 |
| | Lumen symmetry index | 0.74 | 0.79 | 0.76 | 0.029 | 0.37 |
| | Area stenosis (%) | 59.2 | 38.1 | 27.8 | <0.001 | 0.042 |
| | Maximum superficial calcium (˚) | 164 | 164 | 162 | 0.99 | 0.88 |
| | Decrease of calcium area(mm2) | NA | 2.4 | NA | NA | NA |
| | Calcium reduction (%) | NA | 94 | NA | NA | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Surface Shape of calcium** | Convex | 55% | 9% | 9% | 0.018 | 0.99 |
| | Concave | 46% | 91% | 91% | | |
| **Irregularity of superficial calcium** | Irregular | 55% | 27% | 9% | 0.25 | 0.33 |
| | Smooth | 45% | 73% | 9% | | |
| **Reverberation** | | 27% | 73% | 36% | 0.99 | 0.99 |
| **Maximum arc of Reverberation** | | 26˚ | 102˚ | 36˚ | <0.001 | <0.001 |
| **Dissection** | | 0% | 27% | 73% | 0.01 | |

The study found that the Jetstream Atherectomy System removed and modified superficial calcium to achieve significant lumen gain. Adjunctive balloon angioplasty after calcium modification showed further lumen increase without major complications.

## 5. Device Description

The test device is intended to be used as adjunctive therapy for percutaneous intervention to remove atherosclerotic disease, debris, and thrombus from the SFA and/or PPA.

The JETSTREAM™ Atherectomy System is a rotational atherectomy catheter system designed for use in debulking and treating vascular disease in the peripheral vasculature. The catheter includes multiple distal ports located at the catheter tip, which are designed to provide independent infusion and aspiration functions for the active removal of fluid, excised tissue and thrombus from the peripheral treatment site. The Jetstream System consists of two primary components that are packaged separately; Atherectomy Catheter (Jetstream Catheter) set and Atherectomy Console (Jetstream Console) (Figure5.1-1).

Jetstream Catheter Set

Jetstream Console

**Figure 5.1- 1: JETSTREAM™Atherectomy System**

## 5.1. Jetstream Catheter

Jetstream Catheter set is a sterile, single use unit consisting of an electrically driven Catheter and Control Pod with detachable Activation Handle. The Catheter utilizes a differentially cutting tip and includes both aspiration and infusion capabilities. The Activation Handle provides a user interface with keypad controls for device operation. The unit, its electrical connectors, tubing, and aspirant collection bag are packaged in a single pouched tray with retention lid, and sterilized with ethylene oxide (EO). Note that the tray retention lid is not a sterile barrier.

The catheter has four types of model based on existence of expandable blade and size of catheter tip as shown in Table 5.1-1 and Figure 5.1-2. The Jetstream single cutter (SC) catheters are available in 1.6mm and 1.85mm sizes and the Jetstream expandable cutter (XC) catheters are available in 2.1mm (Blade Down)/3.0mm (Blade Up) and 2.4mm (Blade Down)/3.4mm (Blade Up). XC model has a mechanism that expandable blade is fold when blade down and expandable blade rises up (i.e. Blade Up) when MAX button in the control pod is turned on.

**Table 5.1-1: Jetstream Catheter Specifications**

| Model | Catheter Length（cm） | Tip Diameter（mm） | Minimum Matched Introducer Size（F） | Maximal Matched Guidewire Diameter（inch） | Maximum Catheter Profile（mm） |
|---|---|---|---|---|---|
| Jetstream XC 2.1/3.0 | 135 | 2.1/3.0 | 7 | 0.014 | 2.5 |
| Jetstream XC 2.4/3.4 | 120 | 2.4/3.4 | 7 | 0.014 | 2.45 |
| Jetstream SC 1.6 | 145 | 1.6 | 7 | 0.014 | 2.33 |
| Jetstream SC 1.85 | 145 | 1.85 | 7 | 0.014 | 2.33 |

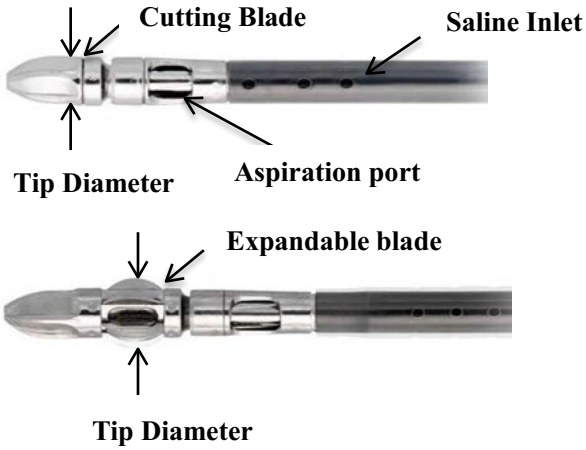


Figure 5.1- 2: Jetstream Catheter Tip

### 5.2. Jetstream Console

A reusable PV Console consists of two (2) peristaltic pumps for aspiration and infusion, power supply, system controller, keypad interface, and LED indicators for device operational status. The PV Console mounts on a standard IV stand and remains outside the sterile field during the procedure (Figure 5.1-1).

### 5.3. Intended Use

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.

### 5.4. Device Labeling

The copies of the Directions for Use (DFU) for the Jetstream System are included in the JETSTREAM CHINA Manual of Operations, including the DFU for the Jetstream console and DFUs for the Jetstream catheters and control pod. The labeling will include at least the following information:

- Product Name
- Universal Part Number (UPN)
- Lot number
- Project Name, Storage & Shipment condition
- Expiration (use by) date

The following statements appear on the JETSTREAM CHINA product labeling for clinical distribution:

**Caution: For Clinical Trial Use Only**

Device labeling will be provided in Chinese per China regulations.

## 6. Study Objectives and Endpoints

### 6.1. *Study Objectives*

The primary objective of this study is 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.

## 6.2. *Study Endpoints*

### 6.2.1. Primary Endpoints

6.2.1.1. The primary safety endpoint:

The primary safety endpoint is the rate of 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.

6.2.1.2. The primary effectiveness endpoint:

The primary effectiveness endpoint is the 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).

### 6.2.2. 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
    - Aneurysm at treated segment
    - Distal embolization

**Notes**

**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.*[16, 17]

# 7. Study Design

The JETSTREAM CHINA 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 qualifying lesions would be considered for enrollment and treated with the Jetstream System.

## 7.1. *Scale and Duration*

The JETSTREAM CHINA trial will be conducted in approximately 10 sites in Mainland China with planned enrollment of approximately 80 subjects, including 20 roll-in subjects with 2 roll-in subjects per site.

The study is planned to have approximately 4 years of enrollment and 1 year of follow up.

All subjects will be screened according to the protocol inclusion and exclusion criteria. Subjects will be enrolled in a non-randomized process. Clinical follow-up will be required at the following time points: pre-discharge, 30 days, 6 and 12 months post-index procedure.

Subjects who are enrolled but the Jetstream System is not used will be followed through the 30-day follow-up visit only.

A schematic of the JETSTREAM CHINA trial design is shown below in Figure 7.1-1.

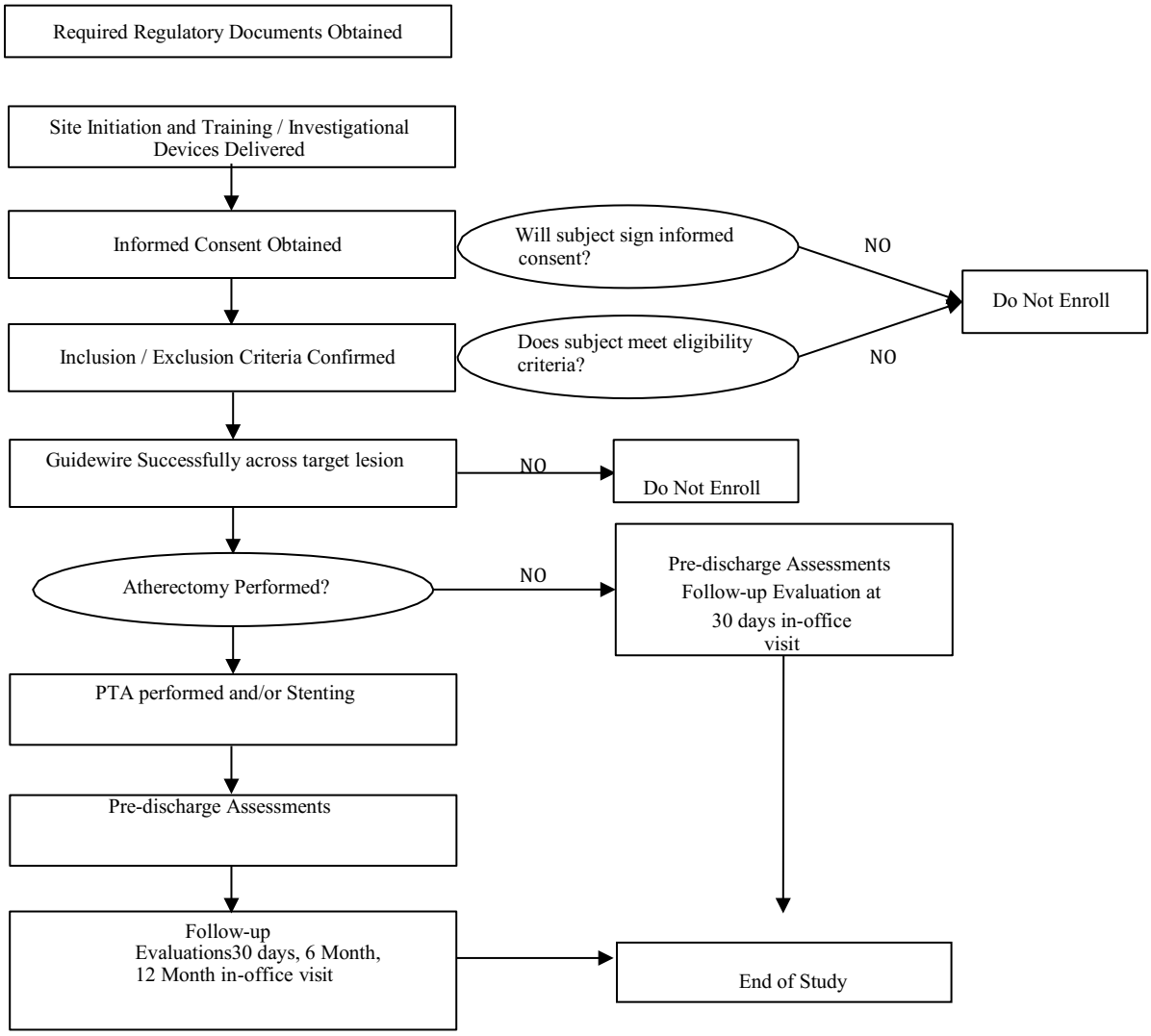


**Figure 7.1: JETSTREAM CHINA Study Design**

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.

## 7.2. *Treatment Assignment*

Patients who sign the Ethics Committee-approved Informed Consent Form (ICF), and have met all inclusion criteria and none of the exclusion criteria, are eligible to be enrolled in the clinical study. All eligible subjects will receive treatment with the Jetstream System. Enrollment occurs at the time of advancement of the Jetstream catheter into the introducer sheath.

### 7.2.1. Treatment and Control

Subjects enrolled in this clinical trial will not be randomized, and there is no control group in this study. All eligible subjects will receive treatment with the Jetstream System.

### 7.2.2. Target Lesion

A target lesion is a lesion selected by the Investigator for treatment with the investigational Jetstream System and a study Jetstream catheter. Target lesions must meet all the angiographic selection criteria. A diffuse lesion or multiple lesions (including CTO lesions) within the same target vessel segment can be considered as one target lesion if the total lesion length (including the distance between lesions) is ≤ 150 mm.

Only ***one*** target lesion is allowed in each enrolled subject; and it is decided by physician's discretion in the case that eligible lesions exist in both limbs.

## 7.3. *Multiple Interventions Using Same Access Site during Index Procedure*

### 7.3.1. Contralateral Limb

**Iliac Lesion**

Using the same access site, iliac lesion(s) in the contralateral limb may be treated during the index procedure under the following conditions:

- Treatment with a commercially available device occurs prior to enrollment of the target SFA/PPA lesion, and
- Treatment of the iliac lesion(s) is deemed an angiographic success without clinical sequelae (success is defined 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.

### 7.3.2. Target Limb

**Inflow Lesion**

Using the same access site, 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 commercially available device occurs prior to enrollment of the target SFA/PPA lesion, and
- Treatment of the inflow 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.

## 7.4. *Justification for the Study Design*

Pathway PV system, which is the first generation model of JETSTREAM™ Atherectomy System (Jetstream), received 510(K) approval in July 2008, and then, the current generation model (Jetstream) in April, 2013. Also, it received CE-Mark certification in September 2013. JETSTREAM™ Atherectomy System is now commercially available in the U.S., EU, Australia or other foreign areas and its' effectiveness and safety have been confirmed.

The Jetstream China trial is designed to evaluate the safety and effectiveness of JETSTREAM™ Atherectomy System (Jetstream) for treating symptomatic Chinese patients with occlusive atherosclerotic lesions in native SFA and/ or PPA, in whom sufficient revascularization cannot be expected from the PTA alone during endovascular treatment in the opinion of operating physician. The Jetstream China trial is a single arm clinical trial compared to the safety performance goal (PG). The PG was set based on published data of PTA/stenting outcomes in the recent clinical trial.[18]

This trial requires at least one roll-in subject per site.

During the trial, dual antiplatelet therapy (DAPT) will be administered for 6 months post index procedure and aspirin use will be required indefinitely post index procedure. Ongoing dynamic data safety monitoring will be performed throughout the trial to minimize subject risk. All enrolled subjects receiving the Jetstream system treatment will be followed for 12 month post index procedure.

## 7.5. *Treatment*

All enrolled subjects will receive treatment with the investigational Jetstream System. Pre-dilation of target lesion is prohibited prior to the treatment of Jetstream System. After target lesion is adequately treated by the Jetstream System, PTA and/or stenting with commercially-available device(s) are allowed for optimizing treatment.

The investigator selects the size of Jetstream Catheter according to the proximal and distal reference vessel diameters

**Handling Instructions of Study Devices**

**It is important for investigators to follow the corresponding DFU for Jetstream system treatment and for the study device product matrix.**

# 8. Subject Selection

## 8.1. *Study Population and Eligibility*

Approximately 80 patients with symptomatic PAD of the femoropopliteal artery (Rutherford clinical category of 2 to 4) receiving percutaneous transluminal balloon angioplasty will be screened for enrollment of this study. Clinical and angiographic inclusion and exclusion criteria for the JETSTREAM China trial are included in Section 8.2 and Section 8.3 respectively. Prior to enrollment in the trial, a subject should meet all of the clinical and angiographic inclusion criteria and none of the exclusion criteria.

## 8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

**Table 8.2-1: Inclusion Criteria**

| | |
|---|---|
| **Inclusion Criteria** | 1. Subjects age 18 and older<br>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<br>3. Subject has documented chronic, symptomatic lower limb ischemia defined as Rutherford categories 2 - 4, and is eligible for percutaneous peripheral vascular intervention<br>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:<br>i. Atherosclerotic lesion with diameter stenosis ≥ 70%<br>ii. Guidewire must cross lesion(s) within the true lumen, without a sub-intimal course by physicians performed, based on visual estimate<br>iii. Minimum vessel diameter proximal to the lesion ≥ 3 mm and ≤ 6 mm<br>iv. Lesion length of single or multiple focal stenosis or chronic total occlusion (CTO) lesion can be up to 15 cm long<br>v. Target lesion located at least 3 cm above the inferior edge of the femur<br>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 |

## 8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8.3-1) will be excluded from this clinical study.

**Table 8.3-1: Exclusion Criteria**

| | |
|---|---|
| **Exclusion Criteria** | 1. Target lesion is located in the iliac artery or above the SFA<br>2. Target lesion stenosis < 70%<br>3. Target lesion is moderately to severely angulated (> 30° ) or torturous at treatment segment<br>4. Target lesion/vessel previously treated with drug-coated balloon within 12 months prior to the index procedure<br>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<br>7. Subjects who have undergone prior surgery or endovascular intervention of SFA/PPA in the target limb to treat atherosclerotic disease within 3 months prior to the index procedure<br>8. Use of 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<br>9. History of major amputation in the target limb<br>10. Documented life expectancy less than 12 months due to other medical co-morbid condition(s)<br>11. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated<br>12. Known history of coagulopathy or hypercoagulable bleeding disorder<br>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)<br>14. Platelet count < 80,000 $mm^3$ or > 600,000 $mm^3$ or history of bleeding diathesis<br>15. Undergoing hemodialysis or concomitant renal failure with a serum creatinine > 2.0 mg/dL (176.8umol/L)<br>16. History of myocardial infarction (MI), stroke/cerebrovascular accident (CVA) or gastrointestinal bleeding within 6 months prior to the enrollment<br>17. Unstable angina pectoris at the time of enrollment.<br>18. History of severe trauma, fracture, major surgery or biopsy of a parenchymal organ within past 14 days<br>19. Pregnant, breast feeding, or plan to become pregnant in the next 12 months<br>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)<br>21. Septicemia at the time of enrollment<br>22. Presence of outflow lesions in the target limb requiring intervention during the index procedure<br>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<br>25. Presence of aneurysm in the target vessel<br>26. Perforated vessel as evidenced by extravasation of contrast media prior to the enrollment |

# 9. Subject Accountability

## 9.1. *Point of Enrollment*

Subject, who has signed the IRB/IEC-approved study ICF, and has met all inclusion criteria and none of the exclusion criteria, will be considered eligible to be enrolled in the trial. Enrollment occurs at the time of advancement of the Jetstream catheter into the introducer sheath.

## 9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. While trial withdrawal is discouraged, subjects may choose to withdraw from the trial at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional trial follow-up, nor will they be replaced. If a subject withdraws from the clinical investigation, the reason(s) shall be reported and documented. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study. The Investigator may discontinue a subject from participation in the trial if the Investigator feels that the subject can no longer fully comply with the requirements of the trial or if any of the trial procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

## 9.3. *Enrollment Controls*

A minimum of 60 enrolled subjects are needed to adequately assess the primary endpoint at 30 days, assuming a maximum attrition of 15% for all reasons at 30 days. With additional 2 roll-in subjects per site, the overall subjects to be enrolled in the study are approximately 80 subjects. The enrollment cap for each study site is 35% of total enrolled subjects.

## 9.4. *Lost to Follow-up*

A subject will be considered lost to follow-up if he or she fails to return for four scheduled visits and is unable to be contacted by the study site staff.

The following action must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address). These contact attempts should be documented in the participant's medical record or study site.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

### 9.5. *End-of-Study Definition*

A subject is considered to have completed the study if he or she has completed all phase of the study including the last visit or the last scheduled procedure shown in the Data Collection Schedule.

The end of the study is defined as completion of the last visit or procedure shown in the Data Collection Schedule in the trial globally.

## 10. Study Methods

### 10.1. *Data Collection*

The data collection schedule is shown in Table 10.1-1. Please note that the time window for 30-day follow-up is +/- 7 days, for 6 or 12 months follow-up is +/- 30 days.

The table below is an overview of all the procedures or tests required per protocol. If an examination/test is required, it is marked with "X"; if it is optional but recommended, it is marked with "O".

**Table 10.1-1: Data Collection Schedule**

| Procedure/Assessment | Screening (≤ 30 days prior to index procedure) | Enrollment | Index Procedure | Post-procedure/ Pre-hospital Discharge | Follow-up Visit[g] | | |
|---|---|---|---|---|---|---|---|
| | | | | | 30-day (± 7 Days) | 6-month (± 30 Days) | 12-month (± 30 Days) |
| **In-person Visit** | X | X | X | X | X | X | X |
| **Informed Consent process, including informed consent signature date** | X | | | | | | |
| **Demographics (including date of birth, gender, and race and ethnicity)** | X | | | | | | |
| **Physical Assessment** | X | | | | | | |
| **Medical History (including, concomitant diseases, concomitant medication and medical treatments)** | X | X[d] | X[d] | X[d] | X[d] | X[d] | X[d] |
| **Routine Laboratory (including serum creatinine, CBC with platelet count tests, and pregnancy test within 7 days of index procedure for potential child-bearing women)[a]** | X | | | | | | |
| **DUS[b]** | O | | | O | | X | X |
| **ABI** | X | | | | X | X | X |
| **Rutherford Categories Assessment** | X[c] | | | | X | X | X |
| **Angiographic assessment[b]** | | X[e] | X[f] | | | | |
| **Procedural assessment (including PTA/stenting)** | | | X[f] | | | | |
| **Adverse Events and Device Deficiency Assessment** | | | X | X | X | X | X |

X = required; O = optional but recommended

DUS = Duplex Ultrasound; ABI = Ankle Brachial Index; PTA = Percutaneous Transluminal Angioplasty

a: Excluded from the study if serum creatinine > 2.0mg/dL (176.8umol/L), or platelet count < 80.000/$mm^3$, or > 600,000 $mm^3$ , or positive pregnancy test (pregnancy test is required within 7 days prior to index procedure for potential child-bearing women)

b: Angiographic and DUS recordings will be sent to the respective core labs for analysis. Follow-up angiograms and DUS will not be required for those subjects who underwent by-pass surgery of the target lesion during the 12-month follow-up time frame.

c: Inclusion criterion: Rutherford category 2 - 4

d: Antiplatelet medication assessments

e: Adhere to Angiographic Inclusion criteria.
f: Procedural (including complications), target lesion, atherectomy, PTA and/or stenting information are collected; angiographic data will be used to localize the target lesion
g: Follow-up dates will be calculated from the date of the index procedure. All follow-ups will be in-person clinic visits. The time window for 30-day follow-up is +/- 7 days; for 6 or 12-month follow-up is +/- 30 days.

### 10.2. *Study Candidate Screening*

Subjects who are suitable for PTA will be informed about the study and will be asked to sign the informed consent form (ICF) before participating in any screening procedure. After signing the ICF, the subject will receive a screening number and will be documented in a screening log. Each clinical investigator must keep a log of all screened subjects, including both eligible and non-eligible subjects (screening failures).

### 10.3. *Informed Consent*

Before any study specific tests or procedures are performed, subjects who meet the clinical inclusion criteria will be asked to sign the IRB/IEC-approved study ICF. Subjects must be given ample time to review ICF and have questions answered before signing ICF.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, vascular angiography may demonstrate that the subject is not a suitable candidate for the clinical trial.

Refer to Section 9.1 for definition of point of enrollment.

### 10.4. *Screening (Up to 30 Days Prior to Index procedure)*

After a subject has signed the IRB/IEC-approved study ICF, the screening process may begin. The screening process will be used to determine the inclusion or exclusion of a subject in the study. This process includes the investigator's assessment of subject's medical records and diagnosis, and following pre-procedure data must be collected within 30 days prior to the index procedure (unless otherwise specified), for all subjects:

- Confirmation of clinical eligibility criteria (inclusion and exclusion criteria)
- Demographics including age, gender, and races others than Han (unless restricted by local laws)
- Physical assessment, including weight and height
  - Ankle brachial Index (ABI)
  - Rutherford category assessment
- Medical history (including concomitant diseases, concomitant medication and medical treatments)
- Routine laboratory tests
  - Serum creatinine
  - Complete blood count (CBC) with platelets
  - Pregnancy test for females of child-bearing potential with analysis per local practice (serum and/or urine) is required within **7 days** prior to the index procedure
- Current antiplatelet medication usage
- Duplex ultrasound (DUS) – optional (at the discretion of the investigator)

### 10.5. *Required Concomitant Medications*

Protocol-required concomitant medications must be reported in the electronic case report form (eCRF) from the time of the pre-procedure visit through the 12 month follow-up. Information pertaining to the use of antiplatelet medications including dose changes, medication interruptions, and medication cessation, must be documented. Additional concomitant medications may be prescribed at the discretion of the investigator based on the standard clinical practice.

Antiplatelet medications such as P2Y12 inhibitor (Clopidogrel) and acetylsalicylic acid (ASA) are administered before the procedure, to minimize thrombotic complications and development of restenosis. Clopidogrel is recommended, unless it is not tolerated by the subject, then other antiplatelet medications or low-dose rivaroxaban (2.5mg twice per day) can be used.

For subjects who are intolerant to aspirin, alternative antiplatelet medications according to investigator's discretion, such as 300mg of clopidogrel.

#### 10.5.1. Prior to the index procedure

- For subjects who have been taking dual antiplatelet therapy (DAPT) for ≥ 72 hours at the time of the index procedure, a loading dose is not required.
- For subjects who do not already take DAPT drugs for ≥ 24 hours at the time of index procedure should receive appropriate loading doses before the index procedure. Recommended loading doses are 300 mg of ASA and 300 mg of clopidogrel.

#### 10.5.2. In the Catheterization Laboratory

- At the time of the procedure, subjects should receive an intra-arterial bolus of heparin (usually 3000-5000 IU), or alternate anticoagulants as substitutes for heparin if justified by individual subject conditions.

#### 10.5.3. Post-procedure

- Subjects shall receive DAPT during a period of at least 6 months post the index procedure, if tolerated. The typical recommended DAPT regimen consists of ASA (minimum 75mg/d) and a P2Y12 inhibitor, e.g. clopidogrel (minimum 75mg/d).
- Alternate DAPT regimens may be followed if justified by individual subject conditions, e.g. if there is documented intolerance to any of these drugs, or the subjects already in a different antiplatelet therapy (with at least 2 approved drugs) due to comorbid conditions. The investigator shall be guided by the drug manufacturer´s instructions, available scientific evidence and medical guidelines applicable to subjects with peripheral arterial disease.
- After6 months of DAPT post procedure, all subjects are suggested to be treated with ASA (minimum 75 mg/d) indefinitely. For subjects who are intolerant to aspirin, alternative antiplatelet medications according to investigator's discretion, such as 300mg of clopidogrel.

  **Note:** The risk of bleeding may be increased in the subjects who need anticoagulation in addition to DAPT. If needed, oral warfarin and low-dose rivaroxaban (2.5mg twice per day) can

be used, but no other new generation of oral anticoagulants, such as apixaban or dabigatran is allowed. subjects receiving anticoagulant therapy **should not** receive additional antiplatelet therapy if, in the opinion of the investigator, this could present an intolerable bleeding risk.

## 10.6. *Enrollment & Index Procedure*

Investigators will manage the cardiovascular risk factors and comorbidities for all subjects according to standard care. Investigators should ensure close monitoring of the amount of contrast for subjects with elevated serum creatinine levels and consider preventive measures (medication and hydration) to reduce the risk of contrast-induced nephropathy (CIN).

Diagnostic angiography of the lower extremities must be performed using standard techniques to confirm angiographic eligibility of the target lesion. Visual angiographic assessment may be used to determine if criteria are met.

Angiographic images must be sent to the Angiographic Core Laboratory for evaluation.

### 10.6.1. Treatment of target lesion

Procedural information must be reported (specific data fields are noted in the electronic database). Refer to the DFU for detailed instructions about preparation and treatment of Jetstream system.

The start of the index procedure is defined as the time of guide catheter insertion.

During the procedure, the following procedures and assessments must be completed:

- Perform angiography according to the Angiographic Core Laboratory procedure guidelines.
- Confirm angiographic eligibility criteria of the target lesion(s).
- Cross target lesion using guidewire, after target lesion is crossed by the guidewire within the true lumen, without a sub-intimal course based on visual assessment by operating physician, the subject will be considered eligible for enrollment.
- The use of body surface ultrasound will be strongly recommended for lesions such as CTO, when the guidewire is difficult to cross the lesion within the true lumen.
- Use of radiopaque rulers to document the exact distance of the lesion from a same anatomical landmark (such as the patella or the iliac or femoral bifurcation) at baseline and during follow-up visits is required.
- To evaluate the performance of Jetstream System exactly, pre-dilation of the target lesion prior to the treatment with Jetstream system is prohibited.
- Select an appropriately sized investigational Jetstream Catheter to adequately treat the target lesion and record the following information:
    - Baseline percent diameter stenosis (%DS) at the target lesion
    - Post atherectomy residual %DS at the target lesion
    - Information of Jetstream Catheter(s) used

- After the treatment with Jetstream System, PTA of the target lesions is required to be performed with optimally sized balloon(s) (nominal size of artery). Record the following information on PTA used:
    - Maximum balloon diameter (mm) inflated
    - Maximum pressure (atmospheres) inflated
    - Maximum length of time (seconds) inflated

**Procedural recommendations:**

- Optimal target lesion/vessel treatment is recommended.
- Bailout stenting with a commercially-available stent or by-pass surgery may be performed at the discretion of operating physician, if the attempts with PTA have resulted any of the following:
    - Final residual stenosis at the target lesion being > 30% by visual assessment
    - Occurrence of Grade C or greater dissection (NHLBI)
    - Occurrence of clinically apparent perforation requiring treatments
    - Occurrence of any obstructive complication (e.g., recoil) demonstrating a marked decrease in the flow in the target vessel
- Angiographic complications, such as distal embolism or no reflow, should also be treated per standard practice. All angiographic complications during procedure should be documented by angiography and submitted to the Angiographic Core Laboratory for analysis.

**Use of Jetstream System**

The DFU for the Jetstream System is provided in the Manual of Operations. Prior to use of the device, the treating physician must carefully read and be familiar with the entire DFU. The Jetstream system DFU must be followed for performing the device.

Anticoagulant therapy should be consistent with the hospital standard of practice during the procedure.

All clinical sites shall have access to an emergency unit to perform interventions as bypass surgery in case of failed PTA.

### 10.6.2. Multiple Interventions during index procedure

Please refer to **Section 7.3. Multiple Interventions Using Same Access Site during Index Procedure** for the treatment of contralateral iliac lesions and the non-target inflow lesions in the target limb**.**

### 10.6.3. Post-procedure Angiogram

Perform the post-procedure angiography according to the Angiographic Core Laboratory procedure guidelines. The final angiogram must be performed and recorded, including distal run-off. Angiographic images must be sent to the angiographic core laboratory for evaluation.

#### 10.6.4. End of the Index Procedure

The end of the index procedure is defined as the time the guiding catheter was removed (post final angiography). The introducer(s) sheaths should be removed per standard local practice. The following procedures must be completed:

- Document procedural, target lesion, device information (Catheter/Console), PTA/stenting information on the appropriate eCRFs
- Record medications
- Record antithrombotic medications
- Complete AE assessment and collect source documents as described in Section 19.
- Finalize angiographic and related required documentation to submit to the Core Laboratories per instructions in the Manual of Operations

### 10.7. *Post-Procedure / Pre-Discharge*

The subject may be discharged from the hospital when clinically stable at the Investigator's discretion. The post-procedure/pre-discharge follow-up is an in-person visit and the following data will be collected prior to hospital discharge:

- Medication assessment
- AE assessment (any ongoing adverse events will be managed and treated by treating physicians per standard of care.)
- Duplex ultrasound (DUS) – optional (at the discretion of the investigator)

### 10.8. *30-Day Follow-up (+/- 7 days)*

30-day follow-up is an in-person interview. The following data will be collected:

- ABI measurements
- Rutherford category assessment
- Medication assessment
- Adverse events (any ongoing adverse events will be managed and treated by treating physicians per standard of care.)

### 10.9. *6-Month Follow-up (+/- 30 days)*

The 6-month follow-up is an in-person interview; and the following data will be collected:

- DUS of target lesion performed according to the DUS Core Laboratory procedure guidelines
- ABI measurements
- Rutherford category assessment
- Medication assessment
- Adverse events (any ongoing adverse events will be managed and treated by treating physicians

per standard of care.)

### 10.10. *12-Month Follow-up (+/- 30 days)*

The 12-month follow-up is an in-person visit and the following data will be collected:

- DUS of target lesion performed according to the DUS Core Laboratory procedure guidelines
- ABI measurements
- Rutherford category assessment
- Medication assessment
- Adverse Events (any ongoing adverse events will be managed and treated by treating physicians per standard of care.)

**Note:** Use of rulers to document the exact distance of the lesion from a same anatomical landmark (such as the patella or the iliac or femoral bifurcation) at baseline and during follow-up visits is required.

### 10.11. *Study Completion*

Each subject received atherectomy by Jetstream system will be followed for 12 months after the index procedure. For primary endpoint evaluation, the data of each such subject must be collected until the 12-month follow-up.

### 10.12. *Source Documents*

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

## 11. Statistical Considerations

The sample size justification and the power analysis described here are associated with the primary hypotheses. Roll-in subjects will be analyzed separately for observational purpose. The details of all statistical analyses will be described in the Statistical Analysis Plan.

### 11.1. *Primary Endpoints*

The overall sample size is consist of the primary cohort and roll-in subjects. The sample size of the primary cohort is justified by hypothesis parameters and driven by the primary safety 30-day endpoint to preserve adequate statistical testing power for both primary effectiveness and safety endpoints.

### 11.1.1. Primary Safety Endpoint

The primary safety endpoint is the rate of 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.

#### 11.1.1.1. Safety Hypotheses

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%.

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%.[9]

The PG of 88% was estimated on the basis of available literature and is consistent with those described atherectomy outcomes. [18]

#### 11.1.1.2. 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.

- 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 approximately 80.

#### 11.1.1.3. Safety Statistical Test Method

A normal approximation test (e.g. Chi-Square Test) will be used to assess the one-sided hypothesis of PG.

### 11.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the 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).

#### 11.1.2.1. Effectiveness Hypotheses

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. $\%DS_{\text{before Jetstream}} - \%DS_{\text{after Jetstream}}$) was 40%; the primary effectiveness hypothesis is to demonstrate there is a significant acute reduction (>0). See Statistical Analysis Plan for detail.

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 ($H_1$) 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 $\Delta t$ 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%.

#### 11.1.2.2. Effectiveness Sample Size/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 percent diameter = 40% with the common standard deviation estimated to be 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.

#### 11.1.2.3. Effectiveness Statistical 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.

## 11.2. *Success Criteria*

Success Criteria for 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%.

Success Criteria for Primary 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.

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.

## 11.3. *General Statistical Methods*

### 11.3.1. Analysis Sets

The primary and pre-specified additional endpoints will be analyzed on an ITT basis and on a pre-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 pre-protocol analysis, only enrolled subjects who are treated with the study device in the target lesion will be included in the analysis sample.

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

### 11.3.2. 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.

### 11.3.3. Number of Subjects per Investigative Site

No study sites will be allowed to enroll more than 35% (N=28) of the total number of enrolled subjects to avoid treatment center bias and ensure homogeneous study results.

### 11.3.4. 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.

### 11.3.5. Secondary Endpoint 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 (details refer to **Section 6.2.2.**). All additional assessments are observational.

### 11.3.6. Interim Analyses

Steering Committee can make the decision to conduct the interim analyses accordingly (such as the process seriously delayed due to epidemic).

### 11.3.7. 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.

### 11.3.8. Sensitivity Analysis

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.

### 11.3.9. Analysis Software

All statistical analyses will be performed 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).

### 11.3.10. 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.

## 12. Data Management

### 12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

### 12.2. *Data Retention*

The Principal Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for 10 years after the formal discontinuation of the clinical investigation of the product. These documents will be retained by BSC until the product/device is no longer in use in compliance with local regulations. The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

### 12.3. *Core Laboratories*

Angiographic and DUS data from Jetstream China trial will be assessed by independent core labs. All centers have to send the de-identified data records of baseline angiograms and the DUS recordings performed at the 6&12-month follow-up visits for blinded assessment to the core lab.

Contact information for Core Laboratories is provided in the study Manual of Operations.

## 13. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals from IRB/EC of the revised protocol must be obtained prior to implementation.

## 14. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

***All protocol deviations (PDs) are classified to "major" and "minor" defined as below:***

- A major PD is a protocol deviation that directly or potentially disrupts the study progress (i.e., the study design, study data and results can be compromised), ***OR*** a protocol deviation that compromises the safety and welfare of study participants.
- A minor PD is a protocol deviation that does not disrupt study progress (i.e., the study design, study data and results will not be compromised), ***AND*** does not compromise the safety and welfare of study participants.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

# 15. Device/Equipment Accountability

The investigational devices shall be securely maintained, controlled, and used only in this clinical study.

Boston Scientific Corporation shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSC or designated facility to the investigation sites until return or disposal.

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following:

- Date of receipt, quantity and specific specifications of received devices
- Internal handover records for device in investigation sites, as applicable
- Identification of each investigational device (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date and quantity on which the investigational device was returned, if applicable
- Date and quantity of return (and number) of unused, expired, or malfunctioning investigational devices, if applicable.

# 16. Compliance

## 16.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155:2011 (2nd Edition; 2011-02-01) Clinical Investigation of Medical Devices for Human Subjects- GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent China's laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/IEC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/IEC or regulatory authority shall be followed, if appropriate.

## 16.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency; and provide analysis report, which includes the causality assessed by both investigator and BSC and decision on study continuance, to IRB/EC per local and/or country requirements.
- Report all SAEs and device deficiencies that could have led to a SAE and potential/USADE or UADE to BSC by written documents, per the protocol requirements.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event; provide all required source documents related to a death event to BSC and the IEC per local requirements.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor and sponsor representatives to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.

- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

### 16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

## 16.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment

of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

### 16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

### 16.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained. If any study related health injury occurs and a site is held responsible for its compensation, where required, BSC will assume the responsibility, except in the case that damages are incurred due to violation of the protocol, intentional or serious negligence at the site.

## 17. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and

relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

# 18. Potential Risks and Benefits

## 18.1. *Risks / Adverse Events Associated with the Study Device and Procedure*

Potential anticipated adverse events associated with the use of study device and other interventional catheters in this study and the PTA procedure include, but are not limited to the following (alphabetical order):

- Abrupt or sub-acute closure
- Allergic reaction (device, contrast medium, medications)
- Amputation
- Arrhythmias
- Arteriovenous fistula
- Bleeding/hemorrhage (access site and/or non-access site)
- Death
- Dissection
- Embolization (air, plaque, thrombus, device, tissue or other)
- Extremity ischemia which may require urgent intervention or surgery
- Fever
- Hematoma
- Hemodynamic instability (hypotensive/hypertensive episodes)
- Infection/sepsis
- Minor burn
- Pain
- Perforation
- Pseudo-aneurysm
- Restenosis of the treated segment
- Renal insufficiency or failure
- Vascular complications which may require surgical repair (e.g., dissection, perforation, rupture)
- Vasospasm

• Vessel occlusion

• Stroke/transient cerebral ischemic attack

• Thrombosis/thromboembolism

### 18.2. *Risks associated with Participation in the Clinical Study*

In addition to the aforementioned risks associated with the use of Jetstream System and PTA procedure, the use of prolonged dual antiplatelet therapy after atherectomy and PTA may increase the risk of bleeding. There may be additional risks linked to the procedure, which are unforeseen at this time

### 18.3. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

### 18.4. *Anticipated Benefits*

Potential anticipated benefits include the improvement of procedural success of atherosclerotic SFA/PPA lesions with improvement in the symptoms of disease. However, the Jetstream system is an investigational device and these potential benefits may or may not actually be present.

### 18.5. *Risk to Benefit Rationale*

The Jetstream System is expected to be suitable for its intended purpose. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of appropriate Directions for Use (DFU). Evaluation of the risks and benefits that are expected to be associated with use of the Jetstream System demonstrate that when used under the conditions intended, the benefits associated with use of the Jetstream System should outweigh the risks.

## 19. Safety Reporting

### 19.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. For centers in Austria cancer must always be reported as a Serious Adverse Event. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 19.2-1 for AE definitions).

Refer to Section 18 for the known risks associated with the study device(s).

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

## 19.2. *Definitions and Classification*

Safety definitions are provided in Table 19.2-1,with reference from ISO 14155-2011 and MEDDEV 2.7/3 12/2010.

**Table 19.2-1: Safety Reporting Definitions**

| Term | Definition |
|---|---|
| Adverse Event (AE)<br><br>*Ref: ISO 14155-2011*<br>*Ref:* MEDDEV2.7/3 12/2010 | Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device.<br>NOTE 1: This includes events related to the investigational medical device or comparator.<br>NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).<br>NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device. |
| Adverse Device Effect (ADE) | Adverse event related to the use of an investigational medical device |

**Table 19.2-1: Safety Reporting Definitions**

| Term | Definition |
|---|---|
| *Ref: ISO 14155-2011*<br>*Ref:* MEDDEV2.7/3 12/2010 | NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.<br>NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device. |
| Serious Adverse Event (SAE)<br><br>*Ref: ISO 14155-2011*<br><br>*Ref:* MEDDEV2.7/3 12/2010 | Adverse event that:<br>• Led to death,<br>• Led to serious deterioration in the health of the subject, that either resulted in:<br>o a life-threatening illness or injury, or<br>o a permanent impairment of a body structure or a body function, or<br>o in-patient hospitalization or prolongation of existing hospitalization of existing hospitalization, or<br>o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function<br>• Led to fetal distress, fetal death, or a congenital abnormality or birth defect.<br>**NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event. |
| Serious Adverse Device Effect (SADE)<br><br>*Ref: ISO 14155-2011*<br><br>*Ref:* MEDDEV2.7/3 12/2010 | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| Unanticipated Adverse Device Effect (UADE)<br><br>*Ref: 21 CFR Part 812* | Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. |
| Unanticipated Serious Adverse Device Effect (USADE)<br><br>*Ref: ISO 14155-2011*<br><br>*Ref:* MEDDEV2.7/3 12/2010 | Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.<br>**NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. |

**Table 19.2-1: Safety Reporting Definitions**

| Term | Definition |
|---|---|
| Device Deficiency<br><br>*Ref: ISO 14155-2011*<br>*Ref:* MEDDEV2.7/3 12/2010 | Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.<br>**NOTE 1**: All device deficiencies that could have led to a SADE if a) suitable action had not been taken or b) if intervention had not been made or c) if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the protocol. |

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

## 19.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 19.3-1:

**Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event**

| Classification | Description |
|---|---|
| **Not Related** | Relationship to the device or procedures can be excluded when:<br>- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;<br>- the event has no temporal relationship with the use of the investigational device or the procedures;<br>- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;<br>- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;<br>- the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);<br>- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error;<br>- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. |
| **Unlikely Related** | The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly Related** | The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| **Probably Related** | The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained. |

**Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event**

| Classification | Description |
|---|---|
| **Causal Relationship** | The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:<br>- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;<br>- the event has a temporal relationship with investigational device use/application or procedures;<br>- the event involves a body-site or organ that<br>o the investigational device or procedures are applied to;<br>o the investigational device or procedures have an effect on;<br>- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);<br>- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);<br>- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;<br>- harm to the subject is due to error in use;<br>- the event depends on a false result given by the investigational device used for diagnosis, when applicable;<br>- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. |

The Investigator must assess the relationship of the AE to the antiplatelet medication using the following categories and definitions (Table 19.3-2).

**Table 19.3-2: Criteria for Assessing Relationship of Antiplatelet Medication to Adverse Event**

| Classification | Description |
|---|---|
| **Not Related** | Relationship to the antiplatelet medication can be excluded when:<br>- the event is not a known side effect of the medication category the antiplatelet medication belongs to or of similar medication;<br>- the event has no temporal relationship with the use of the antiplatelet medication;<br>- the serious event does not follow a known response pattern to the antiplatelet medication (if the response pattern is previously known) and is biologically implausible;<br>- the discontinuation of antiplatelet medication use or the reduction of the dose of antiplatelet medication - when clinically feasible – and reintroduction of its use (or increase of the dose of antiplatelet medication), do not impact on the serious event;<br>- the event involves a body-site or an organ not expected to be affected by the antiplatelet medication; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);<br>- the harms to the subject are not clearly due to use error;<br>- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of antiplatelet medication and the serious event. |
| **Unlikely Related** | The relationship with the use of the antiplatelet medication seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly Related** | The relationship with the use of the antiplatelet medication is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| **Probably Related** | The relationship with the use of the antiplatelet medication seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained. |

**Table 19.3-2: Criteria for Assessing Relationship of Antiplatelet Medication to Adverse Event**

| Classification | Description |
|---|---|
| **Causal Relationship** | The serious event is associated with the antiplatelet medication beyond reasonable doubt when:<br>- the event is a known side effect of the medication category the antiplatelet medication belongs to or of similar medication;<br>- the event has a temporal relationship with antiplatelet medication use;<br>- the event involves a body-site or organ that<br>o the antiplatelet medication are applied to;<br>o the antiplatelet medication have an effect on;<br>- the serious event follows a known response pattern to the antiplatelet medication (if the response pattern is previously known);<br>- the discontinuation of antiplatelet medication use (or reduction of the dose of medication) and reintroduction of its use (or increase of the dose of medication), impact on the serious event (when clinically feasible);<br>- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;<br>- harm to the subject is due to error in use;<br><br>- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of antiplatelet medication and the serious event. |

## 19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 19.4-1.

**Table 19.4-1: Investigator Reporting Requirements**

| Event Classification | Communication Method | Communication Timeline |
|---|---|---|
| Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect (UADE/USADE) | Complete AE eCRF page with all available new and updated information. | • Within 24 hours of first becoming aware of the event.<br>• Terminating at the end of the study |
| Serious Adverse Event including Serious Adverse Device Effects(SADE) | Complete AE eCRF page with all available new and updated information. | • Within 24 hours of first becoming aware of the event<br>• Reporting required through the end of the study |
| | Provide all relevant source documentation (unidentified) for reported event | • When documentation is available |
| Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) | Complete Device Deficiency eCRF with all available new and updated information. | • Within 24 hours of first becoming aware of the event.<br>• Reporting required through the end of the study |

**Table 19.4-1: Investigator Reporting Requirements**

| Event Classification | Communication Method | Communication Timeline |
|---|---|---|
| Note: Any Investigational Device Deficiency that might have led to a serious adverse event if: a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event. | | |
| Adverse Event including Adverse Device Effects | Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device. | • In a timely manner but no later than10 business days after becoming aware of the information<br>• Reporting required through the end of the study |

Abbreviations: AE = adverse event; CRF = case report form; IDE = Investigational Device Exemption; UADE = unanticipated adverse device effect

## 19.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in Device Management Plan. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

And, any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

## 19.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting adverse event information and device deficiencies information to all participating Principal Investigators and regulatory authorities as applicable according to China local reporting requirements.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

According to China local reporting requirements, Boston Scientific Corporation will report all SAEs and device deficiencies that could lead to SAEs to the local Food and Drug Administration and the same level Commission of Health and Family Planning within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sites and IRBs/ECs in a timely manner.

Investigator and investigational site are responsible for reporting all SAEs and device deficiencies that could lead to SAEs to IRBs/ECs, local Food and Drug Administration within 24 hours of investigator becoming aware of the event.

BSC shall notify all participating Chinese study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

## 20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by BSC or its delegate (e.g. CRO), the site's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,

- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, vascular angiography may demonstrate that the subject is not a suitable candidate for the trial. A Screening Log will be maintained to document select information about candidates who fail to meet the Jetstream China trial eligibility criteria, including, but not limited to, the reason for screen failure.

# 21. Committees

## 21.1. *Executive Committee*

An Executive Committee composed of BSC Clinical Management, study Principal Investigator will be convened. This committee will be responsible for the overall conduct of the study which will include protocol development, study progress, subject safety, overall data quality and integrity, and timely dissemination of study results through appropriate scientific sessions and publications. As appropriate the Executive Committee may request participation of Jetstream China Investigators on the Committee.

## 21.2. *Safety Monitoring Process*

To promote early detection of safety issues, the BSC Safety team and its delegated CRO Safety team will provide review, process, monitor and evaluation of the safety events defined in the

study-specific safety plan. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information. The BSC Medical Safety group includes physicians with expertise in vascular intervention and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

### 21.3. *Clinical Events Committee*

The Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise who review and adjudicate important clinical endpoints and relevant AEs reported by study Investigators.

The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, for all following reported 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

Committee membership will include practitioners of vascular interventional therapy, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. Responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

## 22. Suspension or Termination

### 22.1. *Premature Termination of the Study*

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

#### 22.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

### 22.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

Any investigator, or IRB/ EC in the Jetstream China Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

### 22.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

### 22.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled beyond 6 months after site initiation; or if enrollment is significantly slower than expected; or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed through the end of the study. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

# 23. Study Registration and Results

### 23.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

### 23.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

### 23.3. *Publication Policy*

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

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# 25. Abbreviations and Definitions

## 25.1. *Abbreviations*

Abbreviations are shown in **Table 25.1-1**.

**Table 25.1-1: Abbreviations**

| Abbreviation | Terminology |
|---|---|
| **ABI** | Ankle Brachial Index |
| **ADE** | Adverse Device Effect |
| **AE** | Adverse Event |
| **BSC** | Boston Scientific Corporation |
| **CE** | Conformité Européenne (meaning European Conformity) |
| **CEC** | Clinical Event Committee |
| **CIN** | Contrast-Induced Nephropathy |
| **CRA** | Clinical Research Associate |
| **CRF** | Case Report Form |
| **CRO** | Contract Research Organization |

**Table 25.1-2: Abbreviations**

| Abbreviation | Terminology |
|---|---|
| **CVA** | Cerebrovascular Accident |
| **DFU** | Directions for Use |
| **DUS** | Duplex Ultrasound |
| **eCRF** | Electronic Case Report Form |
| **EDC** | Electronic Data Capture |
| **EVT** | Endovascular Therapy |
| **GCP** | Good Clinical Practice |
| **HCP** | Health Care Professional |
| **ICF** | Informed Consent Form |
| **ICMJE** | International Committee of Medical Journal Editors |
| **ICH** | International Conference on Harmonization |
| **IMR** | Independent Medical Reviewer |
| **ITT** | Intent to Treat |
| **IRB** | Institutional Review Board |
| **IVUS** | Intravascular Ultrasound |
| **MAE** | Major Adverse Event |
| **OPC** | Objective Performance Criteria |
| **PAD** | Peripheral arterial disease |
| **PG** | Performance Goal |
| **PPA** | Proximal Popliteal Artery |
| **PSVR** | Peak Systolic Velocity Ratio |
| **PTA** | Percutaneous Transluminal Angioplasty |

**Table 25.1-3: Abbreviations**

| Abbreviation | Terminology |
|---|---|
| **QA** | Quantitative Angiography |
| **QOL** | Quality of Life |
| **SADE** | Serious Adverse Device Effect |
| **SAE** | Serious Adverse Event |
| **SC** | Single Cutter |
| **SFA** | Superficial Femoral Artery |
| **TASC** | Transatlantic Inter-Societal Consensus |
| **TBI** | Tibial Brachial Index |
| **TLR** | Target Lesion Revascularization |
| **TVR** | Target Vessel Revascularization |
| **USADE** | Unanticipated Serious Adverse Device Effect |
| **UPN** | Universal Product Number |
| **XC** | Expandable Cutter |

## 25.2. *Definitions*

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **AMPUTATION** | • Major Amputation: amputation of the lower limb at the ankle level or above; and can be further specified as *below-the-knee* and *above-the-knee* amputations, as well as *planned* and *unplanned* amputations.<br>• Minor Amputation: amputation of the lower limb below the ankle level, i.e. forefoot or toes. |
| **ANKLE-BRACHIAL INDEX (ABI)** | The ratio between the systolic pressure measured at the ankle and the systolic pressure measured in the arm as follows:<br>• Ankle: The systolic pressure will be measured in the target limb at the arteria dorsalis pedis and/or the arteria tibialis posterior. If both pressures are measured, the highest pressures will be used for the ABI calculation.<br>• Brachial: The systolic pressure will be measured in both arms, and the highest of both pressures will be used for the ABI calculation.<br><br>An ABI <0.9 indicates the presence of peripheral arterial disease in symptomatic patients as well as in asymptomatic patients. In addition, an ABI <0.9 reflects the presence of generalized asymptomatic or symptomatic atherosclerotic disease, and its associated increased cardiovascular risk. |
| **ARRHYTHMIA** | Any variation from the normal rhythm of the heartbeat, including but not limited to, sinus arrhythmia, premature beats, heart block, ventricular or atrial fibrillation, ventricular tachycardia, or atrial flutter. |
| **ASSISTED PRIMARY PATENCY** | Percentage (%) of lesions without clinically-driven TLR and those with clinically-driven TLR (not due to complete occlusion or by-pass) that reach endpoint without restenosis. |
| **BLEEDING COMPLICATION** | Includes, but is not limited to, intracranial hemorrhage, GI bleeding, hematoma, bleeding at percutaneous catheterization site, and/or retroperitoneal bleeding. Bleeding that requires surgery qualifies as an SAE. |
| **CALCIFICATION** | Readily apparent densities seen within the artery wall and site of lesion as an x-ray-absorbing mass. |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **CEREBRO-VASCULAR ACCIDENT (CVA)** | CEREBRO-VASCULAR ACCIDENT / STROKE<br>An acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging study or autopsy showing infarction. |
| **CLINICAL SUCCESS** | Clinical success defined as improved Rutherford classification by at least +1 class compared to baseline. |
| **COMPLETE BLOOD COUNT (CBC)** | A blood test used to measure several components and features of blood, including: Red Blood Cells, White Blood Cells, Hemoglobin, Hematocrit and Platelets. |
| **COMPLICATION** | An undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the investigational product(s). |
| **DEATH** | All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, an unexpected death in subjects with coexisting potentially fatal non-cardiac diseases (e.g. Cancer, infection) should be classified as cardiac.<br>All death events will be submitted to CEC and will be categorized as:<br>Cardiac death: any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related deaths including those related to concomitant treatment.<br>Vascular death: death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause**.**<br>Non-cardiovascular death: any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide, or trauma.<br>Index Limb-Related Death: all death will also be adjudicated by the Clinical Event Committee (CEC) as “likely related” to a complication of the index limb.<br>Perioperative Death is the death within 30 days of the index procedure. |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **DIAMETER STENOSIS** | The maximal narrowing of the target lesion relative to the reference vessel diameter. |
| **DISSECTION- NHLBI GRADE TYPES** | Type A- Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.<br>Type B- Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.<br>Type C- Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.<br>Type D- Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow.<br>Type E- Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.<br>Type F- Filling defect accompanied by total vessel occlusion. |
| **DISTAL EMBOLIZATION** | Migration of a filling defect, or thrombus, to distally occlude the target vessel or one of its branches. |
| **HEMATOMA** | A localized swelling filled with blood resulting from a break in a blood vessel. |
| **HEMODYNAMIC IMPROVEMENT** | Improvement of ABI by $\geq 0.1$ or to an ABI $\geq 0.90$ as compared to the pre-procedure value without the need for repeat revascularization. |
| **HEMODYNAMIC SUCCESS** | Hemodynamic success is defined as a positive change in Ankle-Brachial Index compared to baseline. |
| **HYPOTENSION** | Systolic blood pressure < 80 mmHg lasting more than 30 minutes or requiring intervention (e.g. pacing, IABP, intra venous vasopressors to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible. |
| **INTIMAL FLAP** | An extension of the vessel wall into the arterial lumen. |
| **LESION LENGTH** | Measured as the distance from the proximal shoulder to the distal shoulder of the lesion, in the view that demonstrates the stenosis in its most elongated projection. |
| **MAJOR ADVERSE EVENTS (MAEs)** | Major Adverse Events (MAEs) include all-cause death, target limb unplanned major amputation and/or target lesion revascularization (TLR). |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **MINIMAL LUMEN DIAMETER** | The vessel diameter as measured at the narrowest point of the lesion. |
| **PERFORATION** | Perforations are classified as follows:<br>***Angiographic perforation*:** perforation detected by the clinical site or Angiographic Core Laboratory at any point during the procedure.<br>***Clinical perforation*:** perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant hemodynamic compromise, abrupt closure, or death. |
| **PRIMARY PATENCY** | ***Vessel patency*** is defined as freedom from more than 50% diameter stenosis.<br>***Primary patency*** is the absence of more than 50% stenosis assessed by angiography, CTA or DUS (i.e., peak systolic velocity ratio must ≤2.4), without clinically-driven target lesion revascularization (TLR) post the index procedure. |
| **PRIMARY SUSTAINED CLINICAL IMPROVEMENT** | Improvement in Rutherford classification of one or more categories as compared to pre-procedure without the need for repeat TLR. |
| **PROCEDURAL SUCCESS** | Technical success with no MAEs noted within 24 hours of the index procedure. |
| **PSEUDO-ANEURYSM** | An encapsulated hematoma in communication with an artery. |
| **PRODUCT NON-CONFORMITY** | A departure of a quality characteristic from its intended level or state that occurs with a severity sufficient to cause an associated product or service not to meet a specification requirement. |
| **REPEAT INTERVENTION (PERCUTANOUS AND/OR SURGERY)** | Either repeat percutaneous transluminal angioplasty (PTA) or artery bypass surgery, performed subsequently to the subject leaving the cath lab after the index procedure. |
| **REFERENCE VESSEL DIAMETER (RVD) OF NORMAL ARTERY SEGMENT** | Angiographic measurement of the artery proximal and/or distal to the lesion intended for treatment. |
| **RESTENOSIS** | Diameter stenosis > 50% assessed by angiography, CTA or DUS (peak systolic velocity ratio > 2.4) |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **RUTHERFORD / BECKER CLASSIFICATION** | **Category** / **Clinical Description** / **Objective Criteria**<br>0 / Asymptomatic / Normal Treadmill /stress test<br>1 / Mild claudication / Completes treadmill exercise; ankle pressure (AP) after exercise < 50 mm Hg, but > 25 mm Hg less than BP<br>2 / Moderate claudication / Between categories 1 and 3<br>3 / Severe claudication / Cannot complete treadmill exercise and AP after exercise < 50 mm Hg<br>4 / Ischemic rest pain / Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording (PVR); toe pressure (TP) < 30 mm Hg<br>5 / Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal edema / Resting AP < 60 mm Hg, ankle or metatarsal (MT) PVR flat or barely pulsatile; TP < 40 mm Hg<br>6 / Major tissue loss – extending above MT level / Same as Category 5 |
| **SECONDARY SUSTAINED CLINICAL IMPROVEMENT** | Improvement in Rutherford classification of one or more categories as compared to pre-procedure including those subjects with repeat TLR. |
| **SOURCE DATA** | All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies). |
| **SOURCE DOCUMENT** | Original documents, data or records.<br>Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation. |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **TARGET LESION** | Target lesion is the lesion selected by the investigator for treatment with the study device, the length of the target lesion is inclusive of the section of vessel treated with the study device and the 5 mm proximal and 5 mm distal to the treated section. |
| **TARGET LESION REVASCULARIZATION (TLR)** | Target lesion revascularization (TLR) is a repeat revascularization procedure (percutaneous or surgical) within 5mm proximal or distal to the originally treated target lesion segment. A TLR will be considered as clinically driven if the culprit lesion diameter stenosis is > 50% determined by DUS, CTA or angiography AND the subject has either clinical and/or functional recurrent ischemia (e.g., recurrent/progressive intermittent claudication, ≥ 1 change in Rutherford Category associated with the target limb, or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels).<br><br>A target lesion revascularization for an in-lesion diameter stenosis less than 50% might also be considered a major adverse event (MAE) by the CEC if the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels).<br><br>***Non-Target Lesion Revascularization***<br><br>Non-target lesion revascularization is any (de novo or repeat) vascular intervention or bypass surgery of a non-target lesion in a target vessel or a non-target vessel. This includes revascularization at the time of an index (study) vascular intervention of a separate target lesion and subsequent revascularization after the index (study) vascular intervention. |
| **TARGET VESSEL** | Target vessel is defined as the vessel containing the target lesion(s). If the target lesion is entirely within the right superficial femoral artery, then the target vessel is the right superficial femoral artery. If the target lesion extends from the right superficial femoral artery into the right proximal popliteal artery, then both the right superficial femoral artery and right proximal popliteal artery would be considered part of the target vessel. |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **TARGET VESSEL REVASCULARIZATION (TVR)** | ***Target vessel revascularization (TVR)*** is any *repeat* intervention or surgical bypass of any segment of a target vessel. TVR includes target lesion revascularization (TLR) or a non-target lesion revascularization (see definitions below) in the same target vessel.<br>A TVR will be considered clinically-driven if the culprit lesion diameter stenosis is > 50% by DUS, CTA or angiography AND the subject has either clinical and/or functional recurrent ischemia (e.g., recurrent/progressive intermittent claudication, ≥ 1 change in Rutherford Category associated with the target limb, or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels).<br>A target vessel revascularization for a culprit lesion diameter stenosis less than 50% might also be considered a MAE by the CEC if the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels). |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **TRANSATLANTIC INTER-SOCIETAL CONSENSUS (TASC) LESION GUIDELINES FOR FEMOROPOPLITEAL LESIONS** | Type A lesion:<br>• Single stenosis ≤ 10 cm in length.<br>• Single occlusion ≤ 5 cm in length.<br><br>Type B lesion:<br>• Multiple lesions (stenoses or occlusions), each ≤ 5 cm<br>• Single stenosis or occlusion ≤ 15cm not involving the infra geniculate popliteal artery<br>• Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass<br>• Heavily calcified occlusion ≤ 5cm in length<br>• Single popliteal stenosis<br><br>Type C lesion:<br>• Multiple stenoses or occlusions totaling > 15 cm with or without heavy calcification<br>• Recurrent stenoses or occlusions that need treatment after two endovascular interventions<br><br>Type D lesion:<br>• Chronic total occlusions of the CFA or SFA (> 20 cm, involving the popliteal artery)<br>• Chronic total occlusion of the popliteal artery and proximal trifurcation vessels |
| **TECHNICAL SUCCESS** | Technical success is 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). |
| **THROMBUS (ANGIOGRAPHIC)** | Discrete, mobile intraluminal filling with defined borders with/without associated contrast straining; these are classified as either absent or present. |
| **TOTAL OCCLUSION** | Lesion with no flow; implies 100% diameter stenosis. |
| **VASCULAR COMPLICATION** | An occurrence of hematoma > 5 cm, pseudoaneurysm, arteriovenous (AV) fistula, or need for vascular surgical repair. |

**Table 25.2-1: Definitions**

| Term | Definition |
|---|---|
| **VESSEL PATENCY** | Vessel patency is defined as freedom from more than 50% diameter stenosis assessed by angiography, CTA or DUS (with peak systolic velocity ratio > 2.4). |

Abbreviations are defined in Table 25.1-1.

# Investigator Statement （See Chinese version protocol）