# IMPERIAL

A randomIzed trial coMParing the ELUVIA™ dRug-elutIng stent versus Zilver® PTX® stent for treatment of superficiAL femoral and/or proximal popliteal arteries

**CLINICAL PROTOCOL**

Study Reference Number **S2063**

IDE Number **G150171**

**Sponsored By**

**Boston Scientific Corporation**
300 Boston Scientific Way
Marlborough, MA 01752

**European Authorized Representative**
Boston Scientific Limited
Ballybrit Business Park
Galway, Ireland

**Japanese Representative**
Boston Scientific Japan K.K.
4-10-2, Nakano Nakano-ku
Tokyo 164-0001, Japan

**New Zealand Representative**
Boston Scientific (Australia) Pty Ltd
PO Box 322
Botany
NSW 1455, Australia

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## Contact Information

| Role | Contact |
|---|---|
| **Clinical Contact** | Debra Jovanovich<br>Sr. Clinical Trial Manager<br>Peripheral Interventions<br>1 Scimed Place<br>Maple Grove, MN 55311<br>Debra.Jovanovich@bsci.com<br><br>Lieve Cornelis<br>Clinical Trial Manager<br>Green Square<br>Lambroekstraat 5D<br>1831 Diegem<br>Belgium<br>Lieve.Cornelis@bsci.com<br><br>Rieko Kuribayashi<br>Boston Scientific Japan KK<br>Project Manager, Project Management<br>4-10-2, Nakano Nakano-ku<br>Tokyo 164-0001, Japan<br>Rieko.Kuribayashi@bsci.com |
| **Coordinating Principal Investigator** | William Gray, MD<br>System Chief of the Division of Cardiovascular Disease<br>Main Line Health<br>President, Lankenau Heart Institute<br>100 Lancaster Avenue, Suite 356 MOB EAST<br>Wynnewood, PA 19096 |
| **Coordinating Co-Principal Investigator** | Prof. Dr. med Stefan Müller-Hülsbeck<br>Director and Chairman, Vascular Center<br>Head of the Department of Diagnostic and Interventional Radiology/Neuroradiology<br>Ev. Luth. Diakonissenanstalt Flensburg<br>Knuthstrasse 1<br>24939 Flensburg |

| | |
|---|---|
| | Germany |
| **Investigational Sites** | A list of investigational sites is provided in the Manual Of Operations.<br>A list of investigational sites in Japan is provided as a separate attachment to the protocol for Japanese sites only. |
| **Vendors/Labs** | A list of vendors/labs involved in the trial is provided in the Manual Of Operations. |

**Original Release:** July 20, 2015

**Current Version:** March 7, 2016

## Revision History

| Revision Number | Release Date | Section | Change | Reason for Change |
|---|---|---|---|---|
| AB | 10-Sep-2015 | 1. Title Page | IDE number and Revision History added. | Administrative change for new information. |
| | | 2. Synopsis, 11.6 Required Concomitant Medications | Monotherapy antiplatelet requirement clarified. Required through 12 months and recommended through 60 months. | Typographical error between synopsis and protocol section. |
| | | Entire Protocol | Align use of efficacy and effectiveness. | Revisions to address FDA comments on IDE submission. |
| | | 2. Synopsis, 12. Statistical Considerations | Remove sequential hypothesis testing and update sensitivity analysis. | |
| | | 2. Synopsis, 11.12 Assessment of Whole Blood Paclitaxel Levels, 13.3 Core Laboratories | Addition of 48/72 hour blood draw, increase in subject enrollment for PK substudy, and increase in number of allowed PK sites in US. | Revisions to address FDA comments on IDE submission. |
| | | 11.15 Missed or Late Visits | Addition of patient locator service for missed annual visits. | Revisions to address FDA comments on IDE submission. |
| | | 19.2.Risks Associated with the Study Device(s) Unique to Paclitaxel | Reference to side effects reported by the chemotherapy subjects removed. | Clarification to include both paclitaxel and the polymer coating in this section. |
| AC | 7-Mar-2016 | 1. Contact Information | Updated contact for the coordinating principal investigator Dr. William A. Gray. | Updated due to a move. |

# Revision History

| Revision Number | Release Date | Section | Change | Reason for Change |
|---|---|---|---|---|
| | | 2. Protocol Synopsis | Updated to include overview of the Long Lesion Substudy | Updated with overview of the Long Lesion Substudy |
| | | 4.1 Clinical Development Program | Added "and received CE Mark Certification in February 2016" To paragraph 2. | New device approval received in February 2016. |
| | | 4.1.4 MAJESTIC First Human Use Trial | Added 12 month MAJESTIC results to paragraphs 3 and 4. | New data available from the MAJESTIC study. |
| | | 5.1 ELUVIA Drug-Eluting Stent System | Added "CE Mark Certification for the ELUVIA stent system was obtained in February 2016" To paragraph 2. | New device approval received in February 2016. |
| | | 5.4. Device Labeling of Investigational Device | Addition and Revision of the information appear on the product labeling. | Specify the information specific to the Japan labels. |
| | | 7.1. Primary Endpoints | Primary Effectiveness endpoint: correct the language for clinically-driven TLR (…for ≥50% angiographic diameter stenosis) | Correct prior error. |
| | | 8.4. Justification for the Study Design | Correct the statement of monotherapy antiplatelet requirement | Correct prior error to align with the last change for monotherapy antiplatelet requirement. |
| | | 11.9 End of the Index Procedure | Correct the language of removal of the guide catheter at end of procedure. | Correct prior error. |
| | | 20. Safety Reporting | Section updated to include MEDDEV 2.7/3 (2015) requirements | Updated with new MEDDEV guidelines. |
| | | 27. Abbreviations and Definitions | Correct definition for Assisted Primary Patency and Primary Patency (addition of clinically-driven) | Definition is now consistent with endpoints and text throughout document. |
| | | 28. Long Lesion Substudy | Added the Long Lesion Substudy | New substudy to treat long lesions. |

## 2. Protocol Synopsis

<table>
<tr><td colspan="2">IMPERIAL: A randomIzed trial coMParing the ELUVIA™ dRug-elutIng stent versus Zilver® PTX® stent for treatment of superficiAL femoral and/or proximal popliteal arteries</td></tr>
<tr><td>Objective(s)</td><td>To evaluate the safety and effectiveness of the Boston Scientific Corporation (BSC) ELUVIA Drug-Eluting Vascular Stent System (ELUVIA Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions up to 140 mm in length.<br><br>Long Lesion Substudy: To evaluate the safety and effectiveness of the Boston Scientific Corporation (BSC) ELUVIA Drug-Eluting Vascular Stent System (ELUVIA Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions >140 mm and ≤ 190 mm in length.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The ELUVIA Stent System is intended to improve luminal diameter in the treatment of symptomatic de novo or restenotic lesions in the native SFA and/or PPA with reference vessel diameters (RVD) ranging from 4.0-6.0 mm and total lesion lengths up to 140 mm.<br><br>Long Lesion Substudy: The ELUVIA Stent System is intended to improve luminal diameter in the treatment of symptomatic de novo or restenotic lesions in the native SFA and/or PPA with reference vessel diameters (RVD) ranging from 4.0-6.0 mm and total lesion lengths up to 190 mm</td></tr>
<tr><td>Test Device</td><td>The ELUVIA Stent is a paclitaxel-eluting, self-expanding nitinol stent developed on the same stent and delivery system as the BSC Innova™ Vascular Self-Expanding Stent System.</td></tr>
<tr><td>Control Device</td><td>The Zilver PTX Stent (Cook Medical, Bloomington, IN) is a self-expanding nitinol stent coated with the drug paclitaxel and indicated for improving luminal diameter for the treatment of de novo or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries.</td></tr>
<tr><td>Device Sizes</td><td>ELUVIA Stent (Test Device)
<table>
<tr><th>Stent Diameter (mm)</th><th>Stent Length (mm)</th><th>Recommended Vessel Diameter (mm)</th></tr>
<tr><td>6</td><td>40, 60, 80, 100, 120, 150</td><td>4.0 – 5.0</td></tr>
<tr><td>7</td><td>40, 60, 80, 100, 120, 150</td><td>5.0 – 6.0</td></tr>
</table>
The ELUVIA Stent is available in two stent delivery system (SDS) sizes; 75 cm and 130 cm. The sheath compatibility is 6 French used with 0.035 inch</td></tr>
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| | guidewires.<br>**Zilver PTX Stent (Control Device)**<br>The Zilver PTX Stent is commercially available in all geographic regions included in this global trial. To meet all inclusion and exclusion criteria, Zilver PTX stent diameters of 6 and 7 mm will be allowed in this trial. Available Zilver PTX stent lengths range between 20 mm to 120 mm. Use of two overlapping Zilver PTX stents is allowed according to the device Instructions for Use (IFU). The system is also available in two SDS sizes; 80 cm and 125 cm. The sheath compatibility is also 6 French used with 0.035 inch guidewires. |
| **Study Design** | A global, prospective, multi-center trial evaluating the safety and effectiveness of the ELUVIA stent versus Zilver PTX stent in the treatment of lesions 30-140 mm long located in the femoropopliteal arteries in subjects with symptoms classified as Rutherford categories 2-4.<br>The trial consists of a prospective, multicenter, 2:1 randomized (ELUVIA vs Zilver PTX), controlled, single-blind, non-inferiority trial (RCT), a concurrent, non-blinded, non-randomized, single-arm, pharmacokinetic (PK) substudy and a concurrent, non-blinded, non-randomized, Long Lesion substudy. A subject can be enrolled in either the RCT or the PK substudy. A subject cannot be enrolled in both of these studies.<br>If a subject's target lesion is longer than that allowed in the RCT and PK substudy, the subject may be enrolled in the Long Lesion substudy.<br>If a subject is enrolled in the Long Lesion substudy at a site conducting the PK substudy and the subject is willing to undergo PK testing, they will also follow the blood draw schedule for the PK substudy. |
| **Planned Number of Subjects** | Approximately 527-535 subjects will be enrolled in the IMPERIAL trial.<br>• 465 subjects to receive treatment with either an investigational test device (ELUVIA, N=310 subjects) or a control device (Zilver PTX, N=155 subjects) in the RCT<br>• 12-20 subjects to receive treatment with the investigational test device (ELUVIA) in the PK substudy<br>• 50 subjects to receive treatment with the investigational test device (ELUVIA) in the Long Lesion substudy |
| **Planned** | Up to 75 study centers worldwide may enroll subjects in the RCT. Regions |

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| **Number of Centers / Regions** | that may participate include, but are not limited to, the United States, Canada, European Union, Japan and New Zealand.<br><br>Approximately 10 study centers in the US may enroll subjects in the PK substudy.<br><br>Any study center participating in the RCT may opt to also enroll subjects in the Long Lesion substudy. |
| **Primary Endpoints** | <u>Primary Safety Endpoint</u><br><br>The primary safety endpoint assesses the occurrence of Major Adverse Events (MAEs) defined as all causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularization (TLR) through 12 months. This safety endpoint is designed to demonstrate that the 12-month MAE-free rate for the ELUVIA treatment group is non-inferior to the control group.<br><br><u>Primary Effectiveness Endpoint</u><br><br>The primary effectiveness endpoint assesses primary patency at 12 months post-procedure. This effectiveness endpoint is designed to demonstrate that the 12-month primary patency for the ELUVIA treatment group is non-inferior to the Zilver PTX treatment group.<br><br>Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month follow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings will be assessed by an independent core laboratory. |
| **Additional Endpoints** | • Technical success<br>• Procedural success<br>• MAE rate at 1 month post-index procedure defined as all causes of death, target limb major amputation and/or TLR<br>• Primary Patency and Assisted Primary Patency at 6 months, 12 months, 24 months and 60 months using different PSVRs<br>• Clinically-driven TLR and clinically-driven Target Vessel Revascularization (TVR) Rate at each time point<br>• Adverse Event Rates (unanticipated, major, serious, device/procedure-related) at each time point<br>• Non-serious, non-device/procedure-related Adverse Event Rates at each |

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| | time point through 12 months<br>• Stent Fracture Rate at 12 months, 24 months and 60 months utilizing VIVA definitions<br>• Distribution of Rutherford Class during follow-up as compared to baseline at 1 month, 6 months, 12 months, 24 months and 60 months<br>• Rate of Primary and Secondary Sustained Clinical Improvement as assessed by changes in Rutherford Classification from baseline at 1, month, 6 months, 12 months, 24 months and 60 months<br>• Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1 month, 6 months, 12 months, 24 months and 60 months<br>• Walking Improvement at 12 months assessed by change in Six Minute Hall Walk (6MHW) from baseline<br>• Walking Improvement and Patient Utility Values assessed at 1 month, 6 months, 12 months, 24 months and 60 months assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D™ from baseline<br>• Changes in healthcare utilization over time<br>• PK parameters calculated for subjects in the PK substudy |
| **Method of Assigning Patients to Treatment** | Once the subject has signed the approved study informed consent form (ICF), and has met all clinical inclusion and no clinical exclusion criteria, the subject will be considered eligible to be enrolled in the RCT or PK substudy.<br>If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be randomized or receive an investigational device, nor should the subject be followed post-procedure per protocol.<br>For the RCT, if the subject is found to meet the inclusion criteria during the angiographic phase of the procedure, the subject will be considered eligible to be randomized (2:1 allocation treatment versus control). Randomization will be stratified by site. After the Investigator successfully crosses the target lesion with the guidewire, a randomization custom function within the Rave electronic data capture (EDC) database will be used to assign subjects to the test or control treatment group. Subjects will be considered enrolled after they have been successfully randomized (i.e. when a treatment assignment is received by the study site).<br>In the PK substudy and the Long Lesion substudy, subjects will not be randomized; all subjects will be treated with the ELUVIA stent. In the PK |

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| | substudy, subjects will be considered enrolled when the ELUVIA stent is introduced into the subject's vasculature. In the Long Lesion substudy, subjects will be considered enrolled when the first ELUVIA stent is introduced into the subject's vasculature. |
| **Blinding/ Unblinding** | IMPERIAL RCT is a single blind trial. Subjects will be blinded to treatment assigned and treatment received. All subjects must remain blinded until completion of all 12-month follow-up visits (primary endpoint). Packaging of the investigational control and test devices are different, therefore the Investigator performing the procedure will not be blinded to the assigned treatment arm or resulting treatment. Study center personnel will be trained not to disclose the treatment assignment to the subject to minimize the potential unblinding of the subject.<br><br>Site personnel conducting clinical follow-up will be blinded to a subject's treatment assignment whenever possible. Duplex Ultrasound Core Laboratory personnel, Angiography Core Laboratory personnel and the Clinical Events Committee (CEC) will be blinded to a subject's treatment assignment during the trial. Those involved in data analysis for the Sponsor will remain blinded until the primary endpoint analysis.<br><br>Instructions regarding the unblinding of a subject for a medical emergency can be found in the Manual of Operations. |
| **Follow-up Schedule** | All RCT, PK substudy, and Long Lesion substudy subjects will be evaluated at 1 (30 ±7 days), 6 (182 ±30 days), 12 (365 ±30 days), 24 (730 ±30 days), 36 (1095 ±30 days), 48 (1460 ±30 days) and 60 (1825 ±30 days) months post-procedure.<br><br>• Subjects who are randomized but an ELUVIA stent or Zilver PTX stent was not successfully implanted will be followed through the 1-month follow-up visit only. Data for assessment of MAE will be collected for these subjects; other testing is not required.<br>• Assessment of the primary safety and effectiveness endpoints will occur at the 12-month follow-up visit.<br>• All follow-up visits will be conducted in the office/clinic with the exception of long-term follow-up visits conducted 36 months (3 years) and 48 months (4 years) post-procedure which may be conducted either in the office/clinic or via telephone contact.<br><br>Planned protocol-required testing includes the following: |

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| | • PK substudy subjects will have baseline venous blood drawn followed by blood draws at 10 minutes, 30 minutes, 1, 2, 3, 4, 6, 12, and 24 hours and one final blood draw at either 48 hours or 72 hours after placement of the ELUVIA stent. Angiography during the index procedure to assess technical success and procedural success.<br>• DUS at 6 months, 12 months (1 year), 24 months (2 years), and 60 months (5 years) visits to assess lesion and vessel patency.<br>• X-rays at 12 months (1 year), 24 months (2 years), and 60 months (5 years) visits to assess stent integrity. |
| **Study Duration** | The trial will be considered complete (with regard to the primary endpoint) after all subjects have completed the 12 month follow-up visit, were discontinued prior to the 12 month follow-up visit, have died, or the last 12 month follow-up visit window is closed.<br><br>The trial will be considered complete (with regard to all follow-up) after all subjects have completed the 60 month (5 year) follow-up visit, were discontinued prior to the 60 month (5 year) follow-up visit, have died, or the last 60 month (5 year) follow-up visit window is closed.<br><br>It is estimated that it will take approximately 7 years to complete this trial. |
| **Required Medication Therapy** | Investigators must prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice. Antiplatelet medication usage will be collected and reported for compliance for the duration of the trial.<br><br>Minimum requirements include:<br><br>• Anti-coagulation therapy administered during the procedure should be consistent with current clinical practice.<br>• Clopidogrel or ticlopidine starting at least 24 hours prior to the procedure or a peri-procedural loading dose (recommended loading dose of 300 mg clopidogrel or 200 mg ticlopidine) is given within 2 hours after the end of the procedure.<br>• Daily administration of aspirin (recommended dose of at least 75 mg) and clopidogrel (75 mg) or ticlopidine (200 mg) for the first 60 days post-index procedure.<br>• Antiplatelet monotherapy is required through the 12 month (1 year) follow-up and recommended through the 60 month (5 year) follow-up (trial completion).<br><br>Note: a subject could be exempt of antiplatelet requirements if he/she |

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| | requires Coumadin or other similar anti-coagulant due to known comorbidities and in the opinion of the investigator the combination of dual anti-platelet therapy (DAPT) and anticoagulation could pose an intolerable bleeding risk. |
| **Key Inclusion Criteria** | 1. Subjects age 18 and older.<br>2. Subject (or Legal Guardian if applicable) 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. NOTE: For subjects less than 20 years of age enrolled at a Japanese center, the subject's legal representative, as well as the subject, must provide written informed consent.<br>3. Chronic, symptomatic lower limb ischemia defined as Rutherford categories 2, 3 or 4.<br>4. Stenotic, restenotic or occlusive lesion(s) located in the native SFA and/or PPA:<br>a. Degree of stenosis ≥70% by visual angiographic assessment<br>b. Vessel diameter ≥ 4 and ≤ 6 mm<br>c. Total lesion length (or series of lesions) ≥ 30 mm and ≤ 140 mm (Note: Lesion segment(s) must be fully covered with one ELUVIA stent or up to two Zilver PTX stents)<br>Long Lesion Substudy: Total lesion length (or series of lesions) >140 mm and ≤ 190 mm (Note: Lesion segment(s) will require overlapping of two ELUVIA stents).<br>d. For occlusive lesions requiring use of re-entry device, lesion length ≤ 120 mm<br>Long Lesion Substudy: For occlusive lesions requiring use of re-entry device, lesion length > 120 mm and ≤ 170 mm<br>e. Target lesion located at least three centimeters above the inferior edge of the femur<br>5. Patent infrapopliteal and popliteal artery, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot with no planned intervention. |
| **Key Exclusion Criteria** | 1. Previously stented target lesion/vessel.<br>2. Target lesion/vessel previously treated with drug-coated balloon < 12 |

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| | months prior to randomization/enrollment.<br>3. Subjects who have undergone prior surgery of the SFA/PPA in the target limb to treat atherosclerotic disease.<br>4. Use of atherectomy, laser or other debulking devices in the target limb SFA/PPA during the index procedure.<br>5. History of major amputation in the target limb.<br>6. Documented life expectancy less than 24 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the clinical trial, limit the subject's compliance with the follow-up requirements, or impact the scientific integrity of the clinical trial.<br>7. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated.<br>8. Known hypersensitivity/allergy to the investigational stent system or protocol related therapies (e.g., nitinol, paclitaxel, or structurally related compounds, polymer or individual components, and antiplatelet, anticoagulant, thrombolytic medications).<br>9. Platelet count < 80,000 $mm^3$ or > 600,000 $mm^3$ or history of bleeding diathesis.<br>10. Concomitant renal failure with a serum creatinine > 2.0 mg/dL.<br>11. Receiving dialysis or immunosuppressant therapy.<br>12. History of myocardial infarction (MI) or stroke/cerebrovascular accident (CVA) within 6 months prior to randomization/enrollment.<br>13. Unstable angina pectoris at the time of randomization/enrollment.<br>14. Pregnant, breast feeding, or plan to become pregnant in the next 5 years.<br>15. Current participation in another investigational drug or device clinical study that has not completed the primary endpoint at the time of randomization/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>16. Septicemia at the time of randomization/enrollment.<br>17. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of |

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| | randomization/enrollment.<br>18. Presence of aneurysm in the target vessel.<br>19. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to randomization/enrollment.<br>20. Perforated vessel as evidenced by extravasation of contrast media prior to randomization/enrollment.<br>21. Heavily calcified lesions. |
| **Multiple Interventions Using Same Access Site During Index Procedure** | Contralateral Limb<br>• Iliac lesion(s) in the contralateral limb may be treated during the index procedure under the following conditions:<br>− Treatment with a commercially available device occurs prior to randomization/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><br>Target Limb<br>• Additional non-target iliac lesions in the target limb may be treated during the index procedure under the following conditions:<br>− Treatment with a non-drug-eluting commercially available device occurs prior to randomization/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)<br>• Tandem lesions in the SFA/PPA may be treated during the index procedure, provided that the tandem lesions segment is ≤ 140 mm and can be covered with only one ELUVIA stent or up to two Zilver PTX stents according to each device's Directions for Use/Instructions for Use (DFU/IFU). (Refer to Inclusion criterion 4c.)<br>Long Lesion Substudy: Tandem lesions in the SFA/PPA may be treated during the index procedure, provided that the tandem lesions segment is > 140 mm and ≤ 190 mm and can be covered with two ELUVIA stents |

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| | according to the Directions for Use (DFU). (Refer to Inclusion criterion 4c.)<br>• If a second or third stent is required due to complications (e.g., dissection, misplacement or under-sizing of the target lesion), the additional stent(s) placed should be a study stent of the same type used to treat the target lesion. |
| **Statistical Methods for the RCT** | |
| **Primary Safety Statistical Hypothesis** | The primary safety hypothesis to be tested is that the 12-month MAE-free rate in subjects treated with ELUVIA is non-inferior to subjects treated with Zilver PTX by a margin of -10% (negative value) at one-sided significance level of 5%. |
| **Primary Safety Statistical Test Method** | A Farrington-Manning test will be used to assess the one-sided hypothesis of non-inferiority in proportions:<br>$H_0$: Pt - Pc $\leq \Delta$ (inferior)<br>$H_1$: Pt - Pc $> \Delta$ (non-inferior)<br>where Pt and Pc are the 12-month MAE-free rates for the ELUVIA (test) and Zilver PTX (control) groups, respectively, and Δ (delta) is the non-inferiority margin of -10% . |
| **Primary Effectiveness Statistical Hypothesis** | The primary effectiveness hypothesis to be tested is that the 12-month primary patency in subjects treated with ELUVIA is non-inferior to subjects treated with Zilver PTX by a margin of -10% (negative value) at one-sided significance level of 5%. |
| **Primary Effectiveness Statistical Test Method** | A Farrington-Manning test will be used to assess the one-sided hypothesis of non-inferiority in proportions:<br>$H_0$: Pt - Pc $\leq \Delta$ (inferior)<br>$H_1$: Pt - Pc $> \Delta$ (non-inferior)<br>where Pt and Pc are the 12-month primary patency for the ELUVIA (test) and Zilver PTX (control) groups, respectively, and Δ (delta) is the non-inferiority margin of -10%. |
| **Success Criteria for the** | <u>Success Criteria for Primary Safety Endpoint</u><br>ELUVIA will be concluded to be non-inferior to Zilver PTX for device safety |

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| **RCT** | if the one-sided lower 95% confidence bound on the difference between treatment groups (ELUVIA – Zilver PTX) in 12-month MAE-free is greater than -0.1.<br><br>Success Criteria for Primary Effectiveness Endpoint<br><br>ELUVIA will be concluded to be non-inferior to Zilver PTX for device effectiveness if the one-sided lower 95% confidence bound on the difference between treatment groups (ELUVIA – Zilver PTX) in 12-month primary patency is greater than -0.1.<br><br>Success Criteria for the RCT<br><br>If the primary safety and the primary effectiveness endpoints are both met, the RCT will be considered a success and both device safety and effectiveness will be claimed globally. |
| **Sample Size Parameters** | The primary effectiveness endpoint drives the overall sample size.<br><br>Primary Effectiveness Endpoint<br><br>• Power ≥ 80%<br>• One-sided significance level (alpha) = 5%<br>• Expected ELUVIA 12-month primary patency = 83%<br>• Expected Zilver PTX 12-month primary patency = 83%<br>• Non-inferiority margin (Δ) = -10%*<br>• Allocation (ELUVIA vs. Zilver PTX) = 2:1<br>• Attrition rate in 12 months = 15%<br>• N = 393 (total) evaluable subjects are required at 12 months (262 ELUVIA, 131 Zilver PTX)<br>• N = 465 (total) subjects are required to be randomized at enrollment (310 ELUVIA, 155 Zilver PTX)<br><br>*The 10% margin only allows at maximum a 3% difference in observed rates. Assuming 12-month primary patency of 83.2% (109/131) for Zilver PTX is observed, a minimum 12-month primary patency of 80.2% (210/262) for ELUVIA will be required to claim non-inferiority with margin of -10%.<br><br>Primary Safety Endpoint<br><br>• One-sided significance level (alpha) = 5%<br>• Expected ELUVIA 12-month MAE-free rate = 90%<br>• Expected Zilver PTX 12-month MAE-free rate = 90% |

| **IMPERIAL:** A randomIzed trial coMParing the ELUVIA™ dRug-elutIng stent versus Zilver® PTX® stent for treatment of superficiAL femoral and/or proximal popliteal arteries | |
|---|---|
| | • Non-inferiority margin (Δ) = -10%**<br>• Overall sample size is driven by the primary effectiveness endpoint to provide at least 92% power to assess the primary safety endpoint<br>**The 10% margin only allows at maximum a 4% difference in observed rates. Assuming a 12-month MAE-free rate of 90.1% (118/131) for Zilver PTX is observed, a minimum 12-month MAE-free rate of 85.9% (225/262) for ELUVIA will be required to claim non-inferiority with margin of -10%. |
| **Sample Size and Statistical Method for PK Substudy** | In order to support the stated objectives for the PK substudy, the sample size for this substudy will be 12-20 subjects.<br>Descriptive statistics will be presented to describe the PK substudy results. |
| **Sample Size and Statistical Method for Long Lesion Substudy** | The primary effectiveness endpoint assesses the 12-month primary patency. There is a non-statistically driven goal (60%) which was developed from the historical long stent performance (47.2%; 95% Confidence Interval [30.4%, 64.5%]) in subjects treated with Innova Bare Metal Stent System and the expected enhanced performance (10%) for the ELUVIA Stent System. |

# 3. Table of Contents

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# 4. Introduction

Peripheral Arterial Disease (PAD) is the third leading cause of cardiovascular morbidity after myocardial infarction (MI) and stroke. Current estimates state that there are over 8 million US and 200 million global patients with PAD [1] [2] with an age–adjusted prevalence ranging from 12 to 20 percent [3] [4]. Less than twenty percent of patients with PAD have typical symptoms of intermittent claudication such as leg muscle discomfort on exertion that is relieved by rest, or critical limb ischemia (CLI) (i.e., rest pain, ulceration or gangrene); whereas, another third have atypical exertional leg symptoms. Notably, the risk of cardiovascular morbidity and mortality is equally high in patients with PAD, regardless of the presence of symptoms [5]. Non-revascularized lower extremity PAD is the most common cause of lower extremity amputation [6].

**Endovascular Treatment in SFA/PPA**

In general, the debate for state-of-the-art therapy in SFA disease involves endovascular intervention versus bypass surgery. Historically, surgery is generally reserved for resting pain and critical limb ischemia. However, surgical therapy carries significant morbidity, including wound infection, MI and even death. In addition, up to 17 percent of the post-bypass surgery patients do not experience satisfactory clinical improvement [7]. Over the past decade, percutaneous catheter-based techniques have improved such that acute procedural success is high even in complex anatomy. Patency rates have also increased with the use of atherectomy devices and drug-eluting stents (DES). Often, patients with PAD have comorbidities that increase the risk of cardiovascular complications with surgical procedures. These factors have led to the adoption of an endovascular first strategy with surgical management reserved for selected patients [2], [8].

Patients with very short pain-free walking distance are typically candidates for revascularization. According to American College of Cardiologists/ American Heart Association (ACC/AHA) guidelines, endovascular treatment of SFA disease is indicated for individuals with significant disability due to intermittent claudication (IC) or CLI.

The femoropopliteal segment is a challenging vascular territory and has been among the least effective of all endovascular procedures in terms of long-term patency [9], [10], [11]. The SFA is the longest artery in the human body and is located between two major flexion points, the knee and the hip. The relatively small vessel lumen, in conjunction with a high plaque burden, slow flow, and a high frequency of primary occlusions, contributes to considerable technical difficulties. In recent years, however, improvements in device technology and the skill-sets of the interventionalists have facilitated the treatment of complex lesions, including long-segment chronic occlusions with or without moderate calcification. In fact, the current evolution towards treating more complex femoropopliteal lesions as seen in the renewed TransAtlantic Inter-Society Consensus (TASC) II recommendations clearly reflects the continuous evolutions in femoropopliteal stent design [12]. In most cases, the progression of atherosclerotic flow-limiting lesions in the blood vessels of the legs frequently involves the infra-popliteal arteries, resulting in a worsening diagnosis of CLI.

In the past, balloon angioplasty alone was the treatment of choice for the femoropopliteal artery segment. The TASC working group suggested that primary success rates were above 90% with a very low rate of complications (< 4%). However, within one year, patency failure rates above 70% were observed after balloon angioplasty in lesions longer than 10 cm [13]. The application of self-expanding nitinol stent technology seemed to improve the safety and durability of stenting in the SFA [9], [14], [15], [16]. The theoretical basis for improved performance with the use of nitinol stents is due to the unique properties of nitinol such as flexibility, persistent radial force when oversized to a vessel, and ability for crush recovery in these high flexion and torsion force areas in the femoropopliteal arteries. In addition, self-expanding nitinol stents are not as prone to external compression as are balloon-expandable stents. Moreover, due to its smaller arterial diameter and complex nature, the femoropopliteal segment does not respond well to rigid stents. As such, the most flexible nitinol stent is needed to mitigate stent fracture that often occurs in the femoropopliteal arteries.

Although above the knee use of nitinol bare metal stents (BMS) is safe and feasible, it is evidently associated with significant neointimal hyperplasia and early restenosis [17], [18] which may be due to the chronic external forces on the vessel/stent interface resulting in a chronic stimulus for restenosis [19]. Therefore, the interest of investigators turned towards the pharmaceutical ingredients such as paclitaxel and everolimus to suppress neointimal growth and restenosis after stent deployment. DES technology was developed to prevent early thrombosis and late luminal loss to potentially improve long-term patency rates for SFA [20].

In a 2014 contemporary systematic review and meta-analysis, authors examined early outcomes of PTA, DESs, BMSs, or atherectomy for infrapopliteal atherosclerotic disease [8]. A total of 42 studies with 52 treatment arms representing 3,660 unique patients were included. Technical success rates were higher with bare metal stents (BMS; 98.6%) than with atherectomy (92.2%; P <.05) or percutaneous transluminal angioplasty (PTA; 91.2%; P =.01), and higher with drug-eluting stents (DES) than with PTA (P <.001). DES use had higher primary patency rates than atherectomy (P <.05), BMS use (P <.001), and PTA (P <.01). The 30-day rate of target lesion revascularization (TLR) was significantly higher with PTA (8.1%) than with BMS (2.2%; P <.05) and DES (1.1%; P <.05). Thirty-day rates of major unplanned amputation (range, 1.5%-4.4%) and mortality (range, 0.9%-3.3%) were comparable among treatment groups. Significant heterogeneity among studies was noted for most PTA outcomes. The authors concluded that early failure of percutaneous therapies in patients with infrapopliteal atherosclerotic lesions was both device- and technique-dependent. Specialty devices designed to reduce technical failure rates may therefore be of benefit in this selected group of patients.

Studies have shown that paclitaxel inhibits neointimal hyperplasia by disrupting normal microtubule function, thereby inhibiting smooth muscle cell migration, proliferation, and extracellular matrix secretion thus supporting short-term local delivery of paclitaxel for inhibiting restenosis in the SFA [21], [22]. Zilver PTX is currently the only paclitaxel-eluting stent approved for use in the SFA.

**Drug Eluting Peripheral Stents: Zilver PTX**

Zilver PTX is a self-expanding nitinol stent with a polymer-free paclitaxel coating for treating the above-the-knee femoropopliteal segment. Results from the Zilver PTX randomized trial showed a positive effect of a paclitaxel-coated nitinol DES in treating lesions in femoropopliteal arteries [23]. In the RCT, the primary DES group exhibited superior clinical safety and effectiveness when compared to the group randomized to treatment with PTA alone. Primary patency at 12 months post-treatment was determined to be 83.1% in the group treated with Zilver PTX vs. 32.8% in the group treated with PTA.

Dake et al also evaluated the Zilver PTX stent in a prospective, single-arm, multicenter clinical study [15]. The study enrolled 787 patients with symptomatic (Rutherford category 2 - 6) *de novo* or restenotic lesions of the above-the-knee femoropopliteal segment. The primary endpoint of the study was the event free survival (EFS), defined as freedom from major adverse events (MAE) and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6; secondary endpoints were stent patency and stent integrity. Nine hundred lesions (24.3% restenotic lesions) were treated with 1,722 Zilver PTX stents; the mean lesion length was 99.6 ± 82.1 mm. There were no procedural stent fractures, and the 6-month and 12-month stent fracture rates were 1.2% (17/1,438 stents) and 1.5% (22/1,432 stents), respectively. During 12 months of follow-up, ABI and Rutherford classification were significantly improved (p=0.001); the mean ABI improved from 0.6 ±0.3 to 0.9±0.2, and the median Rutherford classification improved from 3 to 0.

The combined studies documented high rates of event free survival and primary patency with a low incidence of stent fractures and no paclitaxel related adverse events, and supported the safety and effectiveness of the Zilver PTX stent in patients with de novo or restenotic lesions of the above-the-knee femoropopliteal segment. The authors concluded that the Zilver PTX stent was effective in treating SFA lesions. Two-year outcomes from complimentary Zilver PTX studies continue to support sustained safety and effectiveness in patients with femoropopliteal artery disease, including the long-term superiority of the DES to PTA and to provisional BMS placement [24]. Five-year outcomes presented at the 2014 VIVA Congress showed a 5-year primary patency of 66.4%, a 48% reduction in reinterventions and a 41% reduction in restenosis compared to standard care (PTA or stenting data).

### 4.1. *Clinical Development Program*

Similar to the Zilver PTX stent system, an investigational paclitaxel-eluting, self-expanding nitinol stent purpose-built by Boston Scientific Corporation (BSC) for use in the femoropopliteal arteries has been developed.

The ELUVIA Stent System leverages many successful BSC programs with global commercial approval for safe and efficacious use in subjects and received CE Mark Certification in February 2016. The ELUVIA stent and stent delivery system (SDS) is leveraged from the Innova™ Stent System, the drug coating polymers are leveraged from the PROMUS Element/PROMUS Element Plus Stent System, while the active pharmaceutical ingredient (paclitaxel) is leveraged from the TAXUS Element/ION Stent System.

### 4.1.1. Innova Stent System

The Innova (bare metal) Stent System has CE Mark Certification for the treatment of peripheral vascular lesions. The delivery system is a triaxial design with an outer shaft to stabilize the stent delivery system, a middle shaft to protect and constrain the stent, and an inner shaft to provide a guidewire lumen. The delivery system is compatible with 0.035 in (0.89 mm) guidewires. The self-expanding stent is made of a nickel titanium alloy (nitinol).

The SuperNOVA clinical trial is currently investigating the Innova Stent System in the superficial femoral artery (SFA) and/or proximal popliteal artery (PPA) for worldwide regulatory approval. The SuperNOVA clinical investigation is in the long term follow-up phase and is expected to be complete in 2016. Analysis of the 12 month primary endpoint data, related to both safety and effectiveness of the Innova Self-Expanding Stent System, is complete.

The Innova Stent System demonstrated a good safety profile. Long-term (12 month) safety was evaluated using major adverse events (MAEs) defined as all causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularization through 12 months. The primary safety endpoint, MAE-free rate at 12 months, is 85.8% with a 95% lower confidence bound of 81.1%. The established performance goal (PG) was 59.6%. The composite rate of MAEs, including all causes of death through 1 month, target limb major amputation and TLR through 12 months, was 14.2% (38/268). MAEs occurred within acceptable and expected ranges and consisted of no deaths, 1 target limb major amputation (0.4%), and 38 TLRs (14.2%).

The co-primary effectiveness analysis (1) assessed vessel primary patency in stented segments treated with the core matrix of stents (20 to 150 mm). The 12 month primary patency rate in the core stent matrix is 69.5% with a 95% lower confidence bound of 63.0%. The established PG was 66%.

The co-primary effectiveness analysis (2) assessed vessel primary patency in stented segments treated with the entire stent matrix (20 to 200 mm). The 12 month primary patency rate in the entire stent matrix is 66.4% with a 95% lower confidence bound of 60.3%. The established PG for the entire matrix was 63%.

Patency rates were influenced by a number of factors including the lesion length, lesion location, degree of calcification, and challenging outflow conditions. Treatment with the Innova Stent System provided significant improvement in the symptoms and quality of life of the subjects enrolled in the SuperNOVA study. The therapy showed a good safety profile and remarkable clinical outcomes despite the challenging anatomical characteristics of the lesions.

### 4.1.2. PROMUS Element /PROMUS Element Plus

The ELUVIA stent system leverages the same drug coating polymers used in the PROMUS (XIENCE V) and PROMUS Element/PROMUS Element Plus coronary stent platforms; the primer polymer of poly (n-butyl methacrylate) (PBMA) and active layer matrix polymer poly

(vinylidene fluoride-co- hexafluoropropylene) (PVDF-HFP). These polymers have a robust profile with long-term safety and effectiveness for use in drug delivery with coronary stents as studied in the PLATINUM clinical trials [25].

Promus Element received CE Mark certification in October 2009 and PMA approval in November 2011 for coronary use. PMDA approval for work horse (WH) stents was received in February 2012 followed by approval for Promus Element Plus stents (2.25-3.5 mm) including long lesion (LL) size in September 2012.

### 4.1.3. TAXUS Element/ION

BSC's TAXUS I, TAXUS II and III trials provided proof of concept that paclitaxel-eluting stents reduces clinical, angiographic and IVUS indices of restenosis with a comparable safety profile to bare-metal stents. The results of the TAXUS IV, V & VI clinical trials led to the worldwide approval of the TAXUS$^2$ Express Stent System, followed by, the ATLAS trial for the TAXUS Liberté and the PERSEUS trial for TAXUS Element/ION stents. This series of clinical trial data has demonstrated long-term clinical safety and effectiveness of paclitaxel-eluting stent technology.

In support of these findings, the TAXUS registries (for example, WISDOM, MILESTONE II, and OLYMPIA) sponsored by Boston Scientific provide real-world data on paclitaxel-eluting stents for treatment of coronary lesions in over 34,000 patients worldwide.

TAXUS Express obtained CE Certification in January 2003 and US PMA Approval in March 2004. TAXUS Liberté was CE Certified in September 2005 and US PMA approved in October 2008. TAXUS Element/ION received CE certification in Nov 2008 and FDA approval in April 2011.

### 4.1.4. MAJESTIC First Human Use Trial

It was expected that paclitaxel would provide similar long-term safety and effectiveness outcomes when evaluated in SFA/PPA atherosclerotic lesions. The MAJESTIC clinical trial was the first BSC clinical study to evaluate a paclitaxel-eluting stent on a nitinol platform for use in SFA and/or PPA atherosclerotic lesions from 30 mm to 110 mm in length.

MAJESTIC is a prospective, single arm, multicenter clinical trial. A total of 57 patients were enrolled at 14 centers in Europe, Australia, and New Zealand. Eligibility for the study included chronic lower limb ischemia defined as Rutherford categories 2, 3, or 4, and *de novo* or restenotic lesions (≥70% stenosis) located in the native superficial femoral artery or proximal popliteal artery with reference vessel diameter 4-6 mm and total lesion length ≥ 30 mm and ≤ 110 mm. The primary effectiveness endpoint is core laboratory-adjudicated 9-month primary patency (ie, duplex ultrasound PSVR ≤ 2.5 and absence of TLR or bypass). Safety assessments include major adverse events defined as Clinical Events Committee (CEC)-adjudicated all-cause death through 1 month, target limb major amputation through 9 months, and TLR through 9 months.

Enrollment was completed in March 2014. Mean age (±SD) of the patients was 69.3±9.3 years and 83% were male; 35% had diabetes and 88% had a history of smoking. Rutherford category was 2 for 35%, 3 for 61%, and 4 for 4% of enrolled patients. Mean baseline lesion length was 70.8±28.1 mm and percent stenosis of the target lesions was 86.3%±16.2%. As recently presented at the 2015 Charing Cross Congress, the primary effectiveness endpoint of primary patency at nine months was 94.4%, with a one-sided lower 95% confidence bound of 86.3% that exceeded the performance goal of 75%. The nine-month composite MAE rate was 3.6%. The 3.6% MAE rate consisted of two TLR events through 9 months, with no all-cause death through 1 month, and no target limb major amputation through 9 months. At 12 months, primary patency was 96.1% and the MAE rate was 3.8%; both MAEs were TLRs. No stent fractures were identified.

In conclusion, the MAJESTIC study of the ELUVIA Drug-Eluting Stent in the femoropopliteal arteries met its primary effectiveness endpoint with a 9-month primary patency rate of 94.4%, accompanied by a low MAE rate (3.6%). The MAJESTIC results showed that patients whose femoropopliteal arteries were treated with the Eluvia stent sustained a high patency and low MAE rate through 12 months.

The trial is currently in long term follow up and is expected to be complete in 2017.

#### 4.1.5. **Summary**

There is a large set of clinical data available for devices from which components have been leveraged for the ELUVIA Stent System. Successful results have been seen to date demonstrating safety and effectiveness for a variety of indications in coronary and peripheral artery stenosis. The first results of the ELUVIA Stent System (MAJESTIC study) demonstrate a favorable effectiveness and safety profile.

Overall, the ELUVIA stent based on the Innova stent platform with additional paclitaxel coating is expected to reduce restenosis and improve long-term vascular patency and quality of life (QOL) compared to balloon angioplasty, balloon expandable stents, and nitinol BMS.

# 5. Device Description

## 5.1. *ELUVIA Drug-Eluting Stent System (Investigational Device)*

The Innova self-expanding nitinol stent platform has been CE Mark approved and is the stent platform used for ELUVIA. The same drug-eluting product (paclitaxel) has been widely used in coronary stents including the TAXUS Express and TAXUS Liberté programs (displayed below). The ELUVIA stent system will use the same proven polymers as in the established PROMUS and PROMUS Element coronary stents. The stent delivery system (SDS) is the same used for delivery of the Innova SFA/PPA stent. **Table 5-1** provides an overview of the stent system components.

CE Mark Certification for the ELUVIA stent system was obtained in February 2016.

**Table 5-1: ELUVIA Stent System Product Description**

| Characteristic | ELUVIA Stent System |
|---|---|
| Stent material | Nitinol |
| Drug product | Paclitaxel |
| Nominal Paclitaxel Content Range (based on stent length and diameter) | 0.167µg/mm$^2$ |
| Polymer(s) | Primer Layer: poly(n-butyl methacrylate) (PBMA)<br>Active Layer: poly (vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) |
| Delivery working length | 75 cm, 130 cm |
| Stent delivery system (SDS) | 6 F tri-axial system |
| Catheter shaft outer diameter | 0.080 +/- 0.002" |
| Stent strut thickness | 0.0039"strut width, 0.0086" strut wall thickness |

## 5.2. *Investigational Device Component Description*

The ELUVIA stent system is comprised of: the implantable endoprosthesis and the stent delivery system (SDS). The stent is a laser cut self-expanding stent composed of a nickel titantium alloy (nitinol). On both the proximal and distal ends of the stent, radiopaque markers made of tantalum increase visibility of the stent to aid in placement. The stent is constrained within a 6 F delivery system. The delivery system is a triaxial design with an outer shaft to stabilize the stent delivery system, a middle shaft to protect and constrain the stent, and an inner shaft to provide a guidewire lumen. The delivery system is compatible with 0.035 in (0.89 mm) guidewires.

The ELUVIA stent is available in a variety of diameters and lengths. The delivery system is offered in two working lengths (75 cm and 130 cm). The ELUVIA stent matrix included in the IMPERIAL Trial is summarized in the below table.

**Table 5-2: Investigational Device Sizes**

| SDS size | ELUVIA Stent sizes (mm) |
|---|---|
| 75 cm | 6.0 x 40, 6.0 x 60, 6.0 x 80, 6.0 x 100, 6.0 x 120, 6.0 x 150 |
| 130 cm | 6.0 x 40, 6.0 x 60, 6.0 x 80, 6.0 x 100, 6.0 x 120, 6.0 x 150 |
| 75 cm | 7.0 x 40, 7.0 x 60, 7.0 x 80, 7.0 x 100, 7.0 x 120, 7.0 x 150 |
| 130 cm | 7.0 x 40, 7.0 x 60, 7.0 x 80, 7.0 x 100, 7.0 x 120, 7.0 x 150 |

### 5.2.1. Drug Component Description

The stent component of the ELUVIA stent system is a stent with a drug/polymer coating formulation consisting of paclitaxel (the active ingredient), and PVDF-HFP Polymer Carrier (the inactive ingredient).

#### 5.2.1.1. Paclitaxel Drug

The active pharmaceutical ingredient is semi-synthetic paclitaxel. Semi-synthetic paclitaxel is synthesized from precursor compounds isolated from a spectrum of Taxus species and hybrids. The chemical name is: Benzenepropanoic acid, β -(benzoylamino) - α - hydroxy - ,6,12b – bis (acetyloxy) - 12- (benzoyloxy)- 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11- dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11 methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester,[2aR-[2aα,4β,4aβ,6β,9α (αR*,βS*), 11α,12α,12aα,12bα]], and its chemical structure is shown in **Figure 5.2-1.**

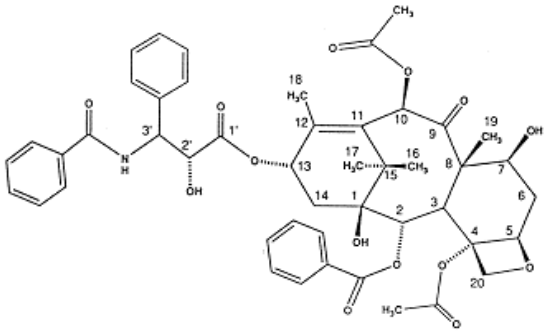

**Figure 5.2-1: The Chemical Structure of Paclitaxel**

#### 5.2.1.2. Primer Polymer and Drug Matrix Copolymer Carrier

The ELUVIA stent contains a primer polymer layer PBMA - poly (n-butylmethacrylate) between the bare metal stent and drug matrix layer. The chemical structure of PBMA is provided below in **Figure 5.2-2**.

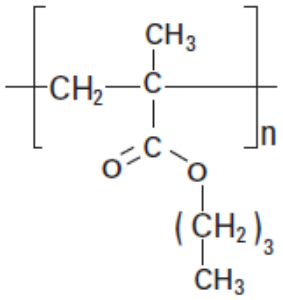

**Figure 5.2-2: The Chemical Structure of PBMA**

The drug matrix layer is comprised of a semi-crystalline random copolymer, PVDF – HFP - poly(vinylidene fluoride-co-hexafluoropropylene), blended with paclitaxel. The chemical structure of PVDF-HFP is provided below in **Figure 5.2-3**.

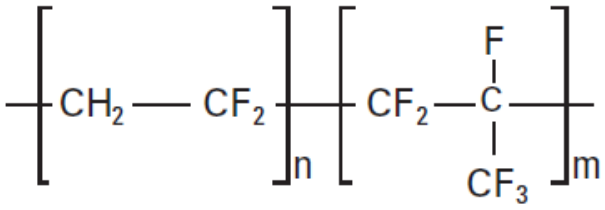


**Figure 5.2-3: The Chemical Structure of PVDF-HFP**

## 5.3. *Zilver PTX Drug-Eluting Peripheral Stent (Control)*

The control stent that will be used in the IMPERIAL RCT is the FDA approved/CE marked/PMDA approved and commercially available Zilver PTX Drug-Eluting Stent System (Zilver PTX). Please refer to the Instructions for Use (IFU) for detailed product description. The Zilver PTX Stent System is a nitinol self-expanding stent coated with the drug paclitaxel.

The matrix of stent sizes available for the Zilver PTX control devices for use in this trial is similar to that supplied for the ELUVIA test devices with the exception of the 150 mm stent lengths which are only available in the ELUVIA test matrix. However, multiple stent placements are allowed for treatment of lesions up to 140 mm in length. Please refer to the Zilver PTX IFU for product information and recommendations.

**Table 5-3: Investigational and Control Product Comparison**

| **Characteristic** | **ELUVIA Stent System** | **Zilver PTX Stent System*** |
|---|---|---|
| Stent material | Nitinol | Nitinol |
| Drug product | Paclitaxel | Paclitaxel |
| Nominal Paclitaxel Content Range (based on stent length and diameter) | 0.167µg/mm$^2$ | 3µg/mm$^2$ |
| Polymer(s) | Primer Layer: poly(n-butyl methacrylate) (PBMA)<br>Active Layer: poly (vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) | No carrier |
| Delivery working length | 75 cm, 130 cm | 80 cm, 125 cm |
| Stent delivery system (SDS) | 6 F tri-axial system | 6 Fr coaxial system<br>6 Fr tri-axial system |
| Catheter shaft outer diameter (OD) | 0.080 +/- 0.002 inches | Coaxial ≤ 0.083 inches<br>Triaxial OD unknown |

| | | |
|---|---|---|
| Stent strut thickness | 0.0039 inches strut width, 0.0086 inches strut wall | 0.00466 inches strut width** 0.00753 inches strut wall** |

*Zilver PTX Summary of Safety and Effectiveness (www.fda.gov)
** Zilver PTX Stent Testing, Boston Scientific internal document 90823327

### 5.4. *Device Labeling of Investigational Device*

A copy of the Directions for Use (DFU) for the ELUVIA Stent System will be included in the Manual of Operations. The study device is labeled on the back and side of the outer carton, and on the inside sterile pouch. Packaging will include peelable, self-adhesive labels for each unit shipped. The labeling will include the following information.

- Product Name
- Universal Part Number (UPN)
- Serial number
- Lot number
- Stent dimensions (stent diameter and stent length in mm) , and Stent delivery system size (in cm)
- Expiration (use by) date

The following statements appear on the ELUVIA product labeling for clinical distribution.
**Caution: Investigational Device. Limited by Federal Law (USA) to Investigational Use.**

Specifically, the following statement appears on the product labeling in relevant local languages: **Exclusively for Clinical Investigations.**

Device labeling will be provided in local language(s) per national regulations. In Japan, identification code, local contact information, and storage condition also appear on the product labeling.

## 6. Objectives

The objective of the IMPERIAL Randomized Controlled Trial (RCT) is to evaluate the safety and effectiveness of the Boston Scientific (BSC) ELUVIA drug eluting stent for treating Superficial Femoral (SFA) and/or Proximal Popliteal Artery (PPA) lesions up to 140 mm in length.

## 7. Endpoints

The primary endpoints and additional assessments will be evaluated on an intent-to-treat analysis and a per-treatment analysis. If a subject is randomized/enrolled but the stent is not

implanted, the subject will be followed through the 1 month follow-up visit only. Data to assess 1 month MAE rate will be collected for these subjects; other testing is not required.

## 7.1. *Primary Endpoints*

Primary Safety Endpoint

The primary safety endpoint assesses the occurrence of Major Adverse Events (MAEs) defined as all causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularization (TLR) through 12 months. This safety endpoint is designed to demonstrate that the 12-month MAE-free rate for the ELUVIA treatment group is non-inferior to the Zilver PTX control group.

Primary Effectiveness Endpoint

The primary effectiveness endpoint assesses primary patency at 12 months post-procedure. This effectiveness endpoint is designed to demonstrate that the 12-month primary patency for the ELUVIA treatment group is non-inferior to the Zilver PTX control group.

Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month follow-up visit, in the absence of clinically-driven TLR or bypass of the target lesion.

Notes:

- Vessel patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment.
- A PSVR > 2.4 suggests >50% stenosis [26].
- The stented segment will be assessed for patency as a single segment regardless of the number of tandem lesions within the stented segment.
- All DUS will be assessed by an independent core laboratory.
- Clinically-driven: A reintervention within 5 mm proximal or distal to the original treatment segment for ≥50% angiographic diameter stenosis in the presence of recurrent symptoms (≥ 1 change in Rutherford class) or associated with decreased ABI/TBI of ≥20% or ≥ 0.15 in the treated segment. Tibial brachial index (TBI) allowed in cases of incompressible vessels.

## 7.2. *Additional Endpoints*

Additional endpoints that will be evaluated, but are not necessarily powered to make statistically based conclusions are as follows:

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

- Procedural success defined as technical success with no MAEs noted within 24 hours of the index procedure
- MAE rate at 1 month post-index procedure defined as all causes of death, target limb major amputation and/or TLR
- Primary Patency and Assisted Primary Patency at 6 months, 12 months, 24 months and 60 months using different PSVRs
- Clinically-driven TLR and Target Vessel Revascularization (TVR) Rate at each time point
- Adverse Event Rates (unanticipated, major, serious, device/procedure-related) at each time point
- Non-serious non-device/procedure-related Adverse Event Rates at each time point through 12 months
- Stent Fracture Rate at 12 months, 24 months and 60 months utilizing VIVA definitions [27]
- Distribution of Rutherford Classification during follow-up as compared to baseline at 1 month, 6 months, 12 months, 24 months and 60 months
- Rate of Primary and Secondary Sustained Clinical Improvement as assessed by changes in Rutherford Classification from baseline at 1 month, 6 months, 12 months, 24 months and 60 months
- Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1 month, 6 months, 12 months, 24 months and 60 months
- Walking Improvement at12 months assessed by change in Six Minute Hall Walk (6MHW) from baseline
- Walking Improvement and Patient Utility Values assessed at 1 month, 6 months, 12 months, 24 months and 60 months assessed by change in Walking Impairment Questionnaire and EQ-5D from baseline
- Changes in healthcare utilization over time
- PK parameters calculated for subjects in the PK substudy

# 8. Design

The IMPERIAL Trial consists of a prospective, multicenter, 2:1 randomized (ELUVIA vs Zilver PTX), controlled, single-blind, non-inferiority trial (RCT) and a concurrent, non-blinded, non-randomized, single-arm, pharmacokinetic (PK) substudy.

A subject can be enrolled in the RCT or the PK substudy. A subject cannot be enrolled in both of these studies.

## 8.1. *Scale and Duration*

Approximately 477 - 485 subjects will be enrolled in the IMPERIAL trial.

- 465 subjects to receive treatment with either an investigational test device (ELUVIA, N=310 subjects) or a control device (Zilver PTX, N=155 subjects) in the RCT
- 12-20 subjects to receive treatment with the investigational test device (ELUVIA) in the PK substudy

The RCT will be conducted in up to 75 sites worldwide in the United States (US), Europe, Japan, New Zealand and Canada with a minimum of 465 subjects planned for randomization. All subjects will be screened according to the protocol inclusion and exclusion criteria. Subjects meeting all inclusion criteria and no exclusion criteria will be randomized in a 2:1 allocation to either ELUVIA or Zilver PTX, respectively.

- N = 465 subjects randomized at enrollment (310 ELUVIA, 155 Zilver PTX)
- Minimum of 393 evaluable subjects required at 12 months (262 ELUVIA, 131 Zilver PTX)

Clinical follow-up will be required at the following time points: pre-discharge, 1 month, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months post index procedure.

In addition, 12-20 subjects (United States only) will be enrolled in the PK substudy and will have baseline venous blood drawn followed by blood draws at 10 minutes, 30 minutes, 1, 2, 3, 4, 6, 12, 24 and either 48 or 72 hours after placement of the ELUVIA study stent to evaluate plasma paclitaxel levels through a pharmacokinetic (PK) sub-study.

The enrollment period is expected to last approximately 12 months. Fifty percent of enrollment is anticipated in the United States. No investigative site will be allowed to enroll more than 20 percent of the total study population. The trial will be considered complete (with regard to the primary endpoint) after all randomized/enrolled subjects have completed the 12 month follow-up visit, were discontinued prior to the 12 month follow-up visit, have died, or the last 12 month follow-up visit window is closed.

The study will be considered complete (with regard to all follow-up) after all randomized subjects have completed the 60 month (5 year) follow-up visit, were discontinued prior to the 60 month (5 year) follow-up visit, have died, or the last 60 month (5 year) follow-up visit window is closed.

It is estimated that it will take approximately 7 years to complete this study.

**Figure 8.1-1** and **Figure 8.1-2** show the schematic of the RCT and PK substudy design, respectively.

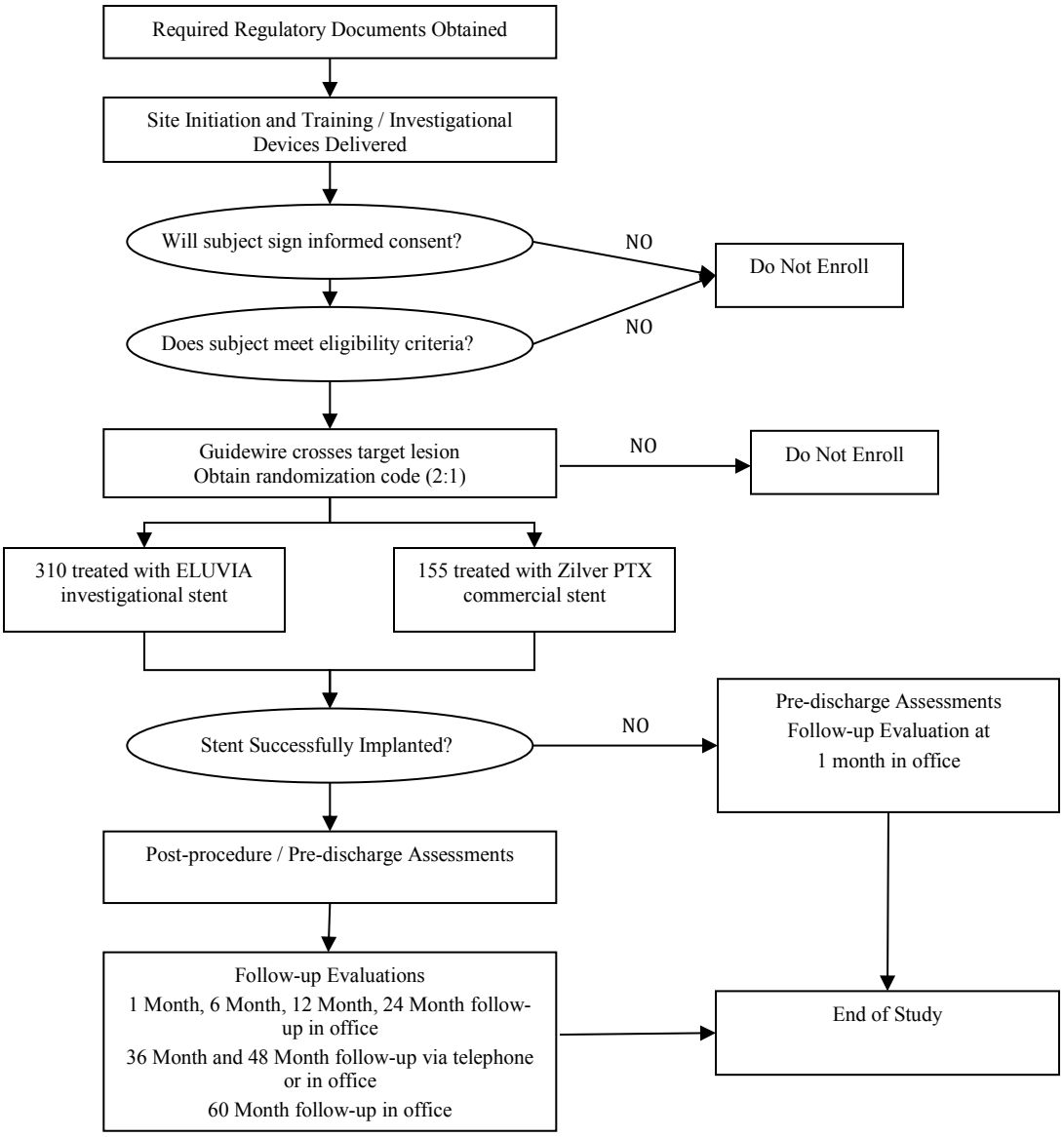


**Figure 8.1-1: IMPERIAL RCT Design**

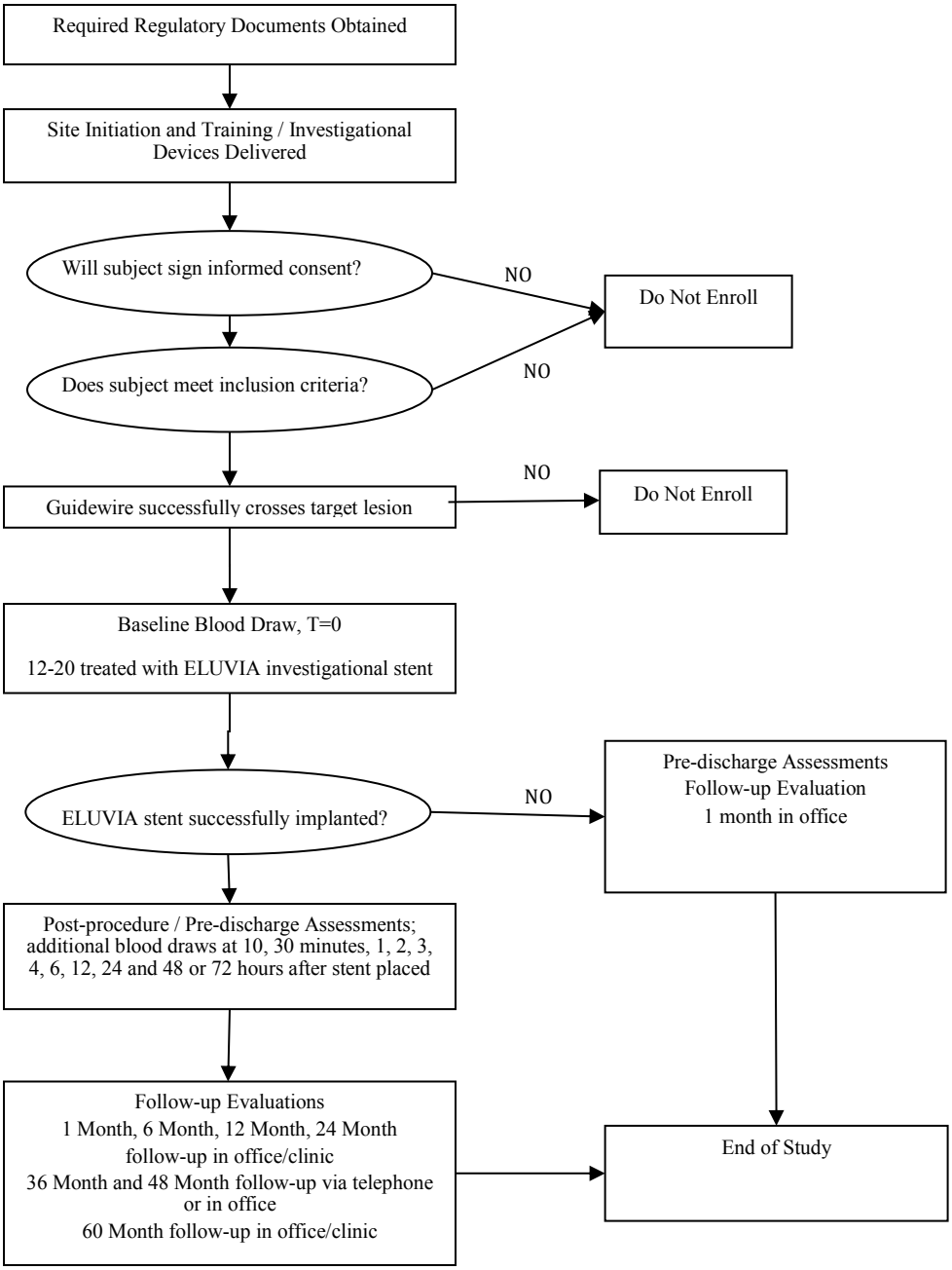


**Figure 8.1-2: IMPERIAL PK Substudy Design**

## 8.2. *Treatment Assignment*

Once the subject has signed the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB)-approved study informed consent form (ICF), and has met all clinical inclusion and no clinical exclusion criteria, the subject will be considered eligible to be enrolled in the RCT or PK substudy.

If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be randomized or receive an investigational device, nor should the subject be followed post-procedure per protocol.

For the RCT, if the subject is found to meet the eligibility criteria during the angiographic phase of the procedure, the subject will be considered eligible to be randomized (2:1 allocation treatment versus control). Randomization will be stratified by site. After the guidewire successfully crosses the target lesion, a randomization custom function within the Rave EDC database will be used to assign subjects to the test or control treatment group. Subjects will be considered enrolled after they have been successfully randomized (i.e. when a treatment assignment is received by the study center).

In the PK substudy, subjects will not be randomized; all subjects will be treated with the ELUVIA stent. Subjects will be considered enrolled when the ELUVIA stent is introduced into the subject's vasculature.

IMPERIAL RCT is a single blind trial. Subjects will be blinded to treatment assigned and treatment received. All subjects must remain blinded until completion of all 12-month follow-up visits (primary endpoint). Packaging of the investigational control and test devices are different, therefore the Investigator performing the procedure will not be blinded to the assigned treatment arm or resulting treatment. Study center personnel will be trained not to disclose the treatment assignment to the subject to minimize the potential unblinding of the subject. Site personnel conducting clinical follow-up assessments will be blinded to a subject's treatment assignment whenever possible, except when clinical follow-up visits are performed by the implanting Investigator. Duplex Ultrasound (DUS) Core Laboratory personnel, Angiography Core Laboratory personnel and the Clinical Events Committee (CEC) will be blinded to a subject's treatment assignment during the trial. Those involved in data analysis for the Sponsor will remain blinded until the primary endpoint analysis.

Instructions regarding the unblinding of a subject for a medical emergency can be found in the Manual of Operations.

## 8.3. *Multiple Interventions Using Same Access Site During Index Procedure*

### 8.3.1. 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 randomization/enrollment of the target SFA/PPA lesion,
- Treatment of the iliac lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation).
- If the above criteria are not met, the subject may not be randomized into the RCT or PK substudy but may be rescreened for eligibility after 30 days.

### 8.3.2. Target Limb

**Iliac Lesion**

Using the same access site, additional non-target iliac lesions in the target limb may be treated during the index procedure under the following conditions:

- Treatment with a non-drug-eluting commercially available device occurs prior to randomization/enrollment of the target SFA/PPA lesion, and
- Treatment of the iliac lesion is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation).
- If the above criteria are not met, the subject may not be randomized into the RCT or PK substudy but may be rescreened for eligibility after 30 days.

**Target Lesion**

The target lesion is a lesion selected by the Investigator for treatment with either the investigational device or control device. The target lesion must meet all angiographic selection criteria. The target lesion may include two or more tandem lesions, provided that the entire segment of tandem lesions is ≤ 140 mm and can be covered with only one ELUVIA stent or up to two Zilver PTX stents according to each device's DFU/IFU. For occlusive lesions requiring the use of a re-entry device, the target lesion length must be ≤ 120 mm allowing the target lesion and re-entry area to be covered with one ELUVIA stent or up to two Zilver PTX stents (Refer to Inclusion criterion 4c and 4d).

NOTE: If a second or third stent is required due to complications (e.g., dissection, misplacement or under-sizing of the target lesion), the additional stent placed should be a study stent of the same type used to treat the target lesion.

### 8.4. *Justification for the Study Design*

The IMPERIAL RCT will evaluate the safety and effectiveness of the ELUVIA stent for the treatment of atherosclerotic lesion(s) in native SFA and/or PPA vessels compared with the Zilver PTX stent. The Zilver PTX stent was chosen as the control device because it is the only commercially available self-expanding nitinol drug-eluting stent approved for treatment of SFA and/or PPA lesions. As reported in **Table 5-3**, the test and control stent platforms have many similarities and deliver the same drug, paclitaxel. Safety and performance has been demonstrated for the ZILVER PTX stent which is CE Marked, has received FDA and PMDA approval and is commercially available in the regions included in this RCT. The study design is consistent with the Draft FDA Guidance for Industry: "Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies," March 2008 as there is no published draft guidance for peripheral drug-eluting stents. Similar to coronary DES studies, a PK sub-study will further evaluate the safety and pharmacokinetics of the ELUVIA stent for the treatment of atherosclerotic lesion(s) up to 140 mm in length in the SFA/PPA.

During the trial, dual anti-platelet therapy (DAPT) is required for at least 60 days post index procedure, with antiplatelet monotherapy required through the 12 month (1 year) follow-up and recommended through the 60 month (5 year) follow-up (trial completion). Ongoing dynamic data safety monitoring will be performed throughout the trial to minimize subject risk. All enrolled subjects receiving the study stent will be followed for 5 years post index procedure.

## 9. Subject Selection

### 9.1. *Study Population and Eligibility*

Clinical and angiographic inclusion and exclusion criteria are included in **Table 9-1** and **Table 9-2**, respectively. Prior to randomization/enrollment, a subject must meet all of the clinical and angiographic inclusion criteria and none of the clinical and angiographic exclusion criteria.

### 9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see **Table 9-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

**Table 9-1: Inclusion Criteria**

| | |
|---|---|
| **Inclusion Criteria** | 1. Subjects age 18 and older.<br>2. Subject (or Legal Guardian if applicable) 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. NOTE: For subjects less than 20 years of age enrolled at a Japanese center, the subject's legal representative, as well as the subject, must provide written informed consent.<br>3. Chronic, symptomatic lower limb ischemia defined as Rutherford categories 2, 3 or 4.<br>4. Stenotic, restenotic or occlusive lesion(s) located in the native SFA and/or PPA:<br>a. Degree of stenosis ≥70% by visual angiographic assessment<br>b. Vessel diameter ≥ 4 and ≤ 6 mm<br>c. Total lesion length (or series of lesions) ≥ 30 mm and ≤ 140 mm (Note: Lesion segment(s) must be fully covered with one ELUVIA stent or up to two Zilver PTX stents)<br>d. For occlusive lesions requiring use of re-entry device, lesion length ≤ 120 mm<br>e. Target lesion located at least three centimeters above the inferior edge of the femur<br>5. Patent infrapopliteal and popliteal artery, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot with no planned intervention. |

## 9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Table 9-2**) will be excluded from this clinical investigation.

**Table 9-2: Exclusion Criteria**

| | |
|---|---|
| **Exclusion Criteria** | 1. Previously stented target lesion/vessel.<br>2. Target lesion/vessel previously treated with drug-coated balloon < 12 months prior to randomization/enrollment.<br>3. Subjects who have undergone prior surgery of the SFA/PPA in the target limb to treat atherosclerotic disease.<br>4. Use of atherectomy, laser or other debulking devices in the target limb SFA/PPA during the index procedure.<br>5. History of major amputation in the target limb.<br>6. Documented life expectancy less than 24 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the clinical study, limit the subject's compliance with the follow-up requirements, or impact the scientific integrity of the clinical study.<br>7. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated.<br>8. Known hypersensitivity/allergy to the investigational stent system or protocol related therapies (e.g., nitinol, paclitaxel, or structurally related compounds, polymer or individual components, and antiplatelet, anticoagulant, thrombolytic medications).<br>9. Platelet count < 80,000 $mm^3$ or > 600,000 $mm^3$ or history of bleeding diathesis.<br>10. Concomitant renal failure with a serum creatinine > 2.0 mg/dL.<br>11. Receiving dialysis or immunosuppressant therapy.<br>12. History of myocardial infarction (MI) or stroke/cerebrovascular accident (CVA) within 6 months prior to randomization/enrollment.<br>13. Unstable angina pectoris at the time of randomization/enrollment.<br>14. Pregnant, breast feeding, or plan to become pregnant in the next 5 years.<br>15. Current participation in another investigational drug or device clinical study that has not completed the primary endpoint at the time of randomization/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>16. Septicemia at the time of randomization/enrollment.<br>17. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of |

| | |
|---|---|
| | randomization/enrollment.<br>18. Presence of aneurysm in the target vessel.<br>19. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to randomization/enrollment.<br>20. Perforated vessel as evidenced by extravasation of contrast media prior to randomization/enrollment.<br>21. Heavily calcified lesions. |

# 10. Subject Accountability

## 10.1. *Point of Enrollment*

Once the subject has signed the IRB/IEC/REB-approved study ICF, and has met all clinical inclusion and no clinical exclusion criteria, the subject will be considered eligible to be enrolled in the trial. If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be enrolled/randomized or receive an investigational device, nor should the subject be followed post-procedure per protocol.

If the subject is found to meet the eligibility criteria during the angiographic phase of the procedure, the subject will be considered eligible to be randomized/enrolled. After the Investigator successfully crosses the target lesion with the guidewire, a randomization custom function within the Rave EDC database will be used to assign RCT subjects to the test or control treatment group. Subjects will be considered enrolled in the RCT after they have been successfully randomized (i.e. when a treatment assignment is received by the study site).

For subjects enrolled in the PK substudy, the point of enrollment occurs when the ELUVIA stent is introduced into the subject's vasculature.

## 10.2. *Withdrawal*

All subjects randomized 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 (the justified sample size considers an estimated allowance for attrition). The reason for withdrawal will be recorded (if given) in all cases of withdrawal. 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.

### 10.3. *Enrollment Controls*

The IMPERIAL trial will implement a formal *Enrollment Communication Plan*. The plan will outline the specific activities and responsibilities of BSC employees and representatives, and nature and timing of communications to Investigators during the enrollment period and as enrollment draws to a close.

The objective of the plan is to minimize the risk of enrollment beyond the protocol-specified overall enrollment cap, including regional and site-specific caps.

## 11. Study Methods

### 11.1. *Data Collection*

The data collection schedule for the IMPERIAL trial is summarized in **Table 11-1**.

**Table 11-1: Data Collection Schedule**

| Procedure/Assessment | Pre-procedure[2] | During Index Procedure | Pre-Discharge | 1-month (30±7 days) | 6-month (182±30 days) | 12-month (365±30 days) | 24-month (730±30 days) | 36-month[5] (1095±30 days) | 48-month[5] (1460 ± 30 days) | 60-month (1825 ± 30 days) |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent[1] | X | | | | | | | | | |
| Confirm Inclusion/Exclusion | X | X | | | | | | | | |
| Demographics and Medical History, Height and Weight | X | | | | | | | | | |
| Serum Creatinine | X | | | | | | | | | |
| Pregnancy Test[2] | X | | | | | | | | | |
| Complete Blood Count (CBC) and platelet count | X | | | | | | | | | |
| ABI Measurements | X | | | X[3] | X | X | X | | | X |
| Rutherford Categorization | X | | | X | X | X | X | | | X |
| Walking Impairment Questionnaire (WIQ) | X | | | X | X | X | X | | | X |
| EQ-5D Questionnaire | X | | | X | X | X | X | | | X |
| 6 Minute Hall Walk (6MHW) | X | | | | | X | | | | |
| Angiogram[4] | | X | | | | | | | | |
| Randomization | | X | | | | | | | | |
| Venous blood draw for subjects in PK sub-study | | X[6] | X | | | | | | | |
| Medication Assessment | X | X | X | X | X | X | X | X | X | X |
| Adverse Events Assessment | | X | X | X | X | X | X[7] | X[7] | X[7] | X[7] |
| Duplex Ultrasound[4] | | | | | X | X | X | | | X |
| X-Ray[4] | | | | | | X | X | | | X |

[1] Subject's consent obtained and informed consent form signed prior to any study-specific tests or procedures
[2] Performed within 30 days of procedure, except urine or blood pregnancy test required for females of childbearing potential performed within 7 days of procedure
[3] ABI measurement may be collected immediately post-procedure through 1 Month Follow-up window (Day 0 – 37).
[4] Angiograms, Ultrasounds and X-rays will be sent to the respective core lab for analysis. Follow-up angiograms, ultrasounds and x-rays will not be required for any subject who underwent bypass surgery of the target lesion during the 60-month follow-up timeframe, or has a documented occluded stent.
[5] The 36 month and 48 month visit may be conducted in the office or by telephone.
[6] Up to 24 hours prior to stent placement.
[7] Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

### 11.2. *Study Candidate Screening*

A Screening Log will be maintained by each investigational site to document selected information about subjects who fail to meet the IMPERIAL trial eligibility criteria, including the reason for screen failure.

### 11.3. *Informed Consent*

Before any study specific tests or procedures are performed, subjects who meet the clinical eligibility criteria will be asked to sign the IRB/IEC/REB-approved study ICF. Subjects must be given ample time to review the ICF and have questions answered before signing. For subjects less than 20 years of age at Japanese sites, the subject and the subject's legal representative must sign the study ICF.

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

Refer to section 10.1 for definition of point of enrollment.

### 11.4. *Pre-Procedure Assessments – Up to 30 Days*

The following pre-procedure data must be collected within 30 days prior to the index procedure (unless otherwise specified) for all subjects:

- Demographics and medical history obtained
- Physical assessment including:
    - Weight and height
    - Rutherford Category Assessment
    - Ankle-Brachial Indices (ABI) measurements
- Laboratory tests
    - Serum creatinine
    - Complete blood count (CBC) with platelets
- Confirmation that all clinical inclusion/exclusion eligibility criteria have been met
- 6-Minute Hall Walk
- Administer Questionnaire Assessments
    - Walking Impairment Questionnaire (WIQ)
    - EQ-5D

### 11.5. *Pre-Procedure Assessments – Up to 7 Days*

The following pre-procedure data must be collected within 7 days prior to the index procedure (unless otherwise specified) for all subjects:

- Pregnancy test for females of childbearing potential with analysis per local practice (serum and/or urine)
- Antiplatelet medication usage (if applicable)

### 11.6. *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 60 month (5 year) follow-up visit. 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 treating physician according to standard of care.

**Minimum antiplatelet medication requirements include:**

Antiplatelet medication usage will be collected and reported for compliance for the duration of the trial.

Minimum requirements include:

- Anti-coagulation and anti-platelet therapy administered during the procedure should be consistent with current clinical practice [28].
- Clopidogrel or ticlopidine starting at least 24 hours prior to the procedure or a peri-procedural loading dose (recommended loading dose of 300 mg clopidogrel or 200 mg ticlopidine) is given within 2 hours after the end of the procedure.
- Daily administration of aspirin (recommended dose of at least 75 mg) and clopidogrel (75 mg) or ticlopidine (200 mg) for the first 60 days post-index procedure.
- Antiplatelet monotherapy is required through the 12 month (1 year) follow-up and recommended through the 60 month (5 year) follow-up (trial completion).

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.

***Note:*** The same strategy for selection of antiplatelet therapy should be used for ELUVIA and Zilver PTX subjects (i.e., treatment assignment should not influence antiplatelet agent selection or duration of therapy). Refer to the assigned stent's DFU/IFU for antiplatelet information.

## 11.7. *Index Procedure*

Investigators will manage the cardiovascular risk factors and comorbidities for all patients 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.

### 11.7.1. **Non-Target Limb (Contralateral)**

Using the same access site, non-target 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 randomization/enrollment of the target SFA/PPA lesion,
- Treatment of the iliac lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation).
- If the above criteria are not met, the subject may not be randomized into the RCT or PK substudy but may be rescreened for eligibility after 30 days.

### 11.7.2. **Target Limb (Treatment of Non-Target Lesions)**

Using the same access site, additional non-target iliac lesions in the target limb may be treated during the index procedure under the following conditions:

- Treatment with a non-drug-eluting commercially available device occurs prior to randomization/enrollment of the target SFA/PPA lesion, and
- Treatment of the iliac lesion is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation).
- If the above criteria are not met, the subject may not be randomized into the RCT or PK substudy but may be rescreened for eligibility after 30 days.

### 11.7.3. **Randomization**

The start of the index procedure is defined as the time of guide catheter insertion into the sheath for the target limb SFA/PPA interventional procedure.

During catheterization, the following procedures and assessments must be completed for the Target Lesion.

- Perform angiography according to the Angiographic Core Laboratory procedure guidelines.
- Confirm angiographic eligibility criteria of the target lesion or tandem lesion(s).
- Cross target lesion using guidewire or re-entry device.
- After target lesion is crossed by the guidewire, access the randomization custom function in Rave EDC to randomize subject in the RCT or enroll subject in the PK substudy.
- If randomized to ELUVIA, retrieve an appropriately sized investigational stent to adequately cover the target lesion with one stent.
- If randomized to Zilver PTX, retrieve one or two appropriately sized control stent(s) from commercial inventory.
- For PK substudy subjects, obtain baseline blood draw prior to ELUVIA stent system advancement into the subject's vasculature.

Note: If difficulties are encountered when accessing the randomization custom function in the Rave EDC system that may put the subject at risk, the subject should not be enrolled in the trial. The subject should be treated per standard of care but must not receive an investigational study stent.

Note: Bypassing the randomization process and manually assigning treatment type is not allowed.

### 11.7.4. Target Lesion Stent Placement

Procedural information must be reported (specific data fields are noted in the electronic database). Refer to the DFU/IFU for detailed instructions about delivery system preparation and placement of the ELUVIA stent or the Zilver PTX stent.

Procedural recommendations:

- Use of a radiopaque ruler or other standard is recommended to help with calibration.
- Optimal target lesion/vessel preparation is recommended.
- Pre-dilation of the target lesion with optimally sized balloon(s) (nominal size of artery) is recommended before stent placement, but is at the discretion of the implanting Investigator. Record the following information on pre-dilation balloon(s) used:
    - Maximum balloon diameter (mm) inflated

- Maximum pressure (atmospheres) inflated
- Maximum length of time (seconds) inflated

- After stent placement, the Investigator should ensure that the stent is in full contact with the arterial wall. In order to achieve full contact, post-dilatation may be performed at the discretion of the Investigator. Record the following information on post-dilation balloon(s) used:
  - Maximum balloon diameter (mm) inflated
  - Maximum pressure (atmospheres) inflated
  - Maximum length of time (seconds) inflated

- Peri-stent dissections should be treated conservatively, with low pressure prolonged balloon inflation, or with additional study stent implantation per standard practice. Haziness, lucency, or filling defects within or adjacent to the stent, and angiographic complications such as distal thromboemboli or no reflow, should also be treated per standard practice. All angiographic complications that occur should be documented by angiography and submitted to the Angiographic Core Laboratory for analysis.

**ELUVIA**

The Directions For Use (DFU) for the ELUVIA Stent 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 ELUVIA DFU must be followed for implanting the investigational stent. Anticoagulant therapy should be consistent with guideline practices and the hospital standard of practice during the procedure.

**Zilver PTX**

As a reference, a sample Instructions for Use (IFU) for the Zilver PTX Stent System is provided in the Manual of Operations. Prior to use of the control device, the treating physician must carefully read and be familiar with the entire IFU packaged with the commercial stent. Anticoagulant therapy should be consistent with guideline practices and the hospital standard of practice during the procedure.

### 11.8. *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.

## 11.9. *End of the Index Procedure*

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

- Document procedural, target lesion, pre-dilatation, post-dilatation (if applicable), and study stent information on the appropriate eCRFs
- Record antithrombotic medications
- Complete AE assessment
- Finalize angiographic procedure film and related required documentation to submit to the Core Laboratory per instructions set in the Manual of Operations.

## 11.10. *Post-procedure/Pre-hospital Discharge*

The subject may be discharged from the hospital when clinically stable at the Investigator's discretion. The following assessments must be completed prior to hospital discharge.

- Venous blood draws for subjects enrolled in the PK substudy as described in Section 11.12.
- Medication assessment
- AE assessment

It is important that trial site personnel review the trial requirements with the subject to maximize compliance with the follow-up schedule and required medication regimen. It is also important that trial site personnel instruct subjects to return for follow-up assessments according to the trial event schedule in **Table 11-1**. Study staff should establish a date for the follow-up visit with the subject and if possible, schedule the visit at the time of hospital discharge.

***Note:*** Randomized subjects will be blinded to treatment assigned and treatment received. All subjects must remain blinded until completion of all 12-month follow-up visits (primary endpoint).

## 11.11. *Angiography*

All RCT and PK substudy subjects will undergo angiographic assessment during the index procedure per standard of care. Subjects requiring reintervention of the target vessel during the 60 month follow-up period will undergo angiographic assessment at the time of reintervention as standard of care.

Angiographic data and images collected during the index procedure and during any reinterventions of the target vessel during the 60 month follow-up period must be forwarded to the Angiographic Core Laboratory for analysis. Angiograms performed at outside institutions should also be sent to the Core Laboratory. Angiograms will be centrally assessed by the Angiographic Core Laboratory, for qualitative and quantitative analysis.

## 11.12. *Assessment of Whole Blood Paclitaxel Levels*

The PK profile of the ELUVIA stent will be analyzed for subjects enrolled in the PK substudy. A total of 11 venous blood samples will be attempted and drawn according to the schedule shown in **Table 11-2**.

SFA stenting is most often performed as an out-patient procedure and sampling time points greater than 12 hours post-procedure will require most subjects to return to the research site for blood draws beyond the 12 hours post-stenting.

To encourage all enrolled PK subjects to return to the research site for blood draws scheduled after release from the out-patient procedure, approximately 50% of subjects will return 48 hours after placement of the study stent and approximately 50% will return 72 hours after placement of the study stent.

A stipend will be provided to cover lodging or travel expenses incurred by subjects as a result of participation in the PK substudy in accordance with pertinent country laws and regulations and per the study site's regulations.

All samples must be forwarded to the PK core laboratory for analysis of whole blood paclitaxel levels.

Instructions for blood sample collection, storage, and shipment are provided in the PK core laboratory Instruction Manual.

**Table 11-2: Blood Draw Schedule for Analysis of Paclitaxel Pharmacokinetics**

| Day | | Blood Draw Schedule |
|---|---|---|
| Before stent placement | | Up to 24 hours prior to placement of study stent |
| After stent placement | Day 0 | 10 minutes (±5 minutes) after placement of study stent |
| | | 30 minutes (±10 minutes) after placement of study stent |
| | | 1 hour (±10 minutes) after placement of study stent |
| | | 2 hours (±10 minutes) after placement of study stent |
| | | 3 hours (±15 minutes) after placement of study stent |
| | | 4 hours (±15 minutes) after placement of study stent |
| | | 6 hours (±30 minutes) after placement of study stent |
| | | 12 hours (±60 minutes) after placement of study stent |
| | Day 1 | 24 hours (±4 hours) after placement of study stent |
| | Day 2-3 | 48 hours (±8 hours) after placement of study stent<br>or<br>72 hours (±8 hours) after placement of study stent |

## 11.13. *Follow-up*

IMPERIAL RCT is a single blind trial. Site personnel conducting clinical follow-up will be blinded to a subject's treatment assignment whenever possible.

All randomized/enrolled subjects who receive a test or control stent, ELUVIA or Zilver PTX will be evaluated prior to discharge from the index procedure and at 1 month, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months after the index procedure.

Subjects who underwent advancement of the ELUVIA or Zilver PTX stent system into the body but a stent was not implanted will be considered enrolled and will be followed for safety through the 1-month follow-up visit only. Data for assessment of MAE will be collected for these subjects; other testing is not required.

For each follow-up visit, the results of the subjects' clinical status and functional testing (Rutherford Categorization and ABI) should be completed prior to initiating the DUS imaging, if required. Subjects requiring reintervention should be treated according to the Investigator's discretion and standard of care. These subjects should receive an approved, commercially available treatment (if appropriate) and must not receive an investigational device for retreatment.

Note: Follow-up angiograms, ultrasounds and x-rays will not be required for any subject who underwent bypass surgery of the target lesion during the 60 month follow-up timeframe, or has a documented occluded stent.

Requirements of each follow-up evaluation are described below.

### 11.13.1. **1-Month Follow-up Visit (30 days ± 7 days)**

All enrolled subjects must be evaluated 1 month after the index procedure. The following assessments must be performed during the 1 Month office visit. For enrolled subjects who did not have a stent implanted, the AE assessment is required; no other tests are required. Site personnel conducting clinical follow-up will be blinded to a subject's treatment assignment whenever possible.

- Rutherford Categorization
- ABI Measurements *(may be collected immediately post-procedure through 1 Month Follow-up window [Day 0 – 37])*
- Walking Impairment Questionnaire
- EQ-5D Questionnaire
- Adverse Events Assessment
- Medication Assessment

### 11.13.2. **6-Month Follow-up Visit (182 days ± 30 days)**

All enrolled subjects must be evaluated 6 months after the index procedure. The following assessments must be performed during the 6 Month office visit. Site personnel conducting clinical follow-up will be blinded to a subject's treatment assignment whenever possible.

- Rutherford Categorization
- ABI Measurements
- Walking Impairment Questionnaire

- EQ-5D Questionnaire
- Adverse Events Assessment
- Medication Assessment
- DUS of stented segment performed according to the DUS Core Laboratory procedure guidelines

### 11.13.3. **12-Month Follow-up Visit (365 days ± 30 days)**

All enrolled subjects must be evaluated 12 months after the index procedure. The following assessments must be performed during the 12 Month office visit. Site personnel conducting clinical follow-up will be blinded to a subject's treatment assignment whenever possible.

- Rutherford Categorization
- ABI Measurements
- 6-Minute Hall Walk
- Walking Impairment Questionnaire
- EQ-5D Questionnaire
- Adverse Events Assessment
- Medication Assessment
- DUS of stented segment performed according to the DUS Core Laboratory procedure guidelines
- X-ray of the stented segment performed according to the X-ray Core Laboratory procedure guidelines

Subjects and site personnel conducting clinical follow-up may be unblinded after completion of this visit, following confirmation from the Sponsor (after completion of all 12-month follow-up visits).

### 11.13.4. **24-Month Follow-up Visit (730 days ± 30 days)**

All enrolled subjects must be evaluated 24 months after the index procedure. The following assessments must be performed during the 24 Month office visit.

- Rutherford Categorization
- ABI Measurements
- Walking Impairment Questionnaire
- EQ-5D Questionnaire
- Adverse Events Assessment (SAEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment
- DUS of stented segment performed according to the DUS Core Laboratory procedure guidelines
- X-ray of the stented segment performed according to the X-ray Core Laboratory procedure guidelines

### 11.13.5. 36-Month Follow-up Visit (1095 days ± 30 days)

All enrolled subjects must be evaluated 36 months after the index procedure. The following assessments must be performed during the 36 Month office or telephone visit.

- Adverse Events Assessment (SAEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment

### 11.13.6. 48-Month Follow-up Visit (1460 days ± 30 days)

All enrolled subjects must be evaluated 48 months after the index procedure. The following assessments must be performed during the 48 Month office or telephone visit.

- Adverse Events Assessment (SAEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment

### 11.13.7. 60-Month Follow-up Visit (1825 days ± 30 days)

All enrolled subjects must be evaluated 60 months after the index procedure. The following assessments must be performed during the 60 Month office visit.

- Rutherford Categorization
- ABI Measurements
- Walking Impairment Questionnaire
- EQ-5D Questionnaire
- Adverse Events Assessment (SAEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment
- DUS of stented segment performed according to the DUS Core Laboratory procedure guidelines
- X-ray of the stented segment performed according to the X-ray Core Laboratory procedure guidelines

## 11.14. *Trial Completion*

The trial will be considered complete (with regard to the primary endpoints) after all subjects have completed the 12-month follow-up visit, were discontinued prior to the 12-month follow-up visit, have died or the follow-up visit window is closed.

The trial will be considered complete (with regard to all follow-up) after all subjects have completed the 60 month (5 year) follow-up visit, were discontinued prior to the 60 month (5 year) follow-up visit, have died or the follow-up visit window is closed.

## 11.15. *Missed or Late Visits*

Every effort must be made by the site to retain study subjects for the duration of the study.

A minimum of 3 attempts (i.e., 2 phone calls followed by a certified letter, or other traceable letter, if necessary) should be made to contact the subject or subject's next of kin for each missed follow-up visit and this information should be documented in the source. Missed or late visits will be recorded as Protocol Deviations. For subjects who miss their 12 Month follow-up visit (primary endpoint), BSC will provide site's access to a patient locator service (if allowed by the site's IRB/IEC/REB). A subject will be considered lost to follow-up after the subject misses 2 consecutive annual follow-up visits without due cause. No subject will be considered lost to follow-up prior to the 24 Month follow-up visit in order to make every effort to collect evaluable data for the primary endpoint.

### 11.16. *Follow-up Visits (Japan only)*

Data from the IMPERIAL trial collected through 12 months will be submitted as the primary data set for Japanese market approval. Follow-up beyond 12 months will continue as planned in this protocol. Once the investigational device is granted regulatory approval in Japan, subjects will continue protocol required follow-up as part of a postmarket clinical trial (by interpreting the word "trial" in this protocol as "post-market clinical trial").

### 11.17. *Source Documents*

It is preferable that original source documents (see **Table 27-2** for definition) are maintained, when available. Where copies of the original source document as well as printouts of original electronic source documents are retained, it is required that the copies 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.

## 12. Statistical Considerations

The sample size justification and the powered analyses for the primary endpoints described in this section are mainly for the RCT. For the PK substudy, the sample size determination is arbitrary and the analysis is based on observation. The details of all statistical analyses will be described in the Statistical Analysis Plan.

### 12.1. *Primary Endpoints*

The overall sample size in the RCT is justified by hypothesis parameters and driven by the primary effectiveness endpoint to preserve adequate statistical testing power for both primary effectiveness and safety endpoints.

The primary hypotheses are planned for being tested simultaneously at the specified one-sided significance level of 5% each without adjustment.

There is no primary endpoint for the PK substudy.

### 12.1.1. Primary Effectiveness Endpoint

The 12-month primary patency is chosen to be assessed for the primary effectiveness endpoint in the RCT. The goal is set to demonstrate that the primary patency for the ELUVIA treatment group (i.e. Test) is non-inferior to the Zilver PTX treatment group (i.e. Control) through 12 months post-procedure. For the definition of primary patency, refer to the section 7.1 Primary Endpoints.

#### 12.1.1.1. Hypotheses for RCT

The primary effectiveness hypothesis to be tested is that the 12-month primary patency in the Test Group is non-inferior to the Control Group by a margin of -10% (negative value) at one-sided significance level of 5%.

The null hypothesis ($H_0$) states that there is no marginal treatment effect of the Test Device vs. the Control Device as opposed to the alternative hypothesis ($H_1$) which states that there is a marginal treatment effect. The hypotheses inequalities are shown below:

$H_0$: Pt - Pc $\leq \Delta$ (inferior)

$H_1$: Pt - Pc $> \Delta$ (non-inferior)

where Pt and Pc are the 12-month primary patency for the Test Device and Control Device, respectively, and $\Delta$ (delta) is the non-inferiority margin of -10%.

#### 12.1.1.2. Sample Size for RCT

The primary effectiveness endpoint drives the overall sample size. Approximately 465 subjects are planned to be enrolled in the RCT. The sample size justification for the RCT is based on the following assumptions.

- Expected ELUVIA (test) rate = 83.0%
- Expected Zilver PTX (control) rate = 83.0%
- Non-inferiority margin ($\Delta$) = (-10%)
- Test significance level ($\alpha$) = 0.05 (1-sided)
- Power ($1-\beta$) > 0.80
- Expected rate of attrition = 15%

The expected 12-month primary patency for both the Test Group and Control Group are estimated to be 83% based on the recent publication. Given a margin of -10% for the treatment effect (Test minus Control) and a sample size allocation (Test vs. Control) of 2 to 1, a minimum of total 393 subjects (262 in the Test Group and 131 in Control Group) will be required at 12 months to provide at least 80% power under a one-sided 5% significance level.

Using a margin of -10% only allows the Test Group to be inferior to the Control group in terms of 12-month observed primary patency by a maximum of 3%. That is, assuming that the observed primary patency in the Control Group is 83.2% (109/131), the observed 12-

month primary patency in the Test Group will need to be at least 80.2% (210/262) in order to claim non-inferiority in the RCT.

Considering no more than 15% attrition rate in 12 months, approximately 465 subjects are required in a 2:1 randomized scheme in the RCT to achieve 393 subjects to be evaluable at 12 months.

#### 12.1.1.3. Statistical Methods for RCT

A non-inferiority test for the difference in 12-month primary patency will be used to assess the effectiveness hypotheses. The standard error will be estimated by the solution to the maximum likelihood equation (Farrington and Manning, 1990). The p-value and/or 95% confidence interval will be constructed based on statistics under this approach.

The non-inferiority for device effectiveness will be claimed if the one-sided lower 95% confidence bound on the observed difference between treatment groups (Test minus Control) in 12-month primary patency is greater than -0.1. This corresponds to the p-value from the one-sided non-inferiority test is less than 0.05.

### 12.1.2. **Primary Safety Endpoints**

The 12-month MAE-free rate is selected to be assessed for the primary safety composite endpoint. The safety goal is designed to demonstrate that Test Group is non-inferior to Control Group in terms of MAE-free rate through 12 months post-procedure. The components of MAE refer to the section 7.1 Primary Endpoints.

#### 12.1.2.1. Hypotheses

The primary safety hypothesis to be assessed is that the 12-month MAE-free rate in the Test Group is non-inferior to Control Group by a margin of -10% (negative value) at a one-sided significance level of 5%.

The null hypothesis ($H_0$) states that there is no marginal treatment effect of the Test Group vs. the Control Group as opposed to the alternative hypothesis ($H_1$) states that there is a marginal treatment effect. The hypotheses inequalities are shown below:

$H_0$: Pt - Pc $\leq \Delta$ (inferior)

$H_1$: Pt - Pc $> \Delta$ (non-inferior)

where Pt and Pc are the 12-month MAE-free rate for the Test Group and Control Group, respectively, and $\Delta$ (delta) is the non-inferiority margin of -10%.

#### 12.1.2.2. Sample Size

The overall sample size determined by the primary effectiveness endpoint is to provide at least 92% statistical power to assess the primary safety endpoint. The statistical power for the primary safety endpoint is calculated by the succeeding assumptions.

The expected 12-month MAE-free rate for both Test and Control Groups are estimated to be 90% based on the recent publication. Given a margin of -10% for the treatment effect, the total 393 evaluable subjects at 12 months will provide at least 92% power for the primary safety endpoint at a one-sided 5% significance level.

The margin of -10% only allows the Test Group to be inferior to the Control Group in terms of 12-month observed MAE-free rate by a maximum of 4%. That is, assuming that the 12-month MAE-free rate in the Control Group is 90.1% (118/131), the observed12-month MAE-free rate in the Test Group will need to be at least85.9% (225/262) in order to claim non-inferiority in the RCT.

12.1.2.3. Statistical Methods

The non-inferiority test described in the primary effectiveness endpoint will be used for the primary safety endpoint.

The non-inferiority for the device safety will be concluded if the one-sided lower 95% confidence bound on the observed difference between treatment groups (Test minus Control) in 12-month MAE-free rate is greater than -0.1. This corresponds to the p-value from the one-sided non-inferiority test is less than 0.05.

### 12.1.3. **Success Criteria**

The following success criteria are defined for the RCT.

ELUVIA will be concluded to be non-inferior to Zilver PTX for device safety if the one-sided lower 95% confidence bound on the difference between treatment groups (ELUVIA – Zilver PTX) in 12-month MAE-free is greater than -0.1.

ELUVIA will be concluded to be non-inferior to Zilver PTX for device effectiveness if the one-sided lower 95% confidence bound on the difference between treatment groups (ELUVIA – Zilver PTX) in 12-month primary patency is greater than -0.1.

If the primary safety and the primary effectiveness endpoints are both met, the RCT will be considered a success and both device safety and effectiveness will be claimed.

## 12.2. *General Statistical Methods*

### 12.2.1. **Analysis Sets**

The as-randomized (i.e. intent-to-treat or ITT) population will be the primary analysis set for assessing non-inferiority of the Test Group to the Control Group. The per-protocol and/or the as-treated population will be assessed for reference.

For the as-randomized analysis, all subjects who sign the written ICF and are randomized in the trial will be included in the analysis population, regardless of whether the subjects receive the assigned treatment. For the per-protocol analysis, only randomized subjects receive the assigned treatment will be included in the analysis population. For as-treated analysis, all

subjects in the per-protocol population will be included based on the actual Test or Control Device that each subject received (i.e. including cross-over subjects).

### 12.2.2. Randomization Scheme

Randomization to treatment will be stratified by study site. A computer generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatments in a 2:1 ratio of Test Group to Control Group. This list will be specific to the subject's site. Random permuted blocks of varying sizes will be employed to ensure approximate balance of treatment allocation within each site.

### 12.2.3. 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 and have signed the protocol-specific ICF will be eligible for enrollment in the trial. Consecutively eligible subjects should be enrolled into the trial to minimize selection bias. Study subjects will be randomly assigned to a treatment group within the investigational site. In determining subject eligibility for the study, the investigator's assessment of imaging will be used. However, the Angiographic Core Laboratory will independently analyze the angiograms and the data obtained from the core laboratory will be used for analyses. An independent CEC composed of medical experts will adjudicate safety assessments, as defined in the CEC Charter.

### 12.2.4. Number of Subjects per Investigative Site

Study sites will not be allowed to randomize more than 10% (N=46) of the total number of randomized subjects without prior approval from the sponsor. No study site will be allowed to enroll more than 20% (N=93) of the total number of randomized subjects.

## 12.3. *Baseline Data Analyses*

Baseline covariates will be summarized for the RCT and the PK substudy. Subject baseline 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 unit may be (but will not be limited to) by subject, lesion, procedure, or device.

The selected baseline covariates may be compared for 'like-to-like' in the Test Group verses the Control Group with appropriate statistical tests for discrete and continuous variables.

### 12.3.1. Additional Assessments/Measurements

Additional assessments may refer to (but not limit to) technical/procedural success, safety/effectiveness endpoints, stent fracture, any type of AE rates, distribution of Rutherford

classification, hemodynamic improvement, walking improvement at time points that data is collected.

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

### 12.3.2. Pharmacokinetics Parameters

Values for the following paclitaxel PK parameters will be calculated by a standard non-compartment analysis for subjects in the PK substudy.

- Maximum observed blood concentration ($C_{max}$)
- First time of occurrence of $C_{max}$ ($t_{max}$) will be the actual observed values
- Terminal phase rate constant ($\lambda z$) will be estimated from log-linear regression analysis of the terminal phase of the blood concentration-time profile
- Associated apparent terminal phase half-life ($t_{½}$) will be calculated as $t_{½} = \ln(2/\lambda z)$
- Area under the blood concentration versus time curve from time zero to 1 hour ($AUC_{0-1}$), time zero to 24 hours ($AUC_{0-24}$), time zero to the time of the last quantifiable concentration ($AUC_{0-t}$) and extrapolated to infinite time ($AUC_{0-\infty}$) will be calculated by a combination of linear and logarithmic trapezoidal methods
- Percentage of $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{ex}$) will be calculated as $[(AUC0\infty - AUC_{0-t})/AUC_{0-\infty}] \times 100$
- Total blood clearance (CL)

For AUC calculation, the linear method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.

Descriptive statistics (mean, standard deviation, sample size, 95% confidence interval) will be used to summarize these parameters for subjects in the PK substudy. No formal statistical testing will be done for these parameters.

### 12.3.3. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility.

### 12.3.4. Subgroup Analyses

Primary endpoints and/or additional assessments will be summarized and treatment groups may be compared in each subgroup identified by the following categories (but not limit to):

- Region

- Race
- Gender (male vs. female)
- Age (≥ 65 and < 65)
- Diabetic status (medically-treated vs. non-diabetic)
- Lesion characteristics (vessel diameter/lesion length)
- Stent matrix (stent diameter/length)
- Other significant predictors identified by regression models

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

### 12.3.5. Justification of Pooling

The poolability analysis regarding the primary safety endpoint across sites will be assessed. Due to the 2:1 randomization scheme using random permuted blocks employed within each site, there will be at least 2 subjects from the Test Group and one subject from the Control Group. Therefore the poolability method is described as below.

The sites with enrollment of 6 subjects or more are reported individually.

The sites with enrollment of 5 or less subjects are pooled into super-sites according to their geographical closeness so that the combined super-sites would have 6 or more enrolled subjects. If a super-site has 6 or more subjects and at least 2 subjects in each treatment group, the pooling of this super-site should stop and the pooling of the next super-site should start.

If the p-value of poolability test in the logistic regression model for the primary safety endpoint is > 0.15, the treatment effect will be presented for overall across all sites. If the p-value is ≤ 0.15, the treatment effect will be presented by each site or super-site in addition to the overall across all sites.

### 12.3.6. Sensitivity Analysis for Missing Data

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

### 12.3.7. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors for the primary safety/effectiveness endpoint in a logistic regression model.

Clinically meaningful baseline covariates will be selected in the regression model.

### 12.3.8. 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).

### 12.3.9. Changes to Planned Analyses

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

# 13. Data Management

## 13.1. *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 Medidata. 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.

## 13.2. *Data Retention*

The 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 at least 2 years after the last approval of a marketing application or until at least 2

years (at least 3 years in Japan) have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator 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.

In Japan, BSC must maintain necessary essential documents for 5 years from the date of the marketing application approval (or during the period of user-results evaluation, if applicable and if longer than 5 years) or until 3 years have elapsed since the formal discontinuation of the clinical investigation of the device, whichever is longer.

If study follow-up is continued beyond 5 years in Japan as part of a postmarket clinical trial after receiving marketing approval, the Investigator and Site must retain essential documents during the period of user-results evaluation, and BSC must retain essential documents in accordance with Good Postmarketing Surveillance Practice and Test of Medical Devices (Ministrial Ordinance 38, 23 March, 2005).

### 13.3. *Core Laboratories*

Core laboratories will be established for the central assessment of key data collected during the IMPERIAL trial. Detailed guidelines for the collection, analysis, and interpretation of the following data will be provided in the Manual of Operations. The following core laboratories have been assigned for this trial:

- Angiographic: to assess angiograms taken during the index procedure and during any subsequent revascularization procedure.
- Ultrasound: to assess duplex ultrasounds taken during the follow-up period (6-month, 12-month, 24-month, and 60-month visits) for primary patency.
- X-Ray: to assess x-rays taken during the follow-up period (12-month, 24-month and 60 month visits) for stent integrity. (Note: Additional X-rays will be collected at Japanese sites in the event of a TLR/TVR and in those cases when, in the opinion of the investigator, an X-ray should be performed).
- Pharmacokinetics: to assess whole blood baseline paclitaxel levels and at defined time points through 48/72 hours post-index procedure.

## 14. 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 (e.g., IRB/IEC/REB/FDA/CA) of the revised protocol must be obtained prior to implementation.

## 15. 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/IEC/REB 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 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/IEC/REB, 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, center re-training, or discontinuation) will be put into place by the sponsor.

## 16. Device/Equipment Accountability

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. The randomization custom function of the Rave EDC system will be used to track subjects and device allocations during the study.

BSC shall keep records to document the physical location of all ELUVIA investigational devices from shipment of investigational devices 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 ELUVIA investigational devices, which shall include the following:

- Date of receipt
- Identification of each investigational device (batch number or unique code)
- Expiry date, as applicable
- Date of use
- Subject identification
- Date on which the investigational device was returned, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices, if applicable.

The Principal Investigator or an authorized designee shall keep records documenting the use of the commercially available Zilver PTX control devices, which shall include the following for each control device attempted/implanted:

- Identification of each device (lot number or unique code)
- Stent diameter and stent length
- SDS size
- Date of use
- Subject identification

Written procedures may be required by national regulations.

# 17. Compliance

## 17.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155 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 individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/IEC/REB and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/IEC/REB or regulatory authority shall be followed, if appropriate.

## 17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the 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/IEC/REB, 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 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 center 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.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- 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 to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/IEC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/IEC/REB 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 ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- 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 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.

#### 17.2.1. **Delegation of Responsibility**

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the 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.

### 17.3. *Institutional Review Board/ Independent Ethics Committee/Research Ethics Board*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB/IEC/REB 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/IEC/REB and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by BSC before recruitment of subjects into the study and shipment of investigational product. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

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

### 17.4. *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.

BSC will keep subjects' health information confidential in accordance with all applicable laws and regulations. BSC 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.

The clinical trial organization in Japan, including investigational sites in Japan, is provided as a separate attachment to the protocol only in Japan.

Also, BSC or Boston Scientific Japan (BSJ) may utilize contract research organizations (CROs) or other contractors to act as their representative for carrying out designated tasks. Responsibilities for these entities are defined in the applicable contracts or agreements. Contact information for the CROs is provided as a separate attachment to the protocol only in Japan or in the Manual of Operation (MOP) for Japanese sites.

#### 17.4.1. **Role of Boston Scientific Representatives**

BSC personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during stent implant and testing required by the protocol during the index procedure. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of the investigational device.

**Boston Scientific personnel will not do the following:**

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

### 17.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

# 18. Monitoring

Monitoring will be performed during the study, according to the study Monitoring Plan, to assess continued compliance with the current, approved protocol/amendments and applicable regulations. In addition, the 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 Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. Pre-defined thresholds for protocol deviation and compliance once met or exceeded, can also trigger increased monitoring frequency and/or the implementation of corrective action plans at clinical sites. For the IMPERIAL trial, source documents include, at a minimum but are not limited to, the ICF; patient medical records, including nursing records and catheterization laboratory records; diagnostic imaging records; laboratory results; reports of SAEs; and device accountability logs. Data documented in the eCRF relevant to device deficiencies, relationship of AE to study device(s), index procedure, antiplatelet medication; and the anticipated assessment of ADEs, may be considered source data for the study.

The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, all reasonable attempts must be made to obtain photocopies of the original source documents for review. Photocopies of original source documents related to MAEs that are adjudicated by the CEC (from either the study site or a non-study institution, if applicable) must also be made available for submission to the BSC Safety Group.

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

# 19. Potential Risks and Benefits

## 19.1. *Anticipated Adverse Events and Risks Associated with Use of the ELUVIA Stent System and Implantation of the ELUVIA Stent*

The risks associated with the implantation of a stent in the SFA/PPA may include, but are not limited to the following:

- Allergic reaction (to drug/polymer, contrast, device or other)
- Bleeding/Hemorrhage
- Death
- Embolization (air, plaque, thrombus, device, tissue or other)
- Extremity ischemia/amputation

- Hematoma
- Need for urgent intervention or surgery
- Pseudoaneurysm formation
- Renal insufficiency or failure
- Restenosis of stented artery
- Sepsis/infection
- Thrombosis / thrombus
- Tissue ischemia / necrosis
- Transient hemodynamic instability (hypotensive/hypertensive episodes)
- Vasospasm
- Vessel injury, including perforation, trauma, rupture and dissection
- Vessel occlusion

### 19.2. *Risks Associated with the Study Device(s) Unique to Paclitaxel*

Certain side effects and discomforts have been reported in subjects that have received paclitaxel in intravenous forms as part of chemotherapy treatment. These subjects may have other comorbid conditions and/or have received concomitant medications that may also contribute to the reported side effects. Under these circumstances the dose is delivered throughout the body by the blood and in doses hundreds of times higher than the total amount on the coated stent for use in the proposed clinical trial. Potential adverse events that may be unique to the paclitaxel drug coating are:

- Allergic/immunologic reactions to drug (paclitaxel or structurally-related compounds) or the polymer stent coating (or its individual components)
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, and thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in the vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/arthralgia
- Peripheral neuropathy

It is unlikely with the total dosages and the way paclitaxel is coated onto the stent and delivered in the vessel that the side effects associated with intravenous, high dose chemotherapy would occur. There may be other potential adverse events that are unforeseen at this time.

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

There may be additional risks linked to the procedure, and follow-up testing which are unforeseen at this time. All testing planned for the follow-up period is standard of care with the exception of the x-ray requirements during follow-up. These additional requirements should not create additional risk to the subject over treatment with an already approved stent system.

In addition, risks associated with venipuncture and the additional blood draws required in the PK substudy include, but are not limited to:

- Ecchymosis
- Hematoma
- Infection/inflammation
- Pain

### 19.4. *Possible Interactions with Concomitant Medical Treatments*

In addition to the aforementioned risks associated with the implantation of stents and the use of paclitaxel, the use of prolonged dual antiplatelet therapy after stent implantation may increase the risk of bleeding. Refer to the local package insert for further information on drug interactions and side effects associated with paclitaxel or antithrombotic/antiplatelet medications.

### 19.5. *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.

### 19.6. *Anticipated Benefits*

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

### 19.7. *Risk to Benefit Rationale*

The ELUVIA stent 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 the use of the ELUVIA stent demonstrate that

when used under the conditions intended, the benefits associated with the use of the ELUVIA stent should outweigh the risks.

# 20. Safety Reporting

## 20.1. *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 Adverse Events (until 12 month follow-up)
- All Device Related Adverse Events/Device Related Serious Adverse Events
- All Serious Adverse Events
- All 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 experienced by the study subject after randomization/enrollment, 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 or frequency during the course of the investigational trial. 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 a specific SAE (see Table 20-1 for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

Device deficiencies and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate eCRF per the study CRF Completion Guidelines. If an AE results from a device deficiency or other device issue, the AE should be reported on the appropriate eCRF.

In-patient hospitalization is defined as the subject being admitted to the hospital (≥ 24 hours), with the following exceptions.

- A hospitalization for routine follow-up per standard of care.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE or AE.
- 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.

## 20.2. *Definitions and Classification*

Adverse event definitions for the IMPERIAL trial are provided in **Table 20-1**. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 (2015). In addition, country-specific definitions may apply per local reporting requirements.

**Table 20-1: Safety Definitions**

| Term | Definition |
|---|---|
| Adverse Event (AE)<br><br>*Ref: ISO 14155-2011*<br><br>*Ref: MEDDEV 2.7/3(2015)* | 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.<br>NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device. |
| Adverse Device Effect (ADE)<br><br>*Ref: ISO 14155-2011*<br><br>*Ref: MEDDEV 2.7/3(2015)* | Adverse event related to the use of an investigational medical device<br>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: MEDDEV 2.7/3(2015)* | 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, or<br>o medical or surgical intervention to prevent life-threatening illness, or<br>o 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. |

**Table 20-1: Safety Definitions**

| Term | Definition |
|---|---|
| | **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: MEDDEV 2.7/3(2015)* | 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: MEDDEV 2.7/3(2015)* | 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. |
| Device Deficiency<br><br>*Ref: ISO 14155-2011*<br><br>*Ref: MEDDEV 2.7/3(2015)* | An Inadequacy of an investigational 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. |

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

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

The Investigator must assess the relationship of the AE to the study device as related or unrelated. Criteria are defined in **Table 20-2**.

## Table 20-2: Criteria for Assessing Relationship of Study Device or Index Procedure to AE

| Classification | Description |
|---|---|
| **Not Related** | Relationship to the device or procedure 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 device or the procedure;<br>- the 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 event;<br>- the event involves a body-site or an organ not expected to be affected by the device or procedure; the 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 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 event. |
| **Unlikely Related** | The relationship with the use of the device or procedure 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 device or procedure 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 related. |
| **Probably Related** | The relationship with the use of the device or procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained. |
| **Causal Relationship** | The event is associated with the device or with procedure 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 device use/application or procedure;<br>- the event involves a body-site or organ that<br>o the device or procedure are applied to;<br>o the device or procedure have an effect on;<br>- the 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 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; |

**Table 20-2: Criteria for Assessing Relationship of Study Device or Index Procedure to AE**

| Classification | Description |
|---|---|
| | - the event depends on a false result given by the 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/procedure and the event. |

The Investigator must assess the relationship of the AE to the antiplatelet medication as related or unrelated. Criteria are defined in **Table 20-3**.

**Table 20-3: Criteria for Assessing Relationship of Antiplatelet Medication to AE**

| Classification | Description |
|---|---|
| **Unrelated** | The adverse event is determined to be due to a concurrent illness or effect of a device/drug and is not determined to be potentially related to the antiplatelet medication. |
| **Related** | The adverse event is determined to be potentially related to the antiplatelet medication, and an alternative etiology is equally or less likely compared to the potential relationship to antiplatelet medication. |

## 20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 20-4.** An Event Document Checklist included in the MOP specifies the required source documents for events requiring CEC adjudication.

**Table 20-4: Investigator Reporting Requirements**

| Event Classification | Communication Method | Communication Timeline<br>(MEDDEV 2.7/3 (2015): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC) |
|---|---|---|
| Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect (UADE/USADE) | Complete AE eCRF page with all available new and updated information. | • Within 1 business day of first becoming aware of the event.<br>• Terminating at the end of the trial |
| Serious Adverse Event (SAE) | Complete AE eCRF page with all available new and updated information. | • Within 3 calendar days of first becoming aware of the event or as per local/regional regulations.<br>• Reporting required through the end of the trial |
| | Provide all relevant source documentation (unidentified) for events to be adjudicated by CEC. | • When documentation is available |

**Table 20-4: Investigator Reporting Requirements**

| Event Classification | Communication Method | Communication Timeline (MEDDEV 2.7/3 (2015): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC) |
|---|---|---|
| Serious Adverse Device Effects (SADE) | Complete AE eCRF page with all available new and updated information. | • Within 3 calendar days of first becoming aware of the event or as per local/regional regulations.<br>• Reporting required through the end of the study |
| | Provide all relevant source documentation (unidentified) for events to be adjudicated by CEC. | • When documentation is available |
| Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)<br>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. | Complete Device Deficiency eCRF with all available new and updated information. | • Within 3 calendar days of first becoming aware of the event or per local/regional regulations.<br>• Reporting required through the end of the trial |
| Adverse Event (AE) including Adverse Device Effects (ADE) | 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 (e.g. Recommend within 10 business days) after becoming aware of the information<br>• ADE reporting required through the end of the trial<br>• AE reporting required through the 12 month follow-up. |

Abbreviations: CEC=Clinical Events Committee; eCRF=electronic case report form

## 20.5. *Boston Scientific Device Deficiencies*

All investigational 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 the Manual of Operations. 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 adverse events. However, an adverse event that results from a device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF.

Any Device Deficiency that might have led to a SAE 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.

Device deficiencies may include, but are not limited to the following:

- Stent fracture, migration, and/or misplacement/jumping
- Packaging or labeling deficiency
- Difficulty advancing or tracking stent delivery system

### 20.6. *Reporting to Regulatory Authorities / IRBs / IECs / REBs / Investigators*

BSC will notify all participating 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.

BSC is responsible for reporting AE and device deficiencies information to all participating investigators, IRBs/IECs/REBs, and regulatory authorities as applicable according to local reporting requirements.

BSC, Investigator, or Site must notify the IRB/IEC/REB of any UADEs, USADEs, SADEs, SAEs, device deficiencies, and other CEC events as applicable according to local reporting requirements (refer to Section 22.3 for information pertaining to the CEC and CEC Events). A copy of the Investigator's reports and other relevant reports (if applicable) to the IRB/IEC/REB must be provided to BSC in accordance with local requirements.

Safety reporting on the control device, which is approved in all regions at the time of the trial initiation, will be handled separately according to local regulations.

## 21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. For patients less than 20 years of age enrolled at a Japanese center, the patient's legal representative, as well as the patient, must provide written informed consent. 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 center's IRB/IEC/REB, 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 center's IRB/IEC/REB. Any modification requires approval 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 center in obtaining a written consent translation. Translated consent forms must also have IRB/IEC/REB 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 center and a copy of the signed and dated document and any other written information must be given to the person signing the form. In Japan, Informed Consent signature can be replaced by printed name and seals of appropriate individuals.

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/IEC/REB), 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/IEC/REB. The new version of the ICF must be approved by the IRB/IEC/REB. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/IEC/REB. The IRB/IEC/REB 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, catheterization may demonstrate that the subject is not a suitable candidate for the trial. A Screening Log will be maintained by the investigational site to document select information about candidates who fail to meet the trial eligibility criteria, including, but not limited to, the reason for screen failure.

# 22. Committees

## 22.1. *Executive Committee*

An Executive Committee composed of BSC Clinical Management and selected Coordinating Principal Investigator(s) 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 IMPERIAL Investigators on the committee.

## 22.2. *Safety Monitoring Process*

To promote early detection of safety issues, the independent Clinical Events Committee (CEC) and Independent Data Review (IDR) will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's Safety Group, which is responsible for coordinating the collection of information for the subject dossier from Medidata Rave EDC database that is entered by the centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

## 22.3. *Clinical Events Committee (CEC)*

The CEC is an independent group of individuals with no affiliation with BSC. Committee membership will include practitioners of peripheral endovascular procedures, as well as other experts with the necessary therapeutic and subject matter expertise to review and adjudicate the following endpoints and major adverse events reported by the trial Investigators:

- All Deaths
- TLR

- TVR
- Target limb amputations
- Stent Thrombosis

CEC members will be blinded to a subject's treatment assignment during the trial. Responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

Contact information for the CEC is included in the Manual of Operations for Japanese sites.

### 22.4. *Independent Data Review (IDR)*

The independent data reviewer (IDR) provides external oversight and review for potential safety concerns. The IDR is a physician expert in peripheral interventional therapy who is not participating in the clinical study and has no affiliation with BSC.

Aggregate accumulating safety data will be reviewed to monitor for the incidence of MAEs and other trends that would warrant modification or termination of the trial. During the course of the trial, data will be supplied to and reviewed by the IDR in blinded fashion (i.e., group A and group B). If, after review of blinded data, the IDR wants to review unblinded data, a request will be made to the Executive Committee for consideration and final decision.

Any IDR recommendations for clinical study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to BSC for consideration.

Contact information for the IDR is included in the Manual of Operations for Japanese sites.

## 23. Suspension or Termination

### *23.1 Premature Termination of the Study*

BSC 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/IECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination. 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 BSC to suspend or discontinue development of the device.

### *23.2 Termination of Study Participation by the Investigator or Withdrawal of IRBs/IECs/REBs Approval*

Any investigator or IRBs/IECs/REBs in the IMPERIAL trial may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IRBs/IECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

### *23.3 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 BSC. The IRB/IEC/REB 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/IEC/REB terminates participation in the study, participating investigators, associated IRBs/IECs/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The investigator must return all documents and investigational product to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

### *23.4 Criteria for Suspending/Terminating a Study Center*

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

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

## 24. 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 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.

# 25. Reimbursement and Compensation for Subjects

## 25.1. *Subject Reimbursement*

Travel expenses (and other expense for Japan only) incurred by subjects as a result of participation in the study will be reimbursed if requested in accordance with pertinent country laws and regulations and per the study site's regulations.

## 25.2. *Compensation for Subject's Health Injury*

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, as required by applicable law.

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# 27. Abbreviations and Definitions

## 27.1. *Abbreviations*

**Table 27-1: Abbreviations**

| Abbreviation | Terminology |
|---|---|
| **ABI** | Ankle Brachial Index |
| **ACC/AHA** | American College of Cardiology/American Heart Association |
| **ADE** | Adverse Device Effect |
| **AE** | Adverse Event |
| **BSC** | Boston Scientific Corporation |
| **CE** | Conformité Européenne (meaning European Conformity) |
| **CEC** | Clinical Events Committee |
| **CIN** | Contrast-Induced Nephropathy |
| **CRA** | Clinical Research Associate |
| **CRF** | Case Report Form |
| **CVA** | Cerebrovascular Accident |
| **DFU** | Directions for Use |
| **DSA** | Digital Subtraction Angiography |
| **DUS** | Duplex Ultrasound |
| **eCRF** | Electronic Case Report Form |
| **EDC** | Electronic Data Capture |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |

| Abbreviation | Terminology |
|---|---|
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Institutional Ethics Committee |
| **ITT** | Intent to Treat |
| **IRB** | Institutional Review Board |
| **MAE** | Major Adverse Event |
| **PMDA** | Pharmaceutical Medical Device Agency |
| **PPA** | Proximal Popliteal Artery |
| **PSVR** | Peak Systolic Velocity Ratio |
| **PTA** | Percutaneous Transluminal Angioplasty |
| **QA** | Quantitative Angiography |
| **REB** | Research Ethic Board |
| **SADE** | Serious Adverse Device Effect |
| **SAE** | Serious Adverse Event |
| **SDS** | Stent Delivery System |
| **SFA** | Superficial Femoral Artery |
| **TBI** | Tibial Brachial Index |
| **TLR** | Target Lesion Revascularization |
| **TVR** | Target Vessel Revascularization |
| **UADE** | Unanticipated Adverse Device Effect |
| **UPN** | Universal Product Number |
| **VIVA** | Vascular InterVentional Advances |

## 27.2. *Definitions*

Terms are defined in **Table 27-2**

**Table 27-2: Definitions**

| Term | Definition |
|---|---|
| **AMPUTATION** | • Major Amputation: amputation of the lower limb at the ankle level or above.<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. |
| **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. |

| 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 DETERIORATION** | Downgrade in Rutherford classification of 1 or more categories as compared to pre-procedure. |
| **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. |
| **DIAMETER STENOSIS** | The maximal narrowing of the target lesion relative to the reference vessel diameter. |

| Term | Definition |
|---|---|
| **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. |
| **EQ-5D™** | Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. |
| **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. |
| **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. |

| Term | Definition |
|---|---|
| **MINIMAL LUMEN DIAMETER** | The vessel diameter as measured at the most narrow 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** | Percentage (%) of lesions that reach endpoint without a hemodynamically significant stenosis on DUS and without clinically-driven TLR or, bypass of the target lesion. |
| **PRIMARY SUSTAINED CLINICAL IMPROVEMENT** | Endpoint determined to be a success when there is an 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. |

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>RESTENOSIS</td><td>DUS systolic velocity ratio (SVR) > 2.4 suggest stenosis >50%.</td></tr>
<tr><td>RUTHERFORD / BECKER CLASSIFICATION</td><td>
<table>
<tr><th>Category</th><th>Clinical Description</th><th>Objective Criteria</th></tr>
<tr><td>0</td><td>Asymptomatic</td><td>Normal Treadmill /stress test</td></tr>
<tr><td>1</td><td>Mild claudication</td><td>Completes treadmill exercise; ankle pressure (AP) after exercise < 50 mm Hg, but > 25 mm Hg less than BP</td></tr>
<tr><td>2</td><td>Moderate claudication</td><td>Between categories 1 and 3</td></tr>
<tr><td>3</td><td>Severe claudication</td><td>Cannot complete treadmill exercise and AP after exercise < 50 mm Hg</td></tr>
<tr><td>4</td><td>Ischemic rest pain</td><td>Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording (PVR); toe pressure (TP) < 30 mm Hg</td></tr>
<tr><td>5</td><td>Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal edema</td><td>Resting AP < 60 mm Hg, ankle or metatarsal (MT) PVR flat or barely pulsatile; TP < 40 mm Hg</td></tr>
<tr><td>6</td><td>Major tissue loss – extending above MT level</td><td>Same as Category 5</td></tr>
</table>
</td></tr>
<tr><td>SECONDARY SUSTAINED CLINICAL IMPROVEMENT</td><td>Endpoint determined to be a success when there is an improvement in Rutherford classification of one or more categories as compared to pre-procedure including those subjects with repeat TLR.</td></tr>
<tr><td>SOURCE DATA</td><td>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).</td></tr>
<tr><td>SOURCE DOCUMENT</td><td>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.</td></tr>
</table>

| Term | Definition |
|---|---|
| **STENT FRACTURE** | A break in one or more places of the stent. The following definitions will be used to determine the type and extent of stent fracture (to be assessed by the x-ray core laboratory):[3]<br>• Grade 0: No Strut fractures<br>• Grade I: single strut fracture<br>• Grade II: multiple strut fractures<br>• Grade III: stent fracture(s) with preserved alignment of the components<br>• Grade IV: stent fracture(s) with mal-alignment of the components<br>• Grade V: Stent fracture(s) in a trans-axial spiral configuration |
| **STENT THROMBOSIS** | The occurrence of either of the following:<br>1. Angiographic documentation (or any other imaging modality if angiography not available) of an acute, complete occlusion of a previously successfully treated lesion and/or<br>2. Angiographic documentation (or any other imaging modality if angiography not available) of a flow-limiting thrombus within, or adjacent to, a previously successfully treated lesion<br>*Acute* stent thrombosis is defined as occurring ≤ 24 hours following the clinical study procedure.<br>*Subacute* stent thrombosis is defined as occurring > 24 hours to ≤ 30 days following the clinical study procedure.<br>*Late* stent thrombosis is defined as > 30 days to 365 days following the clinical study procedure.<br>*Very late* stent thrombosis is defined as > 365 days following the clinical study procedure. |
| **TARGET LESION** | A target lesion is identified as a clinical study lesion intended to be treated with a clinical study device during the index procedure. |

| Term | Definition |
|---|---|
| **TARGET LESION REVASCULARIZATION (TLR)** | Any surgical or percutaneous intervention to the target lesion(s) after the index procedure when one of the following situations is present:<br>• A target lesion revascularization will be considered clinically-driven if it occurs within 5 mm proximal or distal to the original treatment segment with diameter stenosis ≥50% by quantitative angiography (QA) and 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>• A target lesion revascularization for an in-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.) |
| **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. |
| **TARGET VESSEL REVASCULARIZATION (TVR)** | Any surgical or percutaneous intervention to the target vessel(s) after the index procedure when one of the following situations is present:<br>• A target vessel revascularization will be considered as clinically-driven if the culprit lesion stenosis is ≥50% by QA and 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>• 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.) |

| Term | Definition |
|---|---|
| **TRANSATLANTIC INTER-SOCIETAL CONSENSUS (TASC) LESION GUIDELINES** | 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** | Delivery and deployment of the assigned study stent to the target lesion to achieve residual angiographic stenosis no greater than 30% assessed visually. |
| **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. |

| Term | Definition |
|---|---|
| **VESSEL PATENCY** | Freedom from more than 50% stenosis based on duplex ultrasound (DUS) peak systolic velocity ratio (PSVR) comparing data within the treated segment to the proximal normal arterial segment. A PSVR > 2.4 suggests >50% stenosis. All DUS readings are assessed by an independent core lab. |
| **WALKING IMPAIRMENT QUESTIONNAIRE (WIQ)** | The WIQ is a functional-assessment questionnaire that evaluates walking ability with regard to speed, distance and stair climbing ability as well as the reasons that walking ability might be limited. Range of scores is between 0% and 100% with 100% being the best and 0% being the worst score. |

# 28. IMPERIAL Long Lesion Substudy

## 28.1. *Objectives*

The objective of the Long Lesion Substudy is to evaluate the safety and effectiveness of the Boston Scientific (BSC) ELUVIA drug eluting stent for treating Superficial Femoral (SFA) and/or Proximal Popliteal Artery (PPA) lesions > 140 mm and ≤ 190 mm in length.

## 28.2. *Design*

The IMPERIAL Trial consists of a prospective, multicenter, 2:1 randomized (ELUVIA vs Zilver PTX), controlled, single-blind, non-inferiority trial (RCT), a concurrent, non-blinded, non-randomized, single-arm, pharmacokinetic (PK) substudy and a concurrent, non-blinded, non-randomized, single-arm, Long Lesion substudy.

This section describes the Long Lesion substudy only.

### 28.2.1. **Scale and Duration**

Approximately 50 subjects will be enrolled in the IMPERIAL Long Lesion substudy.

All subjects will receive treatment with the investigational test device (ELUVIA) in the Long Lesion substudy.

The Long Lesion substudy will be conducted in any site already participating in the IMPERIAL Trial that is interested in adding this substudy group.

Clinical follow-up will be required at the following time points: pre-discharge, 1 month, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months post index procedure. Testing required at these visits is described in Section 11.13 of the IMPERIAL protocol.

If patients are enrolled at a site conducting the PK substudy and are willing to undergo PK testing, they will have baseline venous blood drawn followed by blood draws at 10 minutes, 30 minutes, 1, 2, 3, 4, 6, 12, 24 and either 48 or 72 hours after placement of the final ELUVIA study stent to evaluate plasma paclitaxel levels.

The enrollment period will run concurrent with the IMPERIAL Trial.

**Figure 28.2-1** shows the schematic of the Long Lesion substudy design.

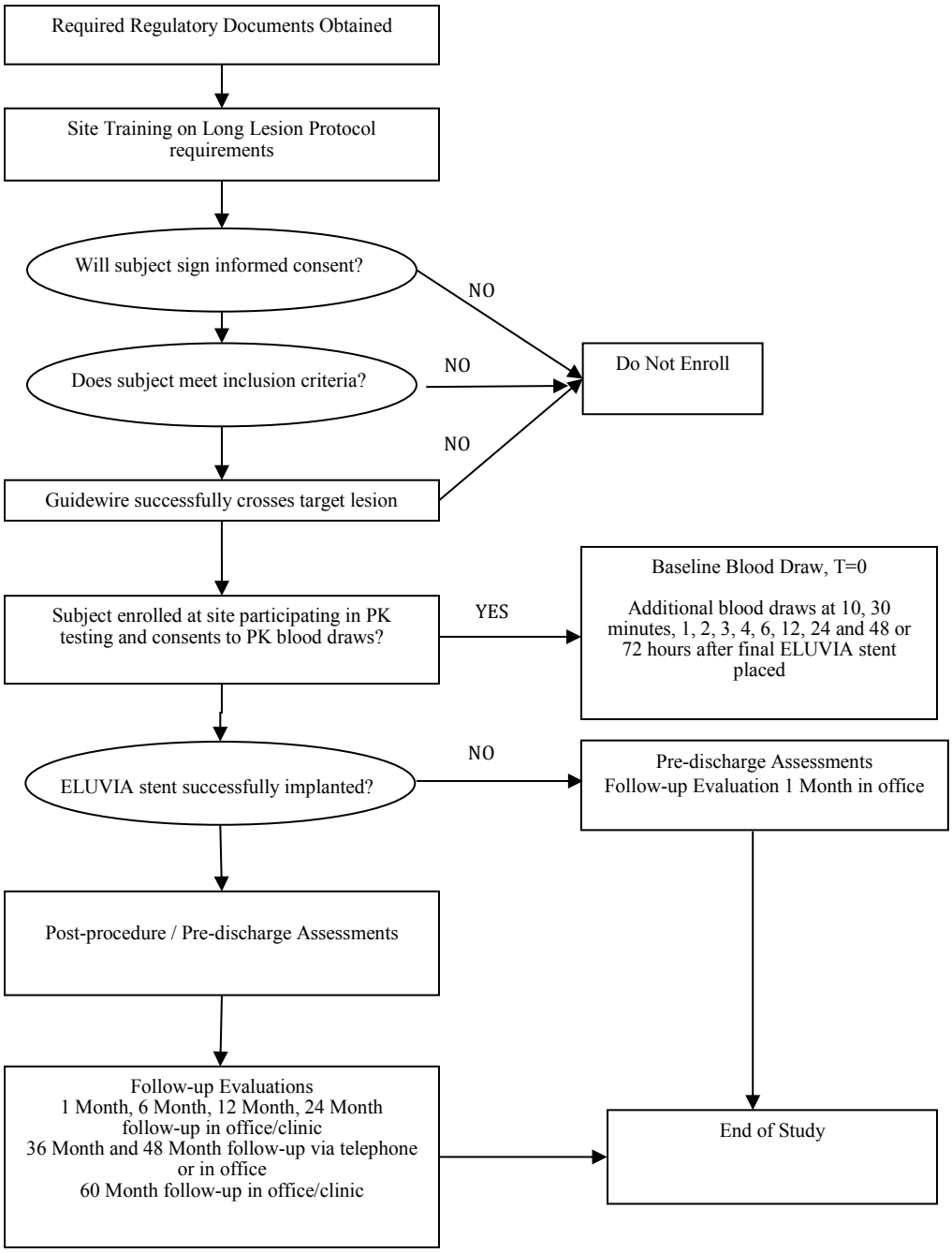


**Figure 28.2-1: IMPERIAL Long Lesion Substudy Design**

### 28.2.2. **Treatment Assignment**

Once the subject has signed the IRB/IEC/REB-approved study informed consent form (ICF), and has met all clinical inclusion and no clinical exclusion criteria, the subject will be considered eligible to be enrolled in the Long Lesion substudy. Subjects can be simultaneously consented for the RCT and the Long Lesion substudy as the lesion groups do not overlap. Once the lesion length is determined via angiographic assessment, the subject would be placed into the appropriate group (i.e. the RCT for lesions 40-140 mm in length or the Long Lesion substudy for lesions from 140-190 mm in length).

If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be randomized or receive an investigational device, nor should the subject be followed post-procedure per protocol.

All subjects will be treated with the ELUVIA Stent System. It is expected that two Eluvia stents will be overlapped in order to cover the entire lesion. Subjects will be considered enrolled when the first ELUVIA stent is introduced into the subject's vasculature.

### 28.2.3. **Multiple Interventions Using Same Access Site During Index Procedure**

**Target Limb**

The target lesion may include two or more tandem lesions, provided that the entire segment of tandem lesions is > 140 mm and ≤ 190 mm and can be covered with two ELUVIA stents according to the Directions for Use (DFU). For occlusive lesions requiring the use of a re-entry device, the target lesion length must be > 120 mm and ≤ 170 mm allowing the target lesion and re-entry area to be covered with two ELUVIA stents (Refer to Inclusion criterion 4c and 4d).

## 28.3. *Subject Selection*

**Study Population and Eligibility**

Clinical and angiographic inclusion criteria are included in **Table 28-1**. Exclusion criteria are identical to the IMPERIAL Trial population and are detailed in Section 9.3 of the IMPERIAL protocol. Prior to enrollment, a subject must meet all of the clinical and angiographic inclusion criteria and none of the clinical and angiographic exclusion criteria.

**Table 28-1 Long Lesion Substudy Inclusion Criteria**

| | |
|---|---|
| **Inclusion Criteria** | 1. Subjects age 18 and older.<br>2. Subject (or Legal Guardian if applicable) 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. NOTE: For subjects less than 20 years of age enrolled at a Japanese center, the subject's legal representative, as well as the subject, must provide written informed consent.<br>3. Chronic, symptomatic lower limb ischemia defined as Rutherford categories 2, 3 or 4.<br>4. Stenotic, restenotic or occlusive lesion(s) located in the native SFA and/or PPA:<br>a. Degree of stenosis ≥70% by visual angiographic assessment<br>b. Vessel diameter ≥ 4 and ≤ 6 mm<br>c. Total lesion length (or series of lesions) > 140 mm and ≤ 190 mm (Note: Lesion segment(s) will require overlapping of two ELUVIA stents)<br>d. For occlusive lesions requiring use of re-entry device, lesion length > 120 mm and ≤ 170 mm<br>e. Target lesion located at least three centimeters above the inferior edge of the femur<br>5. Patent infrapopliteal and popliteal artery, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot with no planned intervention. |

## 28.4. *Subject Accountability*

Subject accountability is as described in Section 10.

## 28.5. *Study Methods*

Subjects enrolled in the Long Lesion substudy will follow the Data Collection schedule outlined in Section 11.1. If a subject in the Long Lesion substudy is enrolled at a PK substudy site and consents to PK testing, assessment of whole blood paclitaxel levels will be completed as described in Section 11.12. Follow-up visits will continue through 5 years post-procedure.

## 28.6. *Statistical Considerations*

Statistical considerations are as defined in Section 12. The details of all statistical analyses will be described in the Statistical Analysis Plan.

### 28.6.1. **Primary Endpoints**

The sample size determination for the long lesion substudy is arbitrary and not statistically driven.

#### 28.6.1.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint assesses the 12-month primary patency. There is a non-statistically driven goal (60%) which was developed from the historical long stent performance (47.2%; 95% Confidence Interval [30.4%, 64.5%]) in subjects treated with Innova Bare Metal Stent System and the expected enhanced performance (10%) for the ELUVIA Stent System.

Statistical Methods

The non-statistically driven performance goal will be compared against the observed 12-month primary patency in the evaluable long-lesion subjects. If the observed 12-month primary patency is greater than or equal to 60%, the ELUVIA Stent System will be considered to have acceptable effectiveness performance in the long lesion population.

#### 28.6.1.2. Primary Safety Endpoints

The primary safety endpoint assesses the 12-month MAE-free rate. It is expected that the MAE-free rate will be similar to the rates observed by the ELUVIA stent group observed in the RCT. The MAE-free Rate as well as its individual components will be reported separately for this subgroup.

### 28.6.2. **Additional Endpoints**

All additional endpoints described in Section 7.2 will be reported separately for this subgroup.