The SAVAL Pivotal Trial

A Randomized Trial comparing the Drug-Eluting Stent (DES) Below-the-Knee (BTK) Vascular Stent System (DES BTK Vascular Stent System) vs Percutaneous Transluminal Angioplasty (PTA) Treating Infrapopliteal Lesions in Subjects With Critical Limb Ischemia

S2348

CLINICAL INVESTIGATION PLAN

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Investigational Centers	A list of investigational centers is provided in the manual of operations. A list of investigational centers in Japan is provided as a separate attachment to the protocol for Japan centers only.
Vendors/Labs	A list of vendors/laboratories involved in the trial is maintained by the sponsor. A complete listing of applicable vendors will be provided to the investigational centers.

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
AA	19 Dec 2017	90702637_Rev Ver AI	N/A	N/A	N/A
B	19 Mar 2018	90702637_Rev Ver AI	• 2. Protocol synopsis • 5. Device Description • 8. Subject Selection • 10. Trial Methods • 11. Statistical Considerations • 12. Health Economics Outcomes • 13. Data Management • 15. Device Accountability • 18. Potential Risks and Benefits • 19. Safety Reporting • 21. Committees • 26. Abbreviations and Definitions	• Update of Reference Vessel Diameter (RVD) • Update of investigational device characteristics • Update of additional endpoints • Update of number of subjects • Update of definitions/terms • Update of eligibility criteria • Update of data collection requirements • Addition of independent wound review/assessments • Updates to core lab requirements • Update of statistical considerations / approach • Update of success criteria • Addition of unscheduled visits related to CLI • Updates of potential risks and benefits • Updates of safety reporting requirements	• Clarification • Updates to support enrollment for the trial • Revision to address FDA comments from pre-submission review
C	26 Mar 2018	90702637_Rev Ver AI	• Revision Date	• Version date updated from 05 March 2018 to 26 March 2018	• Correction of date
D	28 Mar 2018	90702637_Rev Ver AI	• 19. Safety Reporting	• Updates of safety reporting requirements	• Correction (missing text added)

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			• 26. Abbreviations and Definitions	• Update of definitions	• Definition added (Technical Success)
E	23 Sep 2019	90702637_Rev Ver AK	• 2. Protocol synopsis • 6. Trial Objectives and Endpoints • 7. Study Design • 8. Subject Selection • 9. Subject Accountability • 10. Trial Methods • 11. Statistical Considerations • 13. Data Management • 19. Safety Reporting • 26. Abbreviations and Definitions	• Update to additional endpoints • Update of 'enrolled' definition for phase B • Update of target lesion requirements • Addition of potential sites • Addition of 48 and 60 month follow-up for survival status • Update of in- and exclusion criteria (RVD requirements for phase A and phase B, clarification on number of target vessels/lesions, update in timing of pre-existing conditions, Rutherford and wound requirements) • Update of timing of pre-procedure assessments • Clarification of core lab review and central assessment of study data • Update to follow-up after subject withdrawal • Update to potential risks and Benefits section to add meta-analysis results • Clarification of start point for safety reporting and investigator reporting requirements • Update of definitions (clarification of inflow and outflow lesions, addition of definitions)	• Correction (aligning protocol summary with body of protocol) • Clarification • Updates per FDA request

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
F	02 Jul 2021	90702637_Rev Ver AP	• 2. Protocol Synopsis • 5. Device Description • 6. Trial Objectives and Endpoints • 7. Study Design • 9. Subject Accountability • 10. Trial Methods • 11. Statistical Considerations • 13. Data Management • 14. Deviations • 15. Device Accountability for Products Labelled Investigational • 16. Compliance • 19. Safety Reporting • 22. Suspension or Termination • 23. Study Registration and Results • 27. Abbreviations and Definitions	• Update to primary endpoint timing and statistical methods, stent sizes, removal of discussion of interim analysis, update to study assessment (12-month DSA/CTA for non-diagnostic DUS), update to trial duration and description, clarification to start of Phase B enrollment • Clarification to device name and clarification that Investigator Brochure is provided to study sites. • Clarification to study assessment requirements and safety event reporting • Addition of statistical considerations for bailout subjects • Clarification of EDC activities and access during study closure. • Clarification to handling of deviations related to COVID-19; clarification that sponsor will not approve protocol waivers. • Clarification of site device accountability requirements for investigational devices. • Clarification of site and investigator responsibilities • Clarification of reportable events, reporting requirements and definitions. • Clarification of circumstances that could lead to premature trial termination.	• Updates per FDA discussion and feedback • Clarification • Correction • Updates per applicable regulations and guidance

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
				• Addition of study registration and availability of clinical investigation report. • Update of definitions (clarification of source document and source data, addition of definitions)	

2. Protocol Synopsis

<table>
<tr><th colspan="2">A Randomized Trial comparing the Drug-Eluting Stent (DES) Below-the-Knee (BTK) Vascular Stent System (DES BTK Vascular Stent System) vs Percutaneous Transluminal Angioplasty (PTA) treating Infrapopliteal Lesions in Subjects with Critical Limb Ischemia
The SAVAL Pivotal Trial</th></tr>
<tr><td>Trial Objective(s)</td><td>Primary objective: To demonstrate a superior patency rate and acceptable safety rates in below the knee arteries with lesions treated with the DES BTK Vascular Stent System vs percutaneous transluminal angioplasty (PTA).
Secondary objective: To collect additional information on limb salvage and overall quality of life in this patient population.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The DES BTK Vascular Stent System is intended to improve luminal diameter in critical limb ischemia (CLI) subjects with lesions of the infrapopliteal arteries with reference vessel diameters (RVD) ranging from 2.5 – 3.75mm and total lesion lengths up to 140mm.</td></tr>
<tr><td>Test Device and Sizes</td><td>The DES BTK Vascular Stent System for treatment of lesions in the infrapopliteal arteries.
Phase A of the trial will include a single stent size.
<table>
<tr><th>Stent Diameter (mm)</th><th>Stent Length (mm)</th><th>Reference Vessel Diameter</th></tr>
<tr><td>3.5</td><td>80</td><td>2.5 – 3.25mm</td></tr>
</table>
The following additional stent sizes will be added to the trial upon regulatory approval.
<table>
<tr><th>Stent Diameter (mm)</th><th>Stent Length (mm)</th><th>Reference Vessel Diameter</th></tr>
<tr><td>3.0</td><td>30, 80, 120</td><td>2.5 – 2.75mm</td></tr>
<tr><td>3.5</td><td>30, 80, 120</td><td>2.5 – 3.25mm</td></tr>
<tr><td>4.0</td><td>30, 80, 120</td><td>3.0– 3.75mm</td></tr>
</table></td></tr>
<tr><td>Control Device</td><td>Percutaneous Transluminal Angioplasty (PTA) balloon catheter.</td></tr>
<tr><td>Trial Design</td><td>The trial will be conducted in 2 phases.
Phase A is a global, pivotal, prospective, multicenter, 2:1 randomized controlled trial (RCT) evaluating the safety and effectiveness of the DES</td></tr>
</table>

	BTK Vascular Stent System compared to PTA for the treatment of lesions located in the arteries below the knee in subjects with CLI. In phase B of the trial the DES BTK Vascular Stent will be implanted into an additional 100 subjects to collect ongoing safety and effectiveness data.
Planned Number of Subjects	1. Phase A randomized controlled trial (RCT): Approximately 201 subjects are expected to be enrolled to support a 2:1 randomization. 2. Phase B non-randomized: Approximately 100 additional subjects are expected to be enrolled in phase B, which is structured as a non-randomized single arm study, in which all subjects will be treated with the DES BTK Vascular Stent System.
Planned Number of Investigational Centers/ Countries	The trial will be conducted in the United States, Europe, Japan and potentially Singapore, Taiwan and/or Hong Kong, at up to 50 investigational centers, with up to 35 centers located in the US. Enrollment is expected to be distributed approximately equally across regions.
Phase A RCT	
Primary Effectiveness Endpoint	***Primary Effectiveness Endpoint (Phase A RCT)*** 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 DES BTK treatment group is superior to the PTA treatment group at an overall one-sided significance level of 2.5%. Primary vessel patency is defined as a binary endpoint to be determined via duplex ultrasound (DUS) measuring flow or no flow at the 12-month follow-up visit in the absence of clinically-driven target lesion revascularization (TLR) or bypass of the target lesion. All DUS readings will be assessed by an independent core laboratory.
Primary Safety Endpoint(s)	***Primary Safety Endpoint (Phase A RCT)*** The primary safety endpoint assesses major adverse events (MAE) at 12 months post-procedure. This safety endpoint is designed to demonstrate that the 12-month MAE-free rate for the DES BTK treatment group is non-inferior to the PTA treatment group at an overall one-sided significance level of 2.5%. A major adverse event is defined as: • Above ankle amputation of the index limb • Major re-intervention (new bypass graft, jump/interposition graft, or thrombectomy/thrombolysis)

	• Perioperative (30 day) mortality
Additional Endpoints	• Primary and assisted-primary patency at 1, 6, 12, 24, and 36 months post-procedure • Clinically-driven target lesion revascularization (TLR) rate at each time point • Hemodynamic outcomes (changes in Ankle-Brachial Index [ABI] and/or Toe-Brachial Index [TBI]) at 6 and 12 months post procedure • Wound assessment (changes in wound characteristics) • Major amputation rate • Change in Rutherford classification at 3, 6, 12, 24, and 36 months post procedure • Quality of Life (QOL) changes at 1, 3, 6 and 12 months post procedure • Adverse events (AEs) at each time point (to be classified as major, serious, non-serious, unanticipated, procedure-related and device-related) • 30-day unplanned hospital readmission rate[1] • Survival rate at 4 years and 5 years post-procedure
Method of Assigning Subjects to Treatment	Phase A RCT: Eligible subjects will be randomized in a 2:1 fashion (2 DES BTK to 1 PTA).
Phase B Non-Randomized	
Primary Safety Endpoint	***Primary safety endpoint (Phase B non-randomized)*** The primary safety endpoint assesses MAEs at 12 months post-procedure. This safety endpoint is designed to demonstrate that the 12-month MAE-free rate in subjects treated with the DES BTK Vascular Stent System exceeds a performance goal of 71% at an overall one-sided significance level of 2.5%.[2] Note that the 12-month primary patency rate will be observed in phase B non-randomized. A major adverse event is defined as: • Above ankle amputation of the index limb • Major re-intervention (new bypass graft, jump/interposition graft, or thrombectomy/thrombolysis) • Perioperative (30 day) mortality

Additional Endpoints	*Patency-Based Assessments* • Primary and assisted-primary patency at 1, 6, 12, 24, and 36 months post procedure • Need for clinically-driven TLR *Therapeutic success at 12 months post procedure* • Rutherford 4: Ischemic pain relief • Rutherford 5: Partial or complete healing of wound *Other Assessments* • Change in Rutherford classification at 3, 6, 12, 24 and 36 months post procedure • QOL changes at 1, 3, 6, and 12 months post procedure • Hemodynamic outcomes (changes in ABI and/or TBI) at 6 and 12 months post procedure • Wound assessment (changes in wound characteristics) • Limb salvage at each time point • Major amputation-free survival • Adverse events at each time point (to be classified as major, serious, non-serious, unanticipated, procedure-related and device-related) • 30-day unplanned hospital readmission rate • Survival rate at 4 years and 5 years post-procedure
Method of Assigning Subjects to Treatment	All subjects enrolled in phase B non-randomized will be treated with the DES BTK Vascular Stent System.
Follow-up Schedule	*Follow-up visit Schedule:* • Follow-up office visits are required at 1, 3, 6, 12, 24, and 36 months post procedure • Telephone follow-up visits are required at 18 and 30 months post procedure • Telephone follow-up visit and/or medical chart review and/or publicly available records consultation at 48 months and 60 months post-procedure *Endpoint Assessment:* • Assessment of the primary effectiveness endpoint will occur at the 12-month follow-up visit • Assessment of the primary safety endpoint will occur at the 12-month follow-up visit Planned protocol-required testing:

	• ABI and TBI, when subject condition permits (ie, no toe amputation or presence of calcified/incompressible vessels) • Angiography during the index procedure to assess technical success and procedural success • Duplex ultrasound (Note: If a diagnostic duplex ultrasound cannot be adequately achieved for the 12-month follow-up visit, then computerized tomography angiography [CTA] or digital subtraction [DSA] angiography must be conducted) • High definition x-ray of the DES BTK test device(s) • Wound assessment and image Phase A RCT will be considered complete for the primary effectiveness endpoint and the primary safety endpoint after all subjects in phase A RCT have completed the 12-month follow-up visit, are withdrawn prior to the 12-month follow-up visit, have died or, the last 12-month follow-up visit window has closed. Phase B non-randomized will be considered complete for the primary safety endpoint after all subjects in phase B have completed the 12-month follow-up visit, are withdrawn prior to the 12-month follow-up visit, have died or, the last 12-month follow-up visit window has closed. The entire trial will be considered complete with regard to all follow-up, after all subjects have completed the 60-month follow-up visit, are withdrawn prior to the 60-month follow-up visit, have died or, the last 60-month follow-up visit window has closed.
Trial Duration	***Phase A RCT*** Enrollment in phase A RCT is expected to take approximately two years to enroll the approximately 201 subjects, and 5 years of follow-up is planned. ***Phase B non-randomized:*** Enrollment in phase B non-randomized is planned to start after enrollment in phase A RCT is complete. The timing for beginning phase B enrollment will be communicated by the Boston Scientific clinical trial team. Enrollment of the approximately 100 additional subjects into phase B non-randomized is expected to take approximately 1 year, and 5 years of follow-up is planned. The total duration from the enrollment of the first subject in phase A RCT to the last follow-up in phase B non-randomized cohort is expected to be approximately 11 years.
Participant Duration	Subject participation will be 5 years post index procedure. Subjects, who are enrolled/randomized into the DES BTK arm but do not have the

	DES BTK stent successfully implanted, will be followed for 30 days for safety, and be withdrawn from the trial afterwards.
Trial Enrollment	There are 2 stages of evaluation for a subject's trial enrollment: ***1. Pre-procedure criteria*** Trial candidates must satisfy all pre-procedure inclusion criteria and none of the pre-procedure exclusion criteria prior to the intervention. ***2. Intra-procedural criteria*** Subjects must satisfy all intra-procedure inclusion criteria and none of the intra-procedure exclusion criteria to be eligible for randomization/enrollment into the trial. Enrollment occurs at the time of randomization (i.e. when a treatment assignment is received by the study site) for phase A RCT and at the time the DES BTK stent is introduced into the subject's vasculature for phase B non-randomized.
Pre-procedure Inclusion Criteria	1. Subject is 18 years or older and has signed and dated the trial informed consent form (ICF). Note: For subjects in Japan who are less than 20 years of age, the subject's legal representative must provide written informed consent in addition to the subject 2. Subject is willing and able to comply with the trial testing, procedures and follow-up schedule 3. Subject has chronic, symptomatic lower limb ischemia, determined by Rutherford categories 4 or 5 in the target limb, with wound(s) confined to toes/forefoot 4. Subject is a male or non-pregnant female. If female of child-bearing potential, and if sexually active must be using, or agree to use, a medically–acceptable method of birth control as confirmed by the investigator
Pre-Procedure Exclusion Criteria	1. Life expectancy ≤ 1 year 2. Stroke ≤ 90 days prior to the procedure date 3. Prior or planned major amputation in the target limb 4. Previous surgery in the target vessel(s) (including prior ipsilateral crural bypass) 5. Previously implanted stent in the target vessel(s) 6. Failed PTA of target lesion/vessel ≤ 60 days prior to the procedure date 7. Renal failure as measured by a GFR ≤ 30ml/min per 1.73m^2, measured ≤ 30 days prior to the procedure date 8. Subject has a platelet count ≤ 50 or ≥ 600 X $10^3/\mu L$ ≤ 30 days prior to the procedure date 9. NYHA class IV heart failure

	10. Subject has symptomatic coronary artery disease (ie, unstable angina) 11. History of myocardial infarction or thrombolysis ≤ 90 days prior to the procedure date 12. Non-atherosclerotic disease resulting in occlusion (eg, embolism, Buerger's disease, vasculitis) 13. Subject is currently taking Canagliflozin 14. Body Mass Index (BMI) <18 15. Active septicemia or bacteremia 16. Coagulation disorder, including hypercoagulability 17. Contraindication to anticoagulation or antiplatelet therapy 18. Known allergies to stent or stent components 19. Known allergy to contrast media that cannot be adequately pre-medicated prior to the interventional procedure 20. Known hypersensitivity to heparin 21. Subject is on a high dose of steroids or is on immunosuppressive therapy 22. Subject is currently participating, or plans to participate in, another investigational trial that may confound the results of this trial (unless written approval is received from the Boston Scientific study team)
Intra-Procedure Inclusion Criteria	1. Stenotic, restenotic or occlusive target lesion(s) located in the tibioperoneal trunk, anterior tibial, posterior tibial and/or peroneal artery(ies). • Target lesion(s) must be at least 4cm above the ankle joint • A single target lesion per vessel, in up to 2 vessels, in a single limb • Degree of stenosis ≥ 70% by visual angiographic assessment • Reference vessel diameter (RVD) is between 2.5 – 3.25mm for phase A RCT • RVD is between 2.5 – 3.75mm for phase B non-randomized (Note: RVD is dependent on stent size being used. Refer to DFU for specific requirements) • Total target lesion length (or series of lesion segments) to be treated is ≤ 70mm for phase A RCT prior to data monitoring committee (DMC) approval for stent overlap (Note: Lesion segment(s) must be fully covered with one DES BTK stent, if randomized to stent) • Total target lesion length (or series of lesion segments) to be treated is ≤ 140 mm for phase A RCT after DMC approval for stent overlap (Note: Lesion segment(s) must be fully covered with up to two DES BTK stents, if randomized to stent) • Total target lesion length (or series of lesion segments) to be treated is ≤ 140mm for phase B non-randomized

	(Note: Lesion segment(s) must be fully covered with up to two DES BTK stents) 2. Target vessel(s) reconstitute(s) at or above the stenting limit zone (4cm above the ankle joint) 3. Target lesion(s) is located in an area that may be stented without blocking access to patent main branches 4. Treatment of all above the knee inflow lesion(s) is successful prior to treatment of the target lesion 5. Guidewire has successfully crossed the target lesion(s)
Intra-procedure Exclusion Criteria	1. Angiographic evidence of intra-arterial acute/subacute thrombus or presence of atheroembolism 2. Treatment required in > 2 target vessels (Note: a target lesion originating in one vessel and extending into another vessel is considered 1 target vessel) 3. Treatment requires the use of alternate therapy in the target vessel(s)/lesion(s), (eg, atherectomy, cutting balloon, re-entry devices, laser, radiation therapy) 4. Aneurysm is present in the target vessel(s) 5. Extremely calcified lesions
Multiple Interventions / Index Procedure	Multiple interventions in the target limb are permitted during the index procedure for the treatment of above the knee inflow lesions (lesions located in the iliac artery, superficial femoral artery and/or popliteal artery). Inflow lesions may be treated according to the investigator's standard procedures using commercially available devices. If atherectomy is performed, the use of an embolic protection device is strongly recommended. The inflow interventions must be deemed successful (eg, absence of distal embolization, optimal restoration of inflow, etc) prior to the randomization and/or treatment of the target lesion(s). Drug-coated balloons are not permitted for treatment of the target lesion(s) in the trial. Treatment of outflow lesion(s) (lesions located in the segment of the target vessel distal to the target lesion) is not permitted. Successful guidewire crossing of all target lesion(s) is required prior to randomization/enrollment into the trial.
Statistical Methods in Phase A RCT	
Primary Effectiveness Statistical Hypothesis and	The primary effectiveness hypothesis to be tested is that the 12-month primary patency in subjects treated with the DES BTK Vascular Stent System is superior to subjects treated with PTA at an overall one-sided significance level of 2.5%.

Test Method **Phase A RCT**	A Wald z-test for the difference in 12-month primary patency will be used to assess the effectiveness hypothesis. H_0: Pt - Pc ≤ 0 H_1: Pt - Pc > 0 where Pt and Pc are the 12-month primary patency for the DES BTK stent and PTA, respectively.
Primary Safety Statistical Hypothesis and Test Method **Phase A RCT**	The primary safety hypothesis to be tested is that the 12-month MAE-free rate in subjects treated with the DES BTK Vascular Stent System is non-inferior to subjects treated with PTA at an overall one-sided significance level of 2.5%. A Wald z-test for the difference in 12-month MAE-free rate will be used to assess the safety hypothesis. H_0: Pt - Pc ≤ Δ H_1: Pt - Pc > Δ where Pt and Pc are the 12-month MAE-free rate for DES BTK stent and PTA, respectively, and Δ (delta) is the non-inferiority margin of -10%.[3] [4]
Success Criteria for Phase A RCT	The DES BTK Vascular Stent System will be concluded to be superior to PTA for device effectiveness if the one-sided lower bound of 97.5% confidence interval on the difference between treatment groups (DES BTK – PTA) in 12-month primary patency is greater than zero. The DES BTK Vascular Stent System will be concluded to have no safety concerns if the one-sided lower bound of 97.5% confidence interval on the difference between treatment groups (DES BTK – PTA) in 12-month MAE-free is greater than -0.1. The trial will be concluded a success if both the primary effectiveness endpoint and the primary safety endpoint are met.
Sample Size Parameters **Phase A RCT**	The overall sample size is driven by the primary effectiveness endpoint. Approximately 201 subjects are planned to be enrolled in phase A RCT. The sample size justification for phase A RCT is based on the following assumptions. • Power ≥ 84% • One-sided overall significance level (alpha) = 2.5% • Expected PTA 12-month primary patency = 40% • DES BTK to demonstrate 25% treatment effect • Allocation (DES BTK vs PTA) = 2:1 • A minimum of 150 evaluable subjects are required at 12 months (ideally 100 in DES BTK arm and 50 in PTA arm) • Attrition rate in 12 months ≤25%

	• Approximately 201 subjects are planned to be randomized in 2:1 fashion prior to the procedure
Analysis Sets **Phase A RCT**	The intention-to-treat (ITT) population will be the primary analysis set for assessing the primary hypotheses. Both per-protocol (PP) and as-treated (AT) populations will be the secondary analyses sets for reference. • ITT: all randomized subjects will be included in the ITT analysis set, regardless of whether the subjects receive the assigned treatment. The DES BTK and PTA arms will be compared as randomized. • PP: only randomized subjects who receive the assigned index treatment will be included in the PP analysis set. The DES BTK and PTA arms will be compared as randomized and correctly received index treatment. • AT: all subjects who receive either the DES BTK stent or PTA at the index procedure will be included in the AT analysis set. DES BTK and PTA arms will be compared as treated, excluding subjects who do not receive the DES BTK stent or PTA.
Statistical Methods in Phase B Non-randomized	
Testing Hypotheses Strategy **Phase B Non-randomized**	The primary safety hypothesis will be tested at 12 months post index procedure for all evaluable subjects from phase A RCT and the additional 100 phase B subjects.
Primary Safety Statistical Hypothesis and Test Method **Phase B Non-randomized**	The primary safety hypothesis to be tested is that the 12-month MAE-free rate in subjects treated with the DES BTK Vascular Stent System exceeds a performance goal (PG) of 71%[1] at one-sided significance level of 2.5%. A Wald z-test will be used to assess the safety hypothesis of meeting the PG in the 12-month MAE-free rate. H_0: Pt ≤ PG (not met) H_1: Pt > PG (met) where Pt is the 12-month MAE-free rate for the subjects treated with the DES BTK Vascular Stent System and the PG is the performance goal.
Success Criteria **Phase B Non-randomized**	The DES BTK Vascular Stent System will be concluded as meeting the PG for device safety if the one-sided lower bound of 97.5% confidence interval on the observed 12-month MAE-free rate is greater than 0.71.
Sample Size Parameters	The sample size is driven by the safety PG. • Power ≥ 80%

Phase B Non-randomized	• One-sided significance level (alpha) = 2.5% • Safety PG = 71%[2] in the 12-month MAE-free rate • Expected 12-month MAE-free rate = 80% • A minimum of 186 (DES BTK) evaluable subjects are required at 12 months • Attrition rate at 12 months ≤ 20% • Up to 234 (DES BTK) subjects are planned to be enrolled, including 134 DES BTK subjects from phase A RCT and an additional 100 DES BTK subjects to be enrolled in phase B non-randomized.
Analysis Set **Phase B Non-randomized**	All subjects who receive the DES BTK Vascular Stent System will be assessed against the pre-specified safety PG.
Medications	Anti-coagulation and antiplatelet therapy is to be administered prior to and during the index procedure according to the investigator's standard procedures. Dual antiplatelet therapy is required post-procedure through the 6-month visit and is strongly recommended to continue through the 12-month visit for subjects who receive the DES BTK stent.* Subjects who are randomized to PTA in phase A RCT will receive antiplatelet therapy according to the investigator's standard of care. *A subject may be exempt from dual antiplatelet requirement when anticoagulation therapy is required for comorbidity treatment and when, in the judgement of the investigator, the addition of dual antiplatelet therapy would pose an unacceptable hemorrhage risk.
DMC and CEC	The data monitoring committee (DMC) will review overall trial conduct and safety. The DMC will review approximately 46 randomized subjects' aggregate safety data for the approval to use overlapping stents in the trial. The DMC charter will outline this process. The clinical events committee (CEC) will adjudicate the following endpoints and major adverse events reported by the trial investigators: • All deaths • Clinically-driven TLR • TVR • Target limb major amputations • Target Lesion stent thrombosis
Core Laboratories / Central	The following core laboratories will be established for the central assessment of key data collected during the trial: • Angiography:

assessment of study data	○ To assess angiograms taken during the index procedure, and in the follow-up period for subsequent revascularization procedures when collected according to the investigational center's standard procedures ○ To assess CTA or DSA angiographies taken at the 12-month follow-up visit in case the 12-month DUS is non-diagnostic ○ To confirm stent fractures identified by the X-ray core lab • Ultrasound: to assess ultrasounds taken during the follow-up period for lesion and stent patency • X-ray: to assess high definition x-rays for stent integrity • Independent Wound Reviewer: to review wound assessment data and images.

3. Table of Contents

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4. Introduction and Background

Critical Limb Ischemia (CLI) is a progression of peripheral artery disease (PAD), characterized by severe obstruction of arteries (especially in the lower limbs) which reduces blood flow to the extremities and places patient tissue viability at risk. [5] Patients with CLI experience severely debilitating clinical outcomes, including severe pain in the impacted limb even at rest, risk of open ulceration, gangrene and, if not treated properly, amputation of limb(s). These outcomes reduce patient mobility and quality of life. [5] Patients with CLI also experience increased risk of mortality, increasing further for those undergoing limb amputations. Diabetics with CLI are at particularly high risk for advanced complications; studies indicate that within one year of CLI diagnosis, 40% to 50% of diabetics will experience an amputation. [6]

The standard of care for CLI patients has historically utilized one of two methods for revascularization of diseased infrapopliteal vessels, either by surgical bypass or percutaneous transluminal angioplasty (PTA). While surgical bypass has shown to be a potential avenue for revascularization of BTK arteries and was considered the frontline therapy for CLI patients, the surgery is invasive and technically challenging, especially considering the fragile health state of the affected population. Due to these challenges, this procedure continues to experience significant variability in outcomes, patient healing, and costs. [7] There are important limitations and risks associated with bypass surgery, including up to 20% of patients experiencing significant postoperative morbidity and 10 to 20% of patients experiencing frequent wound complications. Additionally, new stenosis within the vein graft conduit occurs in 30% to 40% of patients within the first two years after surgery.

In recent years, the arrival of endovascular treatment of CLI has been driven by the continued evolution of catheter-based technologies due to the benefits of a less invasive approach in treating this fragile population.[8] It is well established that recovery from PTA is significantly faster than open surgery. Patients treated with PTA do not experience common surgical complications associated with bypass, such as wound morbidity. PTA has been shown to have similar outcomes to that of surgical bypass. [9,10]

Intravascular stents were developed in response to the inability of PTA to prevent immediate or near-term loss of arterial patency due to dissection or lesion recoil. The scaffolding support provided by stent technology is a primary reason for their utilization. Drug-eluting stents were developed to reduce neointimal hyperplasia to address the impact of restenosis rates associated with PTA therapy. Infrapopliteal atherosclerotic lesions characterized by longer calcified lesions in smaller diameter vasculature do not respond well to PTA. [11]

The benefits of using short coronary drug-eluting stents has been well-studied in infrapopliteal lesions; randomized clinical trials have shown a benefit in terms of patency and re-intervention rates as compared to PTA [3,4,12] with long-term results reported out to 5 years. [13] However, none of these coronary drug-eluting stents have been approved in the United States for infrapopliteal use. There are major limitations of using coronary drug-eluting stents below the knee, including the limited available lengths relative to the artery lengths to be treated, relative inflexibility, and risk of fracture given the unique conditions of infrapopliteal

anatomy. The DES BTK Vascular Stent System was designed to address the requirements for treatment of the longer lesions associated with CLI below the knee.

4.1. *Boston Scientific Drug-Eluting Stent Regulatory Approval History*

Boston Scientific has an extensive global market history of drug-eluting stents, as summarized in **Table 4.1-1**.

Table 4.1-1: Boston Scientific Drug-Eluting Stent Regulatory Approval Summary

Device	CE Mark Date	Associated IDE#	Associated PMA#	Japan Approval
ELUVIA	Feb 2016	G150171	P180011	Dec.6.2018 23000BZX00374000
PROMUS Element	Oct. 2009	NA	NA	Feb.8.2012* 22400BZX00031000
PROMUS Element Plus	NA	G080202	P110010	Sep.6.2012* 22400BZX00332000
PROMUS PREMIER	Feb 2013	G080202	P110010	Apr.7.2014* 22600BZX00181000 Large Vessel Nov.28.2014 22600BZX00504000
Taxus Liberte	NA	G060237	P060008	Jan.28.2009* 22100BZX00049000
ION/Taxus Element	NA	G060237	P100023	Sep.5.2011* 22300BZX00378000
Taxus Express 2	NA	G060237	P030025	Mar.30.2007* 21900BZX00340000

* The first approved date.

4.2. *Trial Rationale*

Critical limb ischemia is a debilitating disease, associated with poor clinical outcomes, a high rate of amputations, and overall decreased quality of life. Based on the significant clinical complications associated with bypass surgery, the presence of chronic total occlusions, the restenotic characteristics with PTA therapies, and the limitations of using coronary stents in BTK indications, the need for an alternative therapy exists.

The DES BTK Vascular Stent System aims to address these treatment gaps and clinical outcomes not adequately addressed by surgical bypass and/or PTA. The DES BTK Vascular Stent System was designed for the unique considerations of infrapopliteal disease, including long, tortuous lesions and the need for a mechanism of providing an anti-proliferative agent to calcified vessels. The DES BTK Vascular Stent System incorporates existing successful peripheral drug-eluting stent technology to treat a similar disease state below the knee.

5. Device Description

The DES BTK Vascular Stent System or DES BTK (SAVAL) Drug-Eluting Vascular Stent System is a medical device containing an ancillary medicinal substance, that provides a

mechanical scaffold for vascular lumen support (the stent component) and a pharmacological agent (paclitaxel) targeted towards reducing the injury response that leads to restenosis after stent implantation. All references made herein to the DES BTK device and DES BTK Vascular Stent System are synonymous with the SAVAL device and SAVAL Drug-Eluting Vascular Stent System, respectively.

The DES BTK Vascular Stent System is comprised of 3 main parts:

- Stent component
- Stent coating (primer layer and active layer with drug substance)
- Delivery system

5.1. *The DES BTK Vascular Stent System*

The DES BTK stent (**Figure 5.1-1**) is a laser cut self-expanding stent composed of a nickel titanium alloy (nitinol). Shape memory alloys exhibit special properties including super elasticity and shape memory. Nitinol can exist in two phases: a martensite phase and an austenite phase. Changing from the martensite phase to the austenite phase, or the reverse, is referred to as a phase transformation. During a phase transformation, the atoms rearrange and allow the material to exhibit a different behavior. Phase transformations can occur as a result of temperature or stress changes in the material.

During manufacture, the DES BTK stent undergoes heat treatments that impart "memory" on the nitinol material, allowing it to expand to a specified diameter when exposed to certain conditions of stress or temperature. Then the stent is loaded into the delivery system, which constrains the stent until it is deployed at the target lesion. As the stent is exposed to body temperature, it expands to appose the vessel wall. The blood vessel restricts full expansion of the stent diameter; therefore, recommended stent to vessel sizing is up to one to one fourth millimeter less than the stent nominal diameter.

The DES BTK Drug-Eluting Vascular Stent System is intended to improve luminal diameter in the treatment of symptomatic de novo or restenotic lesions in the native infrapopliteal arteries with reference vessel diameters (RVD) ranging from 2.5 – 3.75mm.

The DES BTK Vascular Stent System is designed to optimize stent flexibility, radial/compressive strength, and fatigue properties for performance below the knee. The stent has three tantalum markers on the proximal and distal ends of the stent, for a total of six markers on each stent.

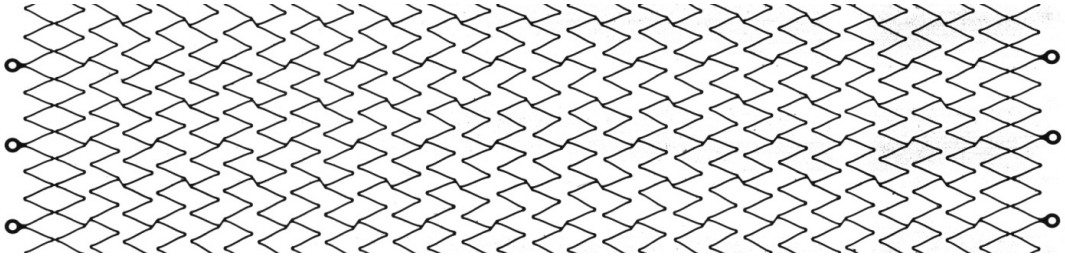
Table 5.1-1: DES BTK stent size for Phase A randomized controlled trial (RCT)

Stent Diameter (mm)	Stent Length (mm)	Reference Vessel Diameter
3.5	80	2.5 – 3.25mm

Table 5.1-2: Additional stent sizes to be added for the trial upon regulatory approval

Stent Diameter (mm)	Stent Length (mm)	Reference Vessel Diameter
3.0	30, 80, 120	2.5 – 2.75mm
3.5	30, 80, 120	2.5 – 3.25mm
4.0	30, 80, 120	3.0 – 3.75mm

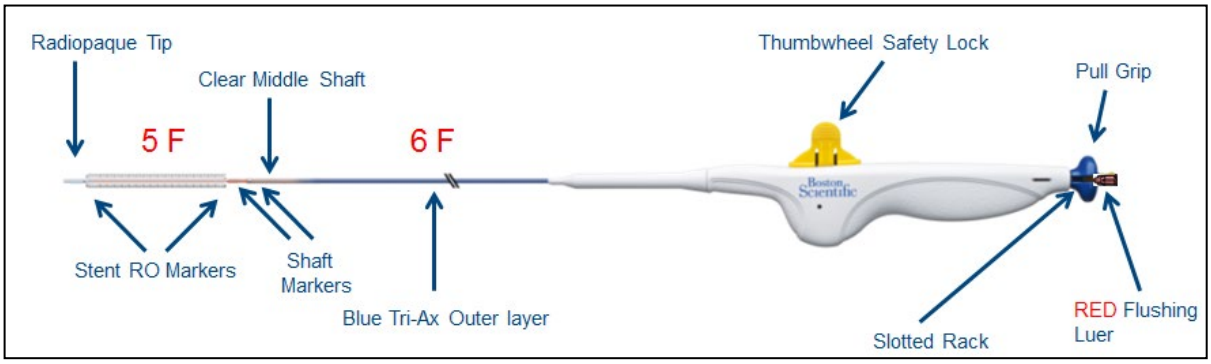
Figure 5.1-1: **DES BTK Geometry**



5.2. *DES BTK Delivery System*

The stent is constrained within a tapered delivery system which is 6F (2.1 mm maximum OD) at the proximal end and has a 5F (1.7 mm) crossing profile. 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 intended for use with 0.014 in (0.36 mm) guidewires. A radiopaque marker at the distal end of the delivery system aids in visibility during deployment. The DES BTK delivery system is offered in a 130 cm working length (**Figure 5.2-1**). Additional delivery systems may be added upon regulatory approval to include them in the trial.

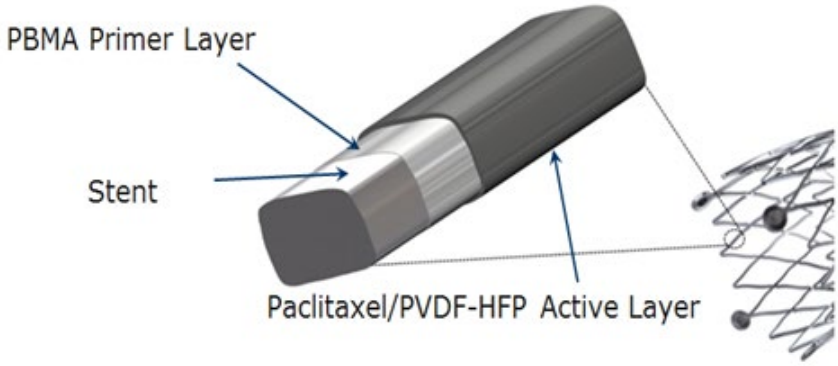
Figure 5.2-1: **DES BTK Delivery System**



5.3. *DES BTK Stent Coating*

The DES BTK stent is a self-expanding stent with a drug/polymer coating. The coating comprises two layers, an inner primer layer and an outer polymer matrix that contains an active pharmaceutical ingredient (paclitaxel). (**Figure 5.3-1**)

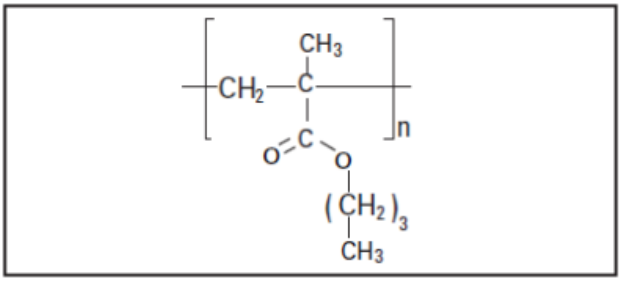
Figure 5.3-1: Dual Layer Illustration



5.3.1. Primer Polymer and Drug Matrix Co-polymer Carrier

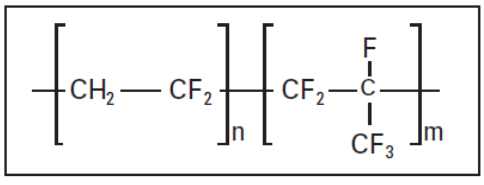
The stent contains a primer polymer layer poly(n-butyl methacrylate) (PBMA) between the bare metal stent and drug matrix layer. The chemical structure of PBMA is provided in **Figure 5.3-2**.

Figure 5.3-2: **Poly(n-butyl methacrylate) (PBMA)**



The drug matrix layer is comprised of a semi-crystalline random copolymer, poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP), blended with paclitaxel. The chemical structure of PVDF-HFP is provided in **Figure 5.3-3**.

Figure 5.3-3: Poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP)

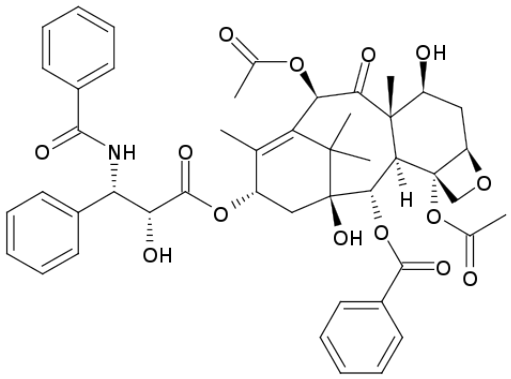


5.3.2. Paclitaxel Drug

The active pharmaceutical ingredient in the DES BTK vascular stent is paclitaxel (PTx). The chemical name of paclitaxel is: Benzenepropanoic acid, ß -(benzoylamino) - α- hydroxy – ,6,12 b – 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,4ß,4aß,6ß,9α (αR*,ßS*),11α,12α,12aα,12bα]]. Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol and a molecular formula of $C_{47}H_{51}NO_{14}$. It is highly lipophilic, insoluble in water, but freely soluble in methanol, ethanol, chloroform, ethyl acetate and dimethyl sulfoxide. [14,15] The chemical structure of paclitaxel is provided in **Figure 5.3-4**.

Figure 5.3-4: **Chemical Structure of Paclitaxel (PTx)**



Paclitaxel is an antiproliferative drug that induces irreversible polymerization of cell microtubules, thus inhibiting mitosis. It is widely used in antineoplastic chemotherapy of cancers; however, doses required in chemotherapeutic treatment are significantly higher per treatment cycle in cancer patients than in peripheral artery disease patients. [15] Paclitaxel has been shown to inhibit proliferation and migration of smooth muscle cells, effectively suppressing neointimal hyperplasia after vessel injury. [15, 16, 17] The drug-to-polymer formulation ratio in DES BTK stents is 1:9 with a resulting paclitaxel loading density (total weight of drug/unit of stent surface area) of 0.236 µg/mm^2.

5.4. *Manufacturer*

The DES BTK Vascular Stent System is manufactured by the Boston Scientific Corporation.

5.5. *Labeling of Investigational Device*

A copy of the directions for use (DFU) for the DES BTK Vascular Stent System and the patient implant card will be included in the manual of operations.

The DES BTK Vascular Stent System components or immediate package will be labeled with the following information: Name and place of the manufacturer, packer or distributor, Quantity of the contents, if appropriate and the following statement “CAUTION - Investigational device. Limited by United States law to investigational use.”

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

5.6. *Product Receipt and Tracking*

In order to allow shipment of investigational product to an investigational center, Boston Scientific (or designee) must declare in writing that the investigational center is activated and ready to enroll subjects. The investigator agrees not to implant or use an investigational device or product on any person except subjects who are enrolled into the SAVAL trial. The investigational product must only be used for the purpose of the clinical trial and in compliance to this clinical investigation plan.

Upon receipt of the investigational products, the center principal investigator or designated individual will visually inspect and notify Boston Scientific (or its designee) of any noted issues or discrepancies. The investigational product will be traced using an investigational product accountability log. Refer to section 15 Device/Equipment Accountability.

5.7. *Investigational Product Storage*

Investigational products must be stored in a secured and locked location accessible only to those delegated individuals who are authorized by the center principal investigator to access them.

5.8. *Product Returns*

The investigational product must be returned to Boston Scientific (or its designee) when it is no longer in use, regardless of the reason for removal from use. At the end of the trial enrollment, all unused investigational product provided for the trial will be returned to Boston Scientific.

5.9. *Control Device*

Commercially available percutaneous transluminal angioplasty balloons will be the control device for this trial. The PTA device used must be market-released in the investigational center's geography and the size (ie, diameter, balloon length and catheter length) will be determined by the investigator. The use of alternate therapy (eg, atherectomy, drug-coated balloons, cutting balloons, re-entry devices, laser, radiation therapy) is not permitted for treatment of the target lesion(s) in the trial.

6. Trial Objectives and Endpoints

Primary objective: To demonstrate a superior patency rate and acceptable safety rates in below the knee arteries with lesions treated with the DES BTK Vascular Stent System vs percutaneous transluminal angioplasty (PTA).

Secondary objective: To collect additional information on limb salvage and overall quality of life in this patient population.

6.1. *Phase A RCT*

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 DES BTK treatment group is superior to the PTA treatment group at an overall one-sided significance level of 2.5%.

Primary vessel patency is defined as a binary endpoint to be determined via duplex ultrasound measuring flow or no flow at the 12-month follow-up visit in the absence of clinically-driven target lesion revascularization or bypass of the target lesion.

Primary Safety Endpoint

The primary safety endpoint assesses major adverse events (MAE) at 12 months post-procedure. This safety endpoint is designed to demonstrate that the 12-month MAE-free rate for the DES BTK treatment group is non-inferior to the PTA treatment group at an overall one-sided significance level of 2.5%.

A major adverse event is defined as:

- Above ankle amputation of the index limb
- Major re-intervention (new bypass graft, jump/interposition graft, or thrombectomy/thrombolysis)
- Perioperative (30 day) mortality

Additional Endpoints

- Primary and assisted-primary patency at 1, 6, 12, 24, and 36 months post-procedure
- Clinically-driven TLR rate at each time point
- Hemodynamic outcomes (changes in ABI and/or TBI) at 6 and 12 months post procedure
- Wound assessment (changes in wound characteristics)
- Major amputation rate
- Change in Rutherford classification at 3, 6, 12, 24, and 36 months post procedure
- Quality of Life (QOL) changes at 1, 3, 6 and 12 months post procedure
- Adverse events (AEs) at each time point (to be classified as major, serious, non-serious, unanticipated, procedure-related and device-related)
- 30-day unplanned hospital readmission rate
- Survival rate at 4 years and 5 years post-procedure

6.2. *Phase B non-randomized*

Primary safety endpoint

The primary safety endpoint assesses MAEs at 12 months post-procedure. This safety endpoint is designed to demonstrate that the 12-month MAE-free rate in subjects treated with

the DES BTK Vascular Stent System exceeds a performance goal of 71% at an overall one-sided significance level of 2.5%.

Note that the 12-month primary patency rate will be observed in phase B non-randomized.

A Major adverse event is defined as:

- Above ankle amputation of the index limb
- Major re-intervention (new bypass graft, jump/interposition graft, or thrombectomy/thrombolysis)
- Perioperative (30 day) mortality

Additional Endpoints

Patency-Based Assessments

- Primary and assisted-primary patency at 1, 6, 12, 24, and 36 months post procedure
- Need for clinically-driven TLR

Therapeutic success at 12 months post procedure

- Rutherford 4: Ischemic pain relief
- Rutherford 5: Partial or complete healing of wound

Other Assessments

- Change in Rutherford classification at 3, 6, 12, 24 and 36 months post procedure
- QOL changes at 1, 3, 6, and 12 months post procedure
- Hemodynamic outcomes (changes in ABI and/or TBI) at 6 and 12 months post procedure
- Wound assessment (changes in wound characteristics)
- Limb salvage at each time point
- Major amputation-free survival
- Adverse events at each time point (to be classified as major, serious, non-serious, unanticipated, procedure-related and device-related)
- 30-day unplanned hospital readmission rate
- Survival rate at 4 years and 5 years post-procedure

7. Study Design

7.1. *Phase A RCT*

A global, pivotal, prospective, multicenter, 2:1 randomized controlled trial evaluating the safety and effectiveness of the DES BTK Vascular Stent System compared to standard percutaneous transluminal angioplasty (PTA) for the treatment of infrapopliteal artery lesions in subjects with critical limb ischemia. Phase A RCT will include one size of the device: 3.5 mm x 80 mm. Additional stent sizes will be added to the trial upon regulatory approval. Refer to section 5.1 The DES BTK Vascular Stent System.

7.2. *Phase B non-randomized*

A global, prospective, multicenter, non-randomized trial collecting additional safety and effectiveness data for the DES BTK Vascular Stent System to treat infrapopliteal artery lesions in subjects with CLI.

7.3. *Scale and Duration*

Approximately 201 subjects will be randomized/enrolled to support a 2:1 randomization in the phase A RCT.

Approximately 100 additional subjects are expected to be enrolled in phase B non-randomized, which is structured as a non-randomized single arm study, in which all subjects will be treated with the DES BTK Vascular Stent System.

The trial will be conducted in the United States, Europe, Japan and potentially Singapore, Taiwan and/or Hong Kong, at up to 50 investigational centers, with up to 35 centers located in the US. Enrollment is expected to be distributed approximately equally across regions.

Inclusion and exclusion criteria will be the same for both phases of the trial, with the exception of the target lesion length (prior to DMC approval for stent overlap) and the reference vessel diameter (RVD).

Phase A RCT is expected to take approximately 2 years to enroll the approximately 201 subjects, and 5 years of follow-up is planned.

Enrollment in phase B non-randomized will begin after enrollment into phase A RCT is complete. The timing for beginning phase B enrollment will be communicated by the Boston Scientific clinical trial team.

Phase B non-randomized is expected to take approximately 1 year to enroll the additional 100 subjects, and 5 years of follow-up is planned.

Clinical follow-up will be the same for both trial phases, with required trial visits at 1, 3, 6, 12, 24 and 36 months post procedure. Telephone follow-up visits will be completed at 18 and 30 months post procedure. Telephone follow-up visit and/or medical chart review and/or publicly available records consultation will be completed at 48 months and 60 months post-procedure.

The total duration from the enrollment of the first subject into phase A RCT to the last follow-up in phase B non-randomized is expected to be approximately 11 years.

Figure 7.3-1: DES BTK Phase A RCT Design

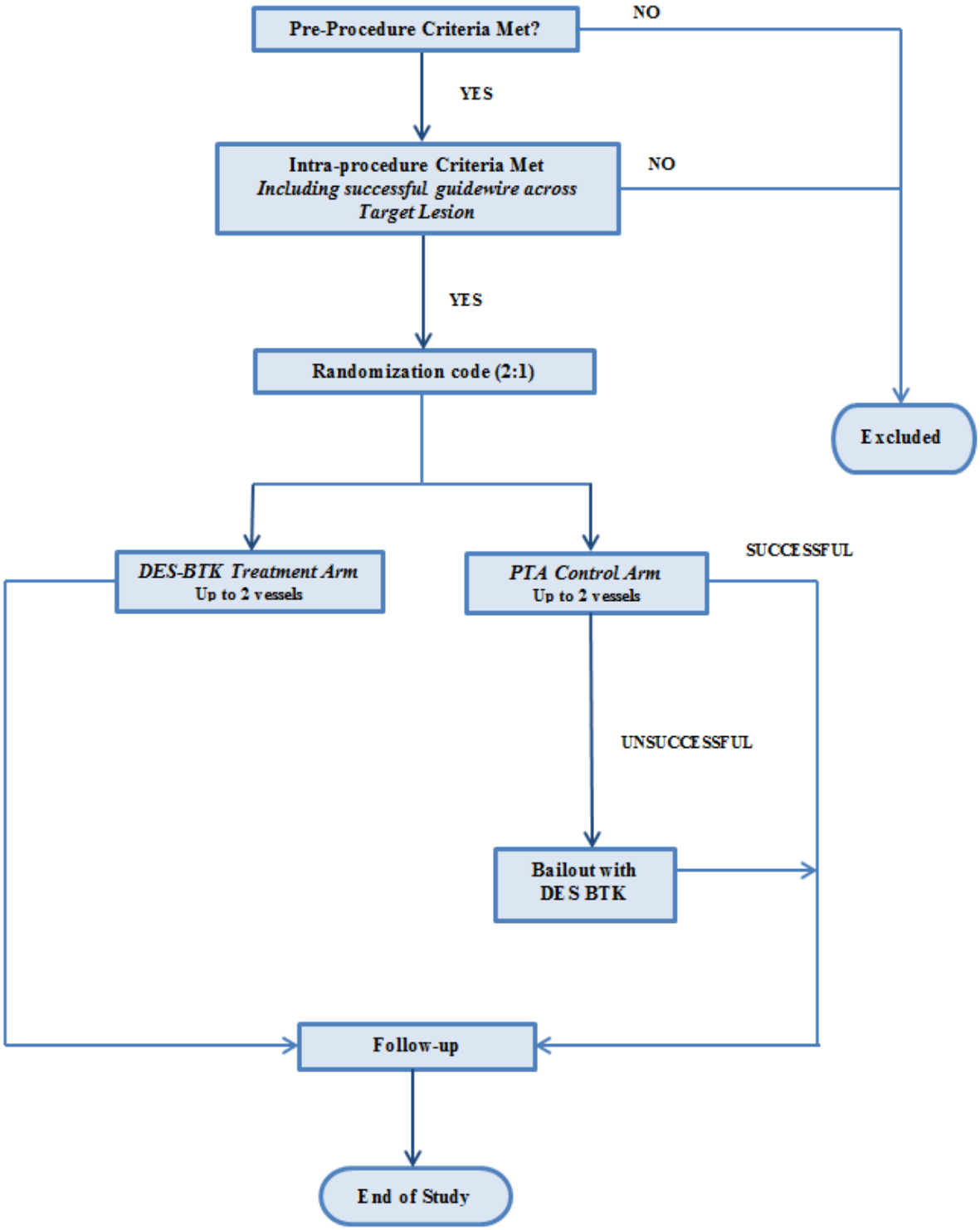
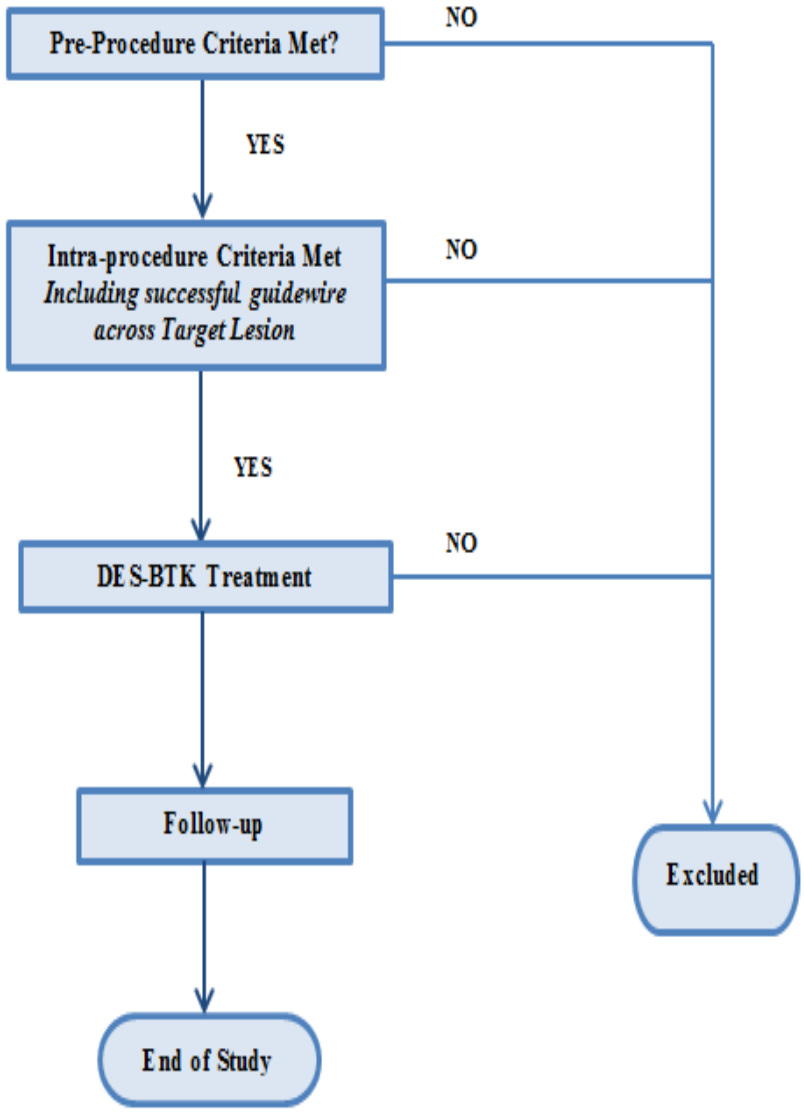


Figure 7.3-2: Phase B non-randomized Design



7.4. *Treatment Assignment*

7.4.1. Phase A RCT

- Trial candidates must satisfy all pre-procedure inclusion criteria and no pre-procedure exclusion criteria prior to the intervention, and
- Subjects must satisfy all intra-procedure inclusion criteria and no intra-procedure exclusion criteria to be eligible for randomization/enrollment into the trial.

The 2:1 randomization for phase A RCT will be stratified by investigational center and lesion length with 2 subjects receiving the DES BTK stent for every 1 subject receiving treatment with standard PTA.

For phase A RCT, the subject is considered 'enrolled' into the trial at the time of randomization (i.e. when a treatment assignment is received by the study site).

7.4.2. Phase B non-randomized

- Trial candidates must satisfy all pre-procedure inclusion criteria and no pre-procedure exclusion criteria prior to the intervention, and
- Subjects must satisfy all intra-procedure inclusion criteria and no intra-procedure exclusion criteria to be eligible for enrollment into the trial.

For phase B non-randomized, the subject is considered 'enrolled' into the trial at the time the DES BTK stent is introduced into the subject's vasculature.

7.5. *Treatment and Control*

The DES BTK Vascular Stent System is the trial test device. Refer to Section 5, Device Description for product information. Commercially available PTA balloons are the control device for this trial.

Drug coated balloons are not permitted for treatment of the target lesion(s).

7.6. *Target and Non-Target Lesions*

Target Lesion(s)
The target lesion(s) is defined as a stenotic, restenotic or occlusive segment located in the tibioperoneal trunk, anterior tibial, posterior tibial and/or peroneal artery(ies) with the following characteristics:

- Target lesion(s) must be at least 4cm above the ankle joint
- A single target lesion per vessel, in up to 2 vessels, in a single limb
- Degree of stenosis ≥ 70% by visual angiographic assessment
- RVD is between 2.5 – 3.25mm for phase A RCT
- RVD is between 2.5 – 3.75mm for phase B non-randomized (Note: RVD is dependent on stent size being used. Refer to DFU for specific requirements)

- Total target lesion length (or series of lesion segments) to be treated is ≤ 70mm for phase A RCT prior to DMC approval for stent overlap
  (Note: Lesion segment(s) must be fully covered with one DES BTK stent, if randomized to stent)
- Total target lesion length (or series of lesion segments) to be treated is ≤ 140mm for phase A RCT after DMC approval for stent overlap
  (Note: Lesion segment(s) must be fully covered with up to two DES BTK stents, if randomized to stent)
- Total target lesion length (or series of lesion segments) to be treated is ≤ 140mm for phase B non-randomized
  (Note: Lesion segment(s) must be fully covered with up to two DES BTK stents)

Successful guidewire crossing of all target lesion(s) is required prior to randomization/enrollment.

Use of alternate therapy is not permitted for the treatment of the target lesion(s) in the trial. (eg, atherectomy, cutting balloon, re-entry devices, laser radiation therapy).

Drug-coated balloons are not permitted for the treatment of the target lesion(s) in the trial.

Non-Target Lesion(s)

Multiple interventions in the target limb are permitted during the index procedure for the treatment of above the knee inflow lesions (lesions located in the iliac artery, superficial femoral artery and/or popliteal artery). Inflow lesions may be treated according to the investigator's standard procedures using commercially-available devices. If atherectomy is performed, the use of an embolic protection device is strongly recommended.

The inflow interventions must be deemed successful (eg, absence of distal embolization, optimal restoration of inflow, etc.) prior to the randomization and/or treatment of the target lesion.

Treatment of outflow lesion(s) (lesions located in the segment of the target vessel distal to the target lesion) is not permitted.

7.7. *Justification for the Trial Design*

The SAVAL phase A RCT will compare the safety and effectiveness of the DES BTK Vascular Stent System vs PTA for the treatment of atherosclerotic lesion(s) in the infrapopliteal arteries. Current revascularization options for infrapopliteal atherosclerotic disease include both endovascular and surgical approaches. The foundation of endovascular revascularization is PTA, and while advancements have been made in endovascular approaches for below the knee disease, patency rates remain suboptimal. [2]

As described in section 4, drug-eluting stents have been used for coronary artery revascularization since their introduction in 2003, and this technology, used for the treatment in coronary vessels of similar diameters as those found in the infrapopliteal anatomy, supports the use of drug-eluting stents below the knee.

Phase A RCT will assess primary effectiveness and safety of the DES BTK Vascular Stent System when compared to PTA at 12 months post procedure, and phase B non-randomized is designed to demonstrate additional safety and effectiveness for the DES BTK Vascular Stent System out to 12 months post procedure.

8. Subject Selection

8.1. *Trial Population and Eligibility*

Eligible subjects are those with chronic, symptomatic lower limb ischemia classified as Rutherford category 4 or 5, with a life expectancy of greater than 1 year, and who are expected to tolerate the interventional procedure and be compliant with the post-procedure follow-up course.

There are 2 stages of evaluation for trial eligibility: pre-procedure and intra-procedure. Trial candidates must satisfy all pre-procedure inclusion criteria and none of the pre-procedure exclusion criteria prior to the intervention.

In addition, subjects must satisfy all intra-procedure inclusion criteria and none of the intra-procedure exclusion criteria to be eligible for randomization/enrollment into the trial. Refer to section 8.2 and 8.3 for the trial inclusion and exclusion criteria.

8.2. *Inclusion Criteria*

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

Table 8.2-1: Inclusion Criteria

Pre-procedure Inclusion Criteria	1. Subject is 18 years or older and has signed and dated the trial informed consent form (ICF). Note: For subjects in Japan who are less than 20 years of age, the subject's legal representative must provide written informed consent in addition to the subject 2. Subject is willing and able to comply with the trial testing, procedures and follow-up schedule 3. Subject has chronic, symptomatic lower limb ischemia, determined by Rutherford categories 4 or 5 in the target limb, with wound(s) confined to toes/forefoot 4. Subject is a male or non-pregnant female. If female of child-bearing potential, and if sexually active must be using, or agree to use, a medically–acceptable method of birth control as confirmed by the investigator
Intra-procedure Inclusion Criteria	1. Stenotic, restenotic or occlusive target lesion(s) located in the tibioperoneal trunk, anterior tibial, posterior tibial and/or peroneal artery(ies). • Target lesion(s) must be at least 4cm above the ankle joint • A single target lesion per vessel, in up to 2 vessels, in a single limb • Degree of stenosis ≥ 70% by visual angiographic assessment • Reference vessel diameter (RVD) is between 2.5 – 3.25mm for phase A RCT • RVD is between 2.5 – 3.75mm for phase B non-randomized (Note: RVD is dependent on stent size being used. Refer to DFU for specific requirements) • Total target lesion length (or series of lesion segments) to be treated is ≤ 70mm for phase A RCT prior to DMC approval for stent overlap (Note: Lesion segment(s) must be fully covered with one DES BTK stent, if randomized to stent) • Total target lesion length (or series of lesion segments) to be treated is ≤ 140mm for phase A RCT after DMC approval for stent overlap (Note: Lesion segment(s) must be fully covered with up to two DES BTK stents, if randomized to stent) • Total target lesion length (or series of lesion segments) to be treated is ≤ 140mm for phase B non-randomized (Note: Lesion segment(s) must be fully covered with up to two DES BTK stents) 2. Target vessel(s) reconstitute(s) at or above the stenting limit zone (4cm above the ankle joint) 3. Target lesion(s) is located in an area that may be stented without blocking access to patent main branches 4. Treatment of all above the knee inflow lesion(s) is successful prior to treatment of the target lesion 5. Guidewire has successfully crossed the target lesion(s)

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria will be excluded from this clinical investigation.

Table 8.3-1: Exclusion Criteria

Pre-procedure Exclusion Criteria	1. Life expectancy ≤ 1 year 2. Stroke ≤ 90 days prior to the procedure date 3. Prior or planned major amputation in the target limb 4. Previous surgery in the target vessel(s) (including prior ipsilateral crural bypass) 5. Previously implanted stent in the target vessel(s) 6. Failed PTA of target lesion/vessel ≤ 60 days prior to the procedure date 7. Renal failure as measured by a GFR ≤ 30ml/min per 1.73m^2, measured ≤ 30 days prior to the procedure date 8. Subject has a platelet count ≤ 50 or ≥ 600 X 10^3/µL ≤ 30 days prior to the procedure date 9. NYHA class IV heart failure 10. Subject has symptomatic coronary artery disease (ie, unstable angina) 11. History of myocardial infarction or thrombolysis ≤ 90 days prior to the procedure date 12. Non-atherosclerotic disease resulting in occlusion (eg, embolism, Buerger's disease, vasculitis) 13. Subject is currently taking Canagliflozin 14. Body Mass Index (BMI) <18 15. Active septicemia or bacteremia 16. Coagulation disorder, including hypercoagulability 17. Contraindication to anticoagulation or antiplatelet therapy 18. Known allergies to stent or stent components 19. Known allergy to contrast media that cannot be adequately pre-medicated prior to the interventional procedure 20. Known hypersensitivity to heparin 21. Subject is on a high dose of steroids or is on immunosuppressive therapy 22. Subject is currently participating, or plans to participate in, another investigational trial that may confound the results of this trial (unless written approval is received from the Boston Scientific study team)
Intra-procedure Exclusion Criteria	1. Angiographic evidence of intra-arterial acute/subacute thrombus or presence of atheroembolism 2. Treatment required in > 2 target vessels (Note: a target lesion originating in one vessel and extending into another vessel is considered 1 target vessel) 3. Treatment requires the use of alternate therapy in the target vessel(s)/lesion(s), (eg, atherectomy, cutting balloon, re-entry devices, laser, radiation therapy) 4. Aneurysm is present in the target vessel(s) 5. Extremely calcified lesions

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects (or legal guardian, if applicable) must sign and date the institutional review board (IRB)/ ethics committee (EC)-approved trial-specific informed consent form (ICF) prior to the completion of any trial-related procedure(s).

The subject must satisfy all pre-procedure inclusion criteria and none of the pre-procedure exclusion criteria prior to the intervention.

Subjects must satisfy all intra-procedure inclusion criteria and none of the intra-procedure exclusion criteria to be enrolled into the trial.

- The point of enrollment for phase A RCT is at the time a subject is randomized for the trial (i.e. when a treatment assignment is received by the study site)
- The point of enrollment for phase B non-randomized is at the time the DES BTK stent is introduced into the subject's vasculature.

Subjects who do not satisfy the pre-procedure eligibility criteria will receive care according to the investigational center's standard procedures and no further trial-related procedures will be completed. They will be considered a screen failure and followed according to the center's standard procedures.

Subjects who do not satisfy the intra-procedure eligibility criteria will not be randomized/enrolled into the trial, and will receive care according to the center's standard procedures and considered a screen failure.

Subjects, who are enrolled/randomized into the DES BTK arm but do not have the DES BTK stent successfully implanted, will be followed for 30 days for safety, and be withdrawn from the trial afterwards.

9.2. *Withdrawal*

All subjects who are enrolled into the trial will be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) will be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator will ask for the subject's permission to follow his/her status/condition outside of the clinical trial.

Subjects may withdraw from the trial at any time by notifying the trial investigator. The investigator may also terminate a subject's participation in the trial (ie, if the subject routinely fails to complete required trial procedures or if the investigator believes it is in the subject's best interest).

Examples of reasons for trial withdrawal include, but are not limited to:

- Failure to comply with the trial-required visit schedule

- Subject is lost to follow-up
- Subject voluntarily withdraws from the trial
- Adverse event such that continued trial participation would not be in the best interest of the subject
- Withdrawal of the subject by the investigator
- Subject death
- Trial closure

It is recommended that the reason for subject withdrawal is also documented in the subject's medical record. If applicable, the investigator will complete an adverse event and/or device deficiency assessment prior to the subject's withdrawal from the trial. All applicable electronic case report forms (eCRFs) are to be completed for all subjects who are enrolled in the trial and are then withdrawn from the trial for any reason.

Withdrawn subjects will not undergo any further trial follow-up, nor will they be replaced because the justified sample size considers an estimated allowance for attrition. Data already collected will be retained and reported, however, no new data will be collected after the withdrawal.

Subjects voluntarily withdrawing from the trial will be asked to participate in a limited capacity allowing their medical status to be followed by telephone contact, medical chart review, or by other agreed upon method. If a subject decides not to continue participation in a limited capacity, the investigator will not access their medical record or other confidential records for new purposes related to the study; however, study data collected prior to their withdrawal may be reviewed and publicly available records may be consulted prior to or after their withdrawal. Note: this applies to all withdrawn subjects (e.g. withdrawn by investigator).

Withdrawn subjects will be followed according to the investigational center's standard procedures. Serious adverse device-effects that are still ongoing at the end of the subject's participation in the trial will be followed up for resolution status and this information will be provided to Boston Scientific for the purpose of regulatory agency reporting for the trial.

9.3. *Lost to Follow-Up*

Additional actions must be taken when a participant fails to attend a required study visit:

The investigational center personnel will attempt to contact the study subject and reschedule the missed visit (within the visit window if possible) and counsel the subject on the importance of maintaining the assigned visit schedule.

Prior to withdrawing a subject as lost to follow-up, the investigational center's personnel must make at minimum 3 documented attempts (1 in writing and sent via a traceable method) to bring the subject in for a final trial visit. Other contacts (ie, telephone calls, emails) must be documented in the subject's records at the investigational center. If all attempts to contact that subject have failed, the investigational center will withdraw the subject and follow the local procedures for notification.

9.4. *End-of-Study Definition*

Phase A RCT will be considered complete for the primary effectiveness endpoint and the primary safety endpoint after all subjects in phase A RCT have completed the 12-month follow-up visit, are withdrawn prior to the 12-month follow-up visit, have died or, the last 12-month follow-up visit window has closed.

Phase B non-randomized will be considered complete for the primary safety endpoint after all subjects in phase B non-randomized have completed the 12-month follow-up visit, are withdrawn prior to the 12-month follow-up visit, have died or, the last 12-month follow-up visit window has closed.

The entire trial will be considered complete with regard to all follow-up, after all subjects have completed the 60-month follow-up visit, are withdrawn prior to the 60-month follow-up visit, have died or, the last 60-month follow-up visit window has closed.

10. Trial Methods

10.1. *Data Collection*

The data collection schedule is shown in **Table 10.1-1.**

Table 10.1-1: Data Collection Requirements by Visit

Procedure/Assessment	Pre-procedure[2]	Index procedure	Pre-discharge	Follow-up Visits based on procedure date = time zero							
				1-mon (30 ± 7 Days) Office Visit	3-mon (90 ± 30 Days) Office Visit	6-mon (182 ± 30 Days) Office visit	12-mon (365 ± 30 Days) Office Visit	24-mon (730 ± 90 Days) Office Visit	36-mon (1095 - 90/+30 Days Office Visit	18 & 30, mon (± 90 Days) Telephone	48 & 60 mon (-90/+30 days)
Informed consent[1]	X										
Inclusion/Exclusion (pre)	X	X									
Inclusion/Exclusion (intra)		X									
Demographics	X										
Physical assessment	X										
BMI	X										
Medical/surgical history	X										
Glomerular filtration rate	X										
Platelet count	X										
Procedure information		X									
Angiography[3]		X									
Pregnancy test[4]	X										
Randomization[5]		X									
X-rays of DES BTK stent[3]							X				
EQ-5D & VascuQol	X			X	X	X	X				
Medications	X	X	X	X	X	X	X	X	X	X	
Adverse event[6]		X	X	X	X	X	X	X	X	X	
Device deficiency		X	X	X	X	X	X	X	X	X	
Rutherford Classification	X				X	X	X	X	X		
Duplex Ultrasound[3]				X		X	X[7]	X	X		
ABI &TBI	X					X	X				
Wound assessment & image		X[8]		X	X	X	X	X	X		
Survival status											X

[1] Subject's consent obtained, and informed consent form signed prior to any study-specific tests or procedures
[2] Performed/Measured ≤ 30 days prior to the procedure date
[3] 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 36-month follow-up timeframe or has a documented occluded target lesion.
[4] Measured ≤ 7 days prior to the procedure date for subjects of child-bearing potential
[5] Phase A RCT only
[6] Reporting required through the end of trial for UADEs and Device Deficiencies. Reporting required through 36-month follow-up visit for SAEs and ADEs. AEs not related to the investigational device or procedure reported only through 12-month follow-up visit.
[7] If a diagnostic DUS cannot be adequately achieved for the 12-month follow-up visit then CTA or DSA angiography must be conducted.
[8] Wound assessment and image ≤ 1 day prior to the procedure date

10.2. *Visit Windows*

Table 10.2-1: Protocol Visit Windows

Visit	Visit windows
Informed consent	Prior to any trial procedures
Pre-procedure	Testing ≤ 30 days prior to procedure unless otherwise specified
Index Procedure	Time point = zero
1 month post procedure	30 days (+/- 7 days) from procedure date
3 months post procedure	90 days (+/- 30 days) from procedure date
6 months post procedure	182 days (+/- 30 days) from procedure date
12 months post procedure	365 days (+/- 30 days) from procedure date
24 months post procedure	730 days (+/- 90 days) from procedure date
36 months post procedure	1095 days (- 90/+30 days) from procedure date

Table 10.2-2: Telephone/medical chart/public record Follow-up Windows

Telephone call	Target Date
18-Months	547 days (+/- 90 days) from procedure date
30-Months	912 days (+/- 90 days) from procedure date
Medical chart / public record	**Target Date**
48-Months	1460 days (+/- 90 days) from procedure date
60-Months	1825 days (- 90/+30 days) from procedure date

10.3. *Trial Candidate Screening*

A screening log will be maintained by each investigational center to document selected information about potential subjects who fail to meet the SAVAL trial eligibility criteria, including the reason for screen failure.

10.3.1. Strategies for Recruitment and Retention

Subjects may be recruited through the investigator's practice, referring physicians and/or the use of recruitment tools. Potential subjects may be identified through an investigational center's database query (chart reviews) or as new or existing patients attend clinic visits. Any information disseminated to potential subjects (eg, advertisements, pamphlets, posters) must be approved by the investigational center's IRB/EC prior to use.

It is important that the investigational center personnel review the trial requirements with the subjects to maximize compliance with the follow-up schedule and required medication regimen. A stipend may be provided to subjects to cover lodging or travel expenses incurred as a result of participation in the SAVAL trial, in accordance with country laws and regulations, and per the trial investigational center's regulations.

Rescreening for the Trial

When a subject fails the pre- or intra-procedure inclusion or exclusion criteria, and it is the opinion of the investigator that the subject may be a suitable candidate for rescreening, the investigator will contact the Boston Scientific trial manager, or designee to request permission to rescreen the subject.

10.4. *Informed Consent*

The subject (or legal guardian, if applicable) must sign and date the ICF prior to any trial-required testing or procedures. For individuals less than 20 years of age enrolled at a Japan center, the subject's legal representative, as well as the subject, must provide written informed consent.

Prior to signing the ICF, the investigator, or qualified designee, will explain to each potential subject the purpose and nature of the trial, procedures, expected trial duration, available alternative therapies, and the benefits and risks involved with trial participation.

Refer to Section 9.1 Point of Enrollment and Section 20 Informed Consent.

10.5. *Medications*

Anticoagulant and antiplatelet medication use will be collected for the trial and reported on the electronic case report forms from the time of the pre-procedure visit through the 36-month follow up. Medication data collection at each visit will include: a complete listing of the anticoagulant and antiplatelet medications the subject is taking, interruptions and cessation.

Anticoagulant and Antiplatelet Medication for the Trial

- Anti-coagulation and antiplatelet therapy is to be administered prior to and during the index procedure according to the investigator's standard procedures.
- Dual antiplatelet therapy is required post-procedure through the 6-month visit and is strongly recommended to continue through the 12-month visit for the trial subjects who receive the DES BTK stent.*
- Subjects who are randomized to PTA in phase A RCT will receive antiplatelet therapy according to the investigator's standard of care.

*A subject may be exempt from dual antiplatelet requirement when anticoagulation therapy is required for comorbidity treatment and when, in the judgement of the investigator, the addition of dual antiplatelet therapy would pose an unacceptable hemorrhage risk.

10.6. *Quality of Life*

The QOL instruments used for the trial will be the EQ-5D questionnaire for general health and the VascuQol questionnaire for disease specific data.

The EQ-5D is a 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.

The VascuQol was developed to evaluate disease-specific QOL measure for patients with chronic lower limb ischemia. The 25-item questionnaire is subdivided into 5 domains: pain, symptoms, activities, social and emotional.

10.7. *Wound Care and Data Collection*

For Rutherford 5 subjects with minor tissue loss, ischemic ulcer, or focal gangrene, these tissue changes must be located only in the digit(s) and/or the forefoot, and these lesions must be able to be fully resected (if needed) by performing digit amputation(s) or complete trans metatarsal amputation. Study subject's wounds must not require mid foot or hind foot amputation. If the investigator plans to undertake digit amputation(s) or transmetatarsal amputation, this plan should be indicated at the time of study enrollment.

It is recommended investigators follow the Wound Healing Society 2014 update on guidelines for arterial ulcers. [18]

Target limb wound characteristics data will be collected and documented on the eCRFs. (ie, wound size, depth, presence of infection, and healing status). Wound images will be collected for the trial. Instructions for collection and submission of images will be provided in the manual of operations.

A review of the wound assessment data will be completed by an independent reviewer who will be blinded to the randomized therapy.

10.8. *Pre-procedure*

The subject (and/or the legal guardian as applicable) must sign and date the ICF prior to the completion of any trial-related procedures. Subjects will be assessed to confirm trial eligibility requirements. The data collection elements for pre-procedure should be collected ≤ 30 days prior to the procedure or as specified below.

When it is determined that a subject does not satisfy the pre-procedure trial eligibility requirements, the trial-related procedures will stop, and the subject will be considered a screen failure and receive care according to the center's standard procedures.

When a subject fails the pre-procedure eligibility criteria, and it is in the opinion of the investigator that the subject may be a suitable candidate for rescreening, the investigator will contact the Boston Scientific trial manager, or designee to request permission to rescreen the subject.

Data Collection Requirements Pre-procedure (≤ 30 days prior to procedure)*:*

- Informed consent (prior to any study-specific tests or procedures)
- Pre-procedure inclusion/exclusion criteria
- Demographics
- Physical assessment
- Body mass index

- Medical and surgical history
- Glomerular filtration rate
- Platelet count
- Pregnancy test ≤ 7 days prior to procedure (if subject is of child-bearing potential)
- EQ-5D Questionnaire
- VascuQol Questionnaire
- Medications
- Rutherford classification
- Ankle-brachial index and toe brachial index*

* When subject condition permits (ie, no toe amputation, calcified/incompressible vessels)

10.9. *Index Procedure*

Diagnostic angiography of the lower extremities will be performed using the investigational center's standard procedures. The investigator will confirm the subject satisfies all inclusion criteria and no exclusion criteria prior to randomization/enrollment into the trial.

Multiple interventions in the target limb are permitted during the index procedure for the treatment of above the knee inflow lesions (lesions located in the iliac artery, superficial femoral artery and/or popliteal artery). Inflow lesions may be treated according to the investigator's standard procedures using commercially-available devices. If atherectomy is performed, the use of an embolic protection device is strongly recommended.

The inflow interventions must be deemed successful (eg, absence of distal embolization, optimal restoration of inflow, etc) prior to the randomization and/or treatment of the target lesion(s).

Successful guidewire crossing of all target lesion(s) is required prior to randomization/enrollment into the trial.

Treatment of outflow lesions(s) (lesions located in the segment of the target vessel distal to the target lesion) is not permitted.

Drug-coated balloons are not permitted for the treatment of the target lesion(s) in the trial.

The use of an adjunctive therapy is not permitted for the target lesion(s) (ie, atherectomy, cutting balloon, re-entry devices, laser, radiation therapy).

The DES BTK Vascular Stent System will be used in compliance with the directions for use.

10.9.1. Target lesion requirements:

Stenotic, restenotic, or occlusive target lesions(s) located in the tibioperoneal trunk, anterior tibial, posterior tribal and/or peroneal artery(ies).

- Target lesion(s) must be below the knee and at least 4cm above the ankle joint
- A single target lesion per vessel, in up to 2 vessels, in a single limb
- Degree of stenosis ≥ 70% by visual angiographic assessment
- RVD is between 2.5 – 3.25mm for phase A RCT

- RVD is between 2.5 – 3.75mm for phase B non-randomized (Note: RVD is dependent on stent size being used. Refer to DFU for specific requirements)
- Total target lesion length (or series of lesion segments) to be treated is ≤ 70mm for phase A RCT prior to DMC approval for stent overlap
  (Note: Lesion segment(s) must be fully covered with one DES BTK stent, if randomized to stent)
- Total target lesion length (or series of lesion segments) to be treated is ≤ 140mm for phase A RCT after DMC approval for stent overlap
  (Note: Lesion segment(s) must be fully covered with up to two DES BTK stents, if randomized to stent)
- Total target lesion length (or series of lesion segments) to be treated is ≤ 140mm for phase B non-randomized
  (Note: Lesion segment(s) must be fully covered with up to two DES BTK stents)

A ruler or radiopaque marking tape must be used as the calibration source to determine the lesion length and location. When possible the zero mark will be placed at the level of an anatomical landmark (ie, tibial plateau, inferior edge of the patella, bifurcation).

10.9.2. Randomization/Enrollment

In phase A RCT the randomization assignment will be obtained only after all of the following are confirmed:

- All pre- and intra-procedure inclusion criteria are met
- No exclusion criteria are met
- Successful guidewire crossing of the target lesion(s) is required prior to randomization/enrollment

The investigator (or delegate) will access the Rave electronic data capture system, and a randomization custom function will be used to assign subjects to the test or control treatment group. Treatment of the target lesion(s) will be in compliance with the randomization assignment.

For phase B non-randomized, the DES BTK stent may be implanted after the following are confirmed:

- All pre- and intra-procedure inclusion criteria are met
- No exclusion criteria are met
- Successful guidewire crossing of the target lesion(s) is required prior to enrollment

If a subject does not satisfy all inclusion criteria and/or does meet one of the exclusion criteria, the investigator will not randomize/enroll the subject and will proceed with treatment according to the center’s standard procedures, and the subject will be considered a screen failure.

Subjects, who are enrolled/randomized into the DES BTK arm but do not have the DES BTK stent successfully implanted, will be followed for 30 days for safety, and be withdrawn from the trial afterwards.

10.9.3. Guidelines for treatment of flow-limiting dissection or other loss of target vessel patency at the completion of the target lesion pre-treatment and definition of bailout stenting

Subjects randomized to the PTA arm, who receive index angioplasty and subsequently demonstrate flow-limiting dissection or other loss of target vessel patency (ie, recoil), based on the operator visual assessment and clinical judgement (ie, presence of contrast in the sub-intimal space), must receive repeat 2 to 5 minutes balloon inflations (up to 3 inflations) using standard PTA balloons. If target vessel compromise persists and requires further intervention (eg, "bailout stent") a DES BTK Vascular Stent System will be used, and these subjects will be considered a study primary endpoint failure and continue to attend study follow-up visits.

Investigators must submit angiography to support the decision for bailout stenting to the angio core lab for review.

Note: The DES BTK Vascular Stent System may not be used for bailout in non-target lesions.

Data Collection Requirements for Index procedure:

- Confirm pre-procedure inclusion and exclusion criteria
- Intra-procedure inclusion and exclusion criteria
- Procedure information
  - Inflow lesion(s) location, characteristics and treatment modalities used
  - Target lesion(s) characteristics and treatment modalities used
  - PTA balloon size(s) and inflation information (if applicable)
  - Guidewire(s) information
  - Stent information (if applicable)
  - Hospitalization information
- Angiographic imaging (to core laboratory)
- Randomization (if applicable)
- Medications
- Adverse events
- Device deficiency
- Wound assessment and image (≤ 1 day prior to procedure)

Data Collection Requirements for Pre-discharge:

- Medications
- Adverse events
- Device deficiency

10.9.4. Re-intervention in the target vessel

Subjects who require re-intervention of the target vessel during the 36-month follow-up period will be treated according to the investigational center's standard of care. The DES BTK Vascular Stent System may not be used for re-intervention procedures.

Data Collection for Re-interventions

- Angiographic imaging (to core laboratory)
- Medications
- Adverse events
- Device deficiency
- Wound assessment and image (≤ 1 day prior to procedure)

10.10. *Follow-up visits*

Subjects will return for trial-required follow-up visits at: 1, 3, 6, 12, 24, and 36 months post procedure. Telephone follow-up visits are required at 18 and 30 months post procedure. Telephone follow-up visit and/or medical chart review and/or publicly available records consultation are required at 48 months and 60 months post-procedure. Refer to **Table 10.2-1** Protocol Visit Windows.

At each follow-up visit the investigator will complete an assessment for the clinical need for target limb revascularization, and document on the eCRF, prior to reviewing the results of diagnostic assessments (eg, DUS, angiography).

Data collection requirements for the follow-up visits are listed below: Refer to **Table 10.1-1**.

Data Collection Requirements for1-Month Post-Procedure Visit

- EQ-5D Questionnaire
- VascuQol Questionnaire
- Medications
- Adverse events
- Device deficiency
- Duplex ultrasound
- Wound assessment and image

Data Collection Requirements for 3, 24, and 36 Months Post-Procedure Visits:

- EQ-5D Questionnaire (3 months only)
- VascuQol Questionnaire (3 months only)
- Medications
- Adverse events (non-serious AEs not related to the investigational device or procedure reported only through 12-month follow-up visit)
- Device deficiency
- Rutherford classification
- Duplex ultrasound (24 and 36 months only)
- Wound assessment and image

Data Collection Requirements for 6 and 12 Months Post Procedure Visits:

- High definition x-ray of index limb with DES BTK stent (12-month visit only)
- EQ-5D Questionnaire
- VascuQol Questionnaire
- Medications
- Adverse events
- Device deficiency
- Rutherford classification
- Duplex ultrasound*
- Ankle-brachial index and toe brachial index**
- Wound assessment and image

* If a diagnostic duplex ultrasound cannot be adequately achieved for the 12-month follow-up visit, then CTA or DSA angiography must be conducted

** When subject condition permits (ie, no toe amputation, calcified/incompressible vessels)

10.11. *Telephone Follow-up*

Telephone follow-up visits will be completed at 18 and 30 months post procedure. Telephone follow-up visit and/or medical chart review and/or publicly available records consultation will be completed at 48 months and 60 months post-procedure

Data Collection Requirements for the 18 and 30 months telephone follow-ups:

- Medications
- Adverse events [SAEs and (U)ADEs]
- Device deficiencies

Data Collection Requirements for the 48 and 60 months telephone/medical chart review/ publicly available records follow-ups:

- Survival status

10.12. *Trial Completion*

Phase A RCT will be considered complete for the primary effectiveness endpoint and the primary safety endpoint after all subjects in phase A RCT have completed the 12-month follow-up visit, are withdrawn prior to the 12-month follow-up visit, have died or, the last 12-month follow-up visit window has closed.

Phase B non-randomized will be considered complete for the primary safety endpoint after all subjects in phase B non-randomized have completed the 12-month follow-up visit, are withdrawn prior to the 12-month follow-up visit, have died or, the last 12-month follow-up visit window has closed.

The entire trial will be considered complete with regard to all follow-up, after all subjects have completed the 60-month follow-up visit, are withdrawn prior to the 60-month follow-up visit, have died or, the last 60-month follow-up visit window has closed.

10.13. *Source Documents*

The investigator is responsible for the preparation, review and retention of records used for the trial. It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (ie, by a dated signature or by generation through a validated process) to have the same information, including data that describes the context, content, and structure, as the original.

The investigator will, at minimum, maintain the following accurate, complete and current records relating to the investigator's participation in the trial.

- Correspondence with another investigator, an IRB/EC, the sponsor, a monitor, or FDA including required reports
- Records of receipt, use or disposition of investigational devices (ie, product accountability)
- Records supporting each subject's case history and exposure to the device. Case history supporting data (source documentation), such as:
  - Signed and dated ICFs
  - Signed HIPAA authorization if separate from the ICF (if applicable)
  - Medical records (ie, progress notes of the physicians, the subject hospital and clinic charts and the nurses' notes
  - All reportable adverse event and adverse device effects information
- The clinical investigational plan and any amendments
- Investigator brochure
- Curriculum vitae for all investigators
- Signed clinical study agreement
- Signed financial disclosure forms for all investigators
- Center personnel trial training records

11. Statistical Considerations

The sample size justification and the power analyses for phase A RCT and phase B non-randomized are described in separate subsections. The general statistical methods are applicable to both phases unless otherwise specified.

The details for sample size justification and all statistical analyses will be described in the statistical analysis plan.

11.1. *Primary Endpoints for Phase A RCT*

The overall sample size in phase A RCT is justified by hypothesis parameters and driven by the 12-month primary effectiveness endpoint, to preserve adequate statistical testing power for both the primary effectiveness endpoint and safety endpoint.

The primary effectiveness and safety hypotheses will be tested simultaneously at the significance level of one-sided 2.5% each without adjustment.

11.1.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint in phase A RCT is the 12-month primary patency. The goal is set to demonstrate that the primary patency for the DES BTK treatment group (ie, Test) is superior to the PTA treatment group (ie, Control) through 12 months post-procedure.

11.1.1.1. Effectiveness Hypothesis

The primary effectiveness hypothesis to be tested is that the 12-month primary patency in subjects treated with the DES BTK Vascular Stent System is superior to subjects treated with PTA at an overall one-sided significance level of 2.5%.

The null hypothesis (H_0) states that there is no pre-specified treatment effect of the DES BTK Vascular Stent System vs PTA, as opposed to the alternative hypothesis (H_1) which states that there is a pre-specified treatment effect. The hypotheses inequalities are shown below:

H_0: Pt - Pc $\leq$ 0

H_1: Pt - Pc > 0 (superior)

where Pt and Pc are the 12-month primary patency for the DES BTK stent and PTA, respectively.

11.1.1.2. Effectiveness Sample Size

The overall sample size is driven by the primary effectiveness endpoint. Approximately 201 subjects are planned to be enrolled in phase A RCT. The sample size justification for phase A RCT is based on the following assumptions.

- Power $\geq$ 84%
- One-sided overall significance level (alpha) = 2.5%
- Expected PTA 12-month primary patency = 40%
- DES BTK to demonstrate 25% treatment effect
- Allocation (DES BTK vs PTA) = 2:1
- A minimum of 150 evaluable subjects are required at 12 months (ideally 100 in DES BTK arm and 50 in PTA arm)
- Attrition rate in 12 months $\leq$25%
- Approximately 201 subjects are planned to be randomized in 2:1 fashion prior to the procedure

11.1.1.3. Effectiveness Statistical Methods

A Wald z-test will be used to assess the primary effectiveness hypothesis. The p-value and corresponding confidence interval for the difference between DES BTK and PTA in 12-month primary patency will be constructed.

A detailed definition of evaluable subjects for the primary effectiveness endpoint will be given in the statistical analysis plan.

11.1.2. Primary Safety Endpoint

The primary composite safety endpoint in phase A RCT is the 12-month MAE-free rate. The safety goal is designed to demonstrate that the DES BTK Vascular Stent System is non-inferior to PTA in terms of MAE-free rate through 12 months post-procedure.

11.1.2.1. Safety Hypothesis

The primary safety hypothesis to be tested is that the 12-month MAE-free rate in subjects treated with the DES BTK Vascular Stent System is non-inferior to subjects treated with PTA at an overall one-sided significance level of 2.5%.

The null hypothesis (H_0) states that there is no marginal treatment effect of the DES BTK Vascular Stent System vs PTA, 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: $Pt - Pc \leq \Delta$

H_1: $Pt - Pc > \Delta$

where Pt and Pc are the 12-month MAE-free rate for the DES BTK stent and PTA, respectively, and Δ (delta) is the non-inferiority margin of -10%.

11.1.2.2. Safety Sample Size/Power Analysis

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

- One-sided overall significance level (alpha) = 2.5%
- The primary safety endpoint will be tested simultaneously with the primary effectiveness endpoint at the same significance level
- Expected PTA 12-month MAE-free rate = 75%
- Expected DES BTK 12-month MAE-free rate = 85%
- Non-inferiority margin (Δ) = -10%

The sample size is driven by the primary effectiveness endpoint to provide approximately 80% power to assess the primary safety endpoint.

11.1.2.3. Safety Statistical Methods

A Wald z-test will be used to assess the primary safety hypothesis. The p-value and corresponding confidence interval for the difference between DES BTK and PTA in 12-month MAE-free rate will be constructed.

A detailed definition of evaluable subjects for the primary safety endpoint will be given in the statistical analysis plan.

11.1.3. Success Criteria

The following success criteria for phase A RCT are defined as both the primary effectiveness and primary safety endpoint to be met simultaneously, therefore there will be no multiplicity issues for the two primary endpoints.

The DES BTK Vascular Stent System will be concluded to be superior to PTA for device effectiveness if the one-sided lower bound of 97.5% confidence interval on the difference between treatment groups (DES BTK – PTA) in 12-month primary patency is greater than zero.

The DES BTK Vascular Stent System will be concluded to have no safety concerns if the one-sided lower bound of 97.5% confidence interval on the difference between treatment groups (DES BTK – PTA) in 12-month MAE-free is greater than -0.1.

The trial will be concluded to be a success if both the primary effectiveness endpoint and the primary safety endpoint are met.

11.2. *Primary Endpoint for Phase B Non-randomized*

The overall sample size in phase B non-randomized is justified by hypothesis parameters and driven by the 12-month primary safety endpoint, to preserve adequate statistical testing power. The 12-month primary patency will be observed without testing hypotheses.

11.2.1. Primary Safety Endpoint

11.2.1.1. Safety Hypotheses

The primary safety hypothesis to be tested is that the 12-month MAE-free rate in subjects treated with the DES BTK Vascular Stent System exceeds a PG of 71% at one-sided significance level of 2.5%.

The null (H_0) and the alternative (H_1) hypotheses for the primary safety endpoint are as follows:

H_0: Pt ≤ PG (not met)

H_1: Pt > PG (met)

where Pt is the 12-month MAE-free rate for the subjects treated with the DES BTK Vascular Stent System and the PG is the performance goal.

11.2.1.2. Safety Sample Size/Power Analysis

The power analysis for the primary safety endpoint to justify an additional 100 subjects in enrollment is based on the following assumptions.

- Power ≥ 80%
- One-sided significance level (alpha) = 2.5%
- Safety PG = 71% in the 12-month MAE-free rate
- Expected 12-month MAE-free rate = 80%

- A minimum of 186 (DES BTK) evaluable subjects are required at 12 months
- Attrition rate at 12 months ≤ 20%
- Up to 234 (DES BTK) subjects are planned to be enrolled, including 134 DES BTK subjects from phase A RCT and an additional 100 DES BTK subjects to be enrolled in phase B non-randomized

11.2.1.3. Safety Statistical Methods

A Wald z-test will be used to assess the primary safety hypothesis. The p-value for testing will be generated and the corresponding confidence interval for the observed 12-month MAE-free rate will be constructed.

11.2.2. Success Criteria

The DES BTK Vascular Stent System will be concluded as meeting the PG for device safety if the one-sided lower bound of 97.5% confidence interval on the observed 12-month MAE-free rate is greater than 0.71.

11.3. *General Statistics Methods*

11.3.1. Analysis Sets

For phase A RCT, the intention-to-treat (ITT) population will be the primary analysis set for assessing the primary hypotheses. Both per-protocol (PP) and as-treated (AT) populations will be the secondary analyses sets for reference.

For phase B non-randomized, all subjects who receive the DES BTK stent will be assessed against the pre-specified PG.

11.3.1.1. Intention-to-treat (ITT)

All subjects who sign the informed consent form and are randomized in phase A RCT will be included in the ITT analysis set, regardless of whether the subjects receive the assigned treatment. The DES BTK and PTA arms will be compared as randomized. The ITT analysis will be the primary analysis for phase A RCT.

11.3.1.2. Per-protocol (PP)

For the PP analysis, only randomized subjects who meet the eligibility criteria and receive the assigned index treatment will be included in the PP analysis set. The DES BTK and PTA arms will be compared as randomized and correctly received index treatment. Subjects who do not receive the randomized index treatment will be excluded from the PP analysis set. The PP analysis, as well as a discussion regarding what protocol deviations excluded subjects from the PP analysis, will be described in the clinical study report.

11.3.1.3. As-treated (AT)

For the AT analysis, all subjects who receive either the DES BTK stent or PTA at the index procedure will be included in the AT analysis set. The DES BTK and PTA arms will be compared as treated, excluding subjects who do not receive the DES BTK stent or PTA.

11.3.1.4. Bailout Subjects Considerations

For phase A RCT, the bailout subjects in the PTA arm will be analyzed in ITT, PP, and AT analysis sets.

- For the ITT analysis, a bailout subject from the PTA arm will stay in the PTA arm and will count as a failure on the 12-month primary patency.
- For the PP analysis, a bailout subject from the PTA arm will be excluded from the PP analysis since the bailout subjects actually receive a device (investigational or not) in addition to randomized PTA.
- For the AT analysis, a bailout subject from the PTA arm will be analyzed in the DES BTK arm if the subject receives the DES BTK test device as a bailout and count as success/failure based on 12-month effectiveness assessment

For phase B non-randomized, the AT analysis will be the primary analysis. That is, all subjects who receive the DES BTK stent will be assessed against the pre-specified PG. Therefore, bailout subjects from the RCT PTA arm (and/or even from test device) who receive the DES BTK stent will be included in the phase B hypothesis.

11.3.2. Randomization Scheme

Randomization to treatment in phase A RCT will be stratified by investigational center and lesion length. A computer-generated list of random treatment allocations (ie, a randomization schedule) will be used to assign subjects to treatments in a 2:1 ratio of DES BTK to PTA. This list will be specific to the investigational center. Random permuted blocks of size 3 and size 6 will be employed to ensure approximate balance of treatment allocation within each stratum.

11.3.3. Control for Systematic Error/Bias

Selection of subjects will be made from the investigators' general or professional referral population. All subjects meeting the inclusion and no 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. Trial subjects will be randomly assigned to a treatment group within the investigational center (phase A RCT). In determining subject eligibility for the trial, the investigator's assessment of imaging will be used. However, an angiographic core laboratory will independently analyze the angiograms, and the data obtained from the core laboratory will be utilized for analyses. An independent clinical events committee (CEC), composed of medical experts, will adjudicate safety assessments, as defined in the CEC charter.

11.3.4. Enrollment for Each Investigative Center

For phase A RCT, investigational centers will not be allowed to randomize more than 10% (N=20) of the total number of randomized subjects without prior approval from the sponsor. No study center will be allowed to enroll more than 20% (N=40) of the total number of randomized subjects.

For phase B non-randomized, investigational centers will not be allowed to enroll more than 10% (N=23) of the total number (including DES BTK from phase A RCT) of subjects without prior approval from the sponsor. No study center will be allowed to enroll more than 20% (N=47) of the total number (including DES BTK from phase A RCT) of study subjects.

11.3.5. Baseline Data Analysis

Baseline covariates will be summarized for phase A RCT and phase B non-randomized. For continuous and/or ordinal variables, the descriptive statistics will include mean, standard deviation, number evaluated, minimum and maximum. Some specific variables may also include additional statistics such as median and confidence intervals. For binary or categorical variables, the descriptive statistics will include percentage, numerator, denominator, and number evaluated. Some variables may include confidence intervals as needed.

11.3.6. Additional Endpoint Assessments

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

All additional endpoints are observational.

11.3.7. Interim Analyses

No interim analyses are planned.

11.3.8. Subgroup Analyses

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

- Race
- Gender (male vs female)
- Age (≥ 65 and < 65)
- Diabetes status (medically-treated vs non-diabetic)
- Lesion characteristics (vessel diameter/lesion length)
- Device matrix (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.

In addition, an interaction test for the primary effectiveness assessment at two-sided significance level of 0.15 will be performed for the following subgroups:

- Gender (male vs female)

11.3.9. Justification of Pooling

The concept of poolability analysis described below is applicable to both phase A RCT and phase B non-randomized.

The poolability analysis regarding the primary effectiveness and/or safety endpoint across investigational centers, as well as among US, Europe, and Japan will be assessed only when the success criteria are met, by using the logistic regression model with a two-sided significance level of 0.15. If the p-value of an interaction test is greater than or equal to 0.15, the non-significance suggests that the homogeneity of treatment effect is shown, and the primary endpoints data are poolable. However, when the p-value of an interaction test is smaller than 0.15, the significance suggests that the heterogeneity of treatment effect is detected, and poolability analysis regarding prognostic factors and/or poolability adjusted for prognostic factors will be performed.

11.3.9.1. Investigational Center Poolablity

Due to the 2:1 randomization scheme using random permuted blocks (ie, blocks of 3 and 6) employed within each center, ideally there will be 2 DES BTK subjects for every 1 PTA subject. Only sites that enrolled sufficient subjects (i.e. 5 or more subjects) will be included for this poolability analysis and these sites will be reported individually.

11.3.9.2. US, Europe, and Japan Poolablity

The focus is mostly on the applicability of the European and Japanese populations with the US population. If the treatment effect is significantly different among US, Europe, and Japanese populations then possible/plausible explanation is required and/or potential bias needs to be addressed.

11.3.10. Sensitivity Analysis for Missing Outcome Data

Sensitivity analyses for the primary effectiveness and/or safety endpoints 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 and PP analyses sets to consider all combinations of present/absent for all subjects with missing primary outcome in the DES BTK group and the PTA group.

11.3.11. Multivariable Analyses

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

Clinically and/or statistically meaningful baseline covariates will be selected in the regression model. No formal conclusion will be made by this secondary post-hoc analysis.

11.3.12. Analyses Software

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

11.3.13. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the interim and/or the final primary analyses will be documented in an amended statistical analysis plan, approved prior to performing the analyses.

Changes from the planned statistical methods after performing the analyses will be documented in the clinical trial report along with a reason for the deviation.

12. Health Economics Outcomes

A formal health economics analysis may be completed as part of this trial, given meaningful clinical results are obtained. This will take into consideration any differences in survival, complication rates, quality of life, and resource utilization. The EQ-5D questionnaire, generic quality of life measure, and the VascuQol questionnaire, disease specific quality of life measure, will be used to assess health utilities.

Non-inpatient health care visits related to CLI will be documented using an unscheduled visit eCRF. (ie, clinic visit, emergency room or urgent care visit, etc).

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 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 trials pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The investigator is responsible for the accuracy, completeness and timeliness of the data submitted and must review all data for accuracy and 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 Medidata EDC system and will be issued to the investigational center for appropriate response. Investigational center staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to “Read only” after all data is either “Hard Locked” or “Entry Locked”. Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the “Database Locked” or “Decommissioned” and all database access revoked.

13.2. *Data and Record Retention*

The principal investigator or his/her designee or investigational center will maintain all essential study documents and source documentation that support the data collected on the trial subjects in compliance with applicable regulatory requirements.

The principal investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the principal investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and Boston Scientific must receive written notification of this custodial change. Investigational centers are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

In Japan, Boston Scientific will 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 trial follow-up is continued beyond 5 years in Japan as part of a post market clinical trial after receiving marketing approval and using the data as part of a use-results evaluation, the investigator and investigational center must retain essential documents during the period of use-results evaluation.

13.3. *Core Laboratories / Central assessment of study data*

Core laboratories will be established for the central assessment of key data collected for the trial. Guidelines for the collection, analysis, and interpretation of the data will be provided in the manual of operations. The following core laboratories / central reviewers have been assigned for the SAVAL trial:

- Angiography:
    - To assess the angiograms collected for the trial during the index procedure and during subsequent revascularization procedures when collected according to the investigational center's standard procedures
    - To assess CTA or DSA angiographies taken at the 12-month follow-up visit in case the 12-month DUS is non-diagnostic
    - To confirm stent fractures identified by the X-ray core lab
    - When bailout stenting is required the angiography core lab will assess angiograms collected to document the bailout process
- X-ray: to review the x-rays collected for the trial to assess stent integrity*
- Ultrasound: to assess duplex ultrasound studies collected for the trial for lesion and stent patency
- Independent Wound Reviewer: to review wound assessment data and images.

*Note: When a stent fracture is identified, the x-ray will be reviewed by the angiography core lab to confirm the fracture.

14. Deviations

A trial deviation is an event where the investigator or the invitational center personnel did not conduct the clinical trial according to the clinical protocol, clinical study agreement, or applicable laws and regulations.

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 will notify the sponsor and the reviewing IRB/EC, and the regulatory authority if applicable 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 will 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.

Deviations may include but are not limited to:

- Failure to obtain subject informed consent prior to beginning trial activities
- Violation of inclusion/exclusion criteria
- Failure to report serious or unanticipated adverse device effect or serious or unexpected AEs
- Failure to collect protocol-required assessments
- Subject missed visit or visit outside of window

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 the EDC system.

Investigational centers may also be required to report deviations to the IRB/EC, and the regulatory authority, per local guidelines and national government regulations.

Deviations attributable to the worldwide COVID-19 virus pandemic will be documented and reported to the sponsor using the EDC system. The statistical analysis plan provides further detail on the handling of missing data, drop-outs, and protocol deviation.

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

The sponsor will not approve protocol waivers.

15. Device Accountability for Products Labelled Investigational

The investigational devices/equipment will be securely maintained, controlled, and used only in this clinical trial. Investigational product must be stored in a secured and locked location accessible only to those delegated individuals who are authorized by the investigational center principal investigator to access them.

For investigational-labelled items, the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g. temperature, humidity, etc., as applicable)
- Return remaining items upon Sponsor request and in the condition in which they were provided; reasonable wear and tear excepted

The sponsor (or delegate) will keep records to document the physical location of all investigational devices from shipment from Boston Scientific (or designated facility) to the investigational centers until return or disposal.

Records will be maintained by the investigational center trial personnel to document the physical location and conditions of storage of all investigational devices.

The principal investigator or an authorized designee will keep records documenting the receipt, use, return and disposal of the investigational devices that include the following.

Maintain accurate and timely Device Accountability Records, providing copies to Sponsor upon request. Such records shall include the following content, at minimum:

- Name(s) of person(s) who received, used, returned, or disposed of each item;
- Date of receipt
- Identification and quantity of each investigational device (ie, batch number)
- 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, no longer needed, and/or malfunctioning investigational device, if applicable
- Date and documentation of disposal, as directed by sponsor, if applicable

16. Compliance

16.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with US FDA 21 CFR 812; European Medical Device Regulation, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; the relevant parts of the ICH Guidelines for Good Clinical Practice; Japan Medical Device GCP Ordinance ethical principles that have their origins in the Declaration of Helsinki and individual country laws and regulations.

The trial will not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Also, the trial will not begin prior to issuance of the center authorization to enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC or a regulatory authority will be followed, if appropriate.

16.2. *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 clinical investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The principal investigator's responsibilities include, but are not limited to, the following:

- Prior to beginning the study, sign the clinical study agreement and comply with the investigator responsibilities as described in such agreement
- Prior to beginning the study, sign the investigator brochure signature page and protocol signature page documenting his/her agreement to conduct the study in accordance with the protocol
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the investigational 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 as applicable per the protocol and observed device deficiency
- Report to sponsor, per the protocol requirements, all reportable events
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC, and supply Boston Scientific (or delegate) 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 clinical research monitor or auditor and respond to questions during monitoring visits or audit(s)
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the informed consent form
- 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, 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 investigational center team and facilities exist and are maintained and documented during the clinical investigation

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the principal investigator is responsible for providing appropriate training, ensuring team members are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a center, the sub investigator should not be delegated the primary supervisory responsibility for the investigational center. The principal investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. *Institutional Review Board/ Ethics Committee*

The investigational center will obtain the written and dated approval/favorable opinion of the IRB/EC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor (or designee) before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the ICF will be IRB/EC approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previous version of the ICF.

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

16.4. *Sponsor Responsibilities*

All information and data sent to Boston Scientific (or delegate) concerning subjects or their participation in this study will be considered confidential by Boston Scientific and will be

kept confidential in accordance with all applicable laws and regulations. Only authorized Boston Scientific personnel and/or a Boston Scientific representative including, but not limited to Contract Research Organization (CRO) will have access to this information. 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 Boston Scientific for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1. Role of Boston Scientific Representatives

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

In addition, Boston Scientific personnel may perform certain activities to ensure trial quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and trial documentation for completeness and accuracy

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
- Independently collect critical trial data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

16.5. *Insurance*

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

17. Monitoring

Monitoring will be performed to assess continued compliance with the protocol and applicable regulations. The monitoring plan contains the strategy for frequency of monitoring visits and source data verification to be completed for the trial.

The monitor verifies that trial 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 trial safely and effectively. The investigator/institution guarantees direct access to original source documents (ie, paper and electronic hospital charts, appointment books, laboratory records) by Boston Scientific personnel, their designees, and applicable regulatory authorities.

The trial may also be subject to a quality assurance audit by Boston Scientific or its designees, as well as inspection by appropriate regulatory authorities. It is important that the principal investigator and relevant trial personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

18.1. *Anticipated Adverse Events Associated with use and the Implantation of the DES BTK Vascular Stent System during an endovascular procedure*

- Allergic reaction (to drug/polymer, contrast, device or other)
- Amputation
- Bleeding/Hemorrhage
- Death
- Embolization (air, plaque, thrombus, device, tissue or other)
- Hematoma
- Ischemia
- Need for urgent intervention or surgery
- Pseudoaneurysm formation
- Renal insufficiency or failure
- Restenosis of stented artery
- Sepsis/infection
- Thrombosis/thrombus
- Transient hemodynamic instability (hypotensive/hypertensive episodes)
- Vasospasm
- Vessel injury, including perforation, trauma, rupture and dissection
- Vessel occlusion

18.2. *Adverse Events Unique to the Paclitaxel Drug Coating*

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. In these circumstances the dose was 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

Meta-analyses of randomized controlled trials of paclitaxel-coated balloons and paclitaxel-eluting stents used to treat peripheral arterial disease in the femoropopliteal arteries have identified an increased risk of late mortality at 2 years and beyond. The magnitude and mechanism for the increased risk in mortality is currently unclear. The analyses also demonstrated reduced revascularization rates with the drug-containing products. The impact of future device exposure is unknown as is the impact of other drug-containing devices. Inadequate information is available to evaluate the potential mortality risk associated with the use of paclitaxel-coated devices for the treatment of other diseases/conditions. Physicians should discuss the benefits and risks of all available treatment options with patients.

18.3. *Risks Associated with Participation in the Clinical Trial*

Risks associated with venipuncture include ecchymosis, hematoma, infections, inflammation and pain. There may be additional risks linked to the investigational device procedure and follow-up testing that are unknown. Tests planned for the trial follow-up phase is standard of care procedures except for the collection of high definition x-ray to assess stent integrity.

18.4. *Possible Interactions with Concomitant Medical Treatments*

In addition to the 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 package insert for further information on drug interactions and side effects associated with paclitaxel or antithrombotic/antiplatelet medications.

18.5. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate healthcare 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 Boston Scientific with all pertinent information required by this protocol.

18.6. *Anticipated Benefits*

Potential anticipated benefits include the effective treatment of atherosclerotic infrapopliteal lesions with improvement in the symptoms of disease. However, the DES BTK Vascular Stent System is an investigational device and these potential benefits may or may not actually be present.

18.7. *Risk to Benefit Rationale*

The DES BTK Vascular Stent System is expected to be suitable for its intended purpose. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of appropriate directions for use (DFU). The DES BTK Vascular Stent System is expected to have an acceptable adverse event profile when used under the conditions intended; the benefits associated with the use of the DES BTK Vascular Stent System are expected to outweigh the risks.

19. Safety Reporting

19.1. *Reportable Events by investigational center to Boston Scientific*

It is the responsibility of the investigator to assess and report to Boston Scientific (or delegate) the following events for enrolled subjects:

- Adverse events/ serious adverse events related to Study Device (Investigational Device) and Comparator Device
- All Serious Adverse Events related to the Procedure
- Serious adverse events
- Device Deficiencies
- Unanticipated adverse device effects/unanticipated serious adverse device effects
- New findings/updates in relation to already reported events
- New wounds on the index limb
- All other adverse events (through the 12-month follow-up visit)

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.

An AE experienced by the trial subjects after randomization/enrollment and during protocol-required testing must be recorded in the eCRF.

Underlying diseases are not reported as an AE unless there is an increase in severity or frequency during the course of the investigation.

Death will not be recorded as an AE, but will be reflected as an outcome of a specific SAE. Refer to Table 19.2-1 for AE definitions.

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

Device deficiencies will be reported on the appropriate eCRF per the trial CRF completion guidelines. When an AE results from a device deficiency or other device issue, the AE will be reported separately.

An in-patient hospitalization is defined as the subject being admitted to the hospital for ≥ 24 hours with the following exceptions:

- A hospitalization for routine follow-up per standard of care.
- A hospitalization that is uncomplicated and elective/planned (ie, planned prior to enrollment) does not have to be reported as an SAE or AE.
- If complications or AEs occur during an elective/planned 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.

If subjects are hospitalized during the course of the trial, the data about the hospitalization associated with adverse events will be collected in the EDC system.

Planned minor amputations (ie, below the ankle) or debridement that are performed as part of the subject's care pathway will not be reported as an AE, however, clinical sequelae resulting from the minor amputation must be reported as an AE.

The underlying pathology for an unplanned debridement and/or amputation procedure (ie, one that is not part of the care path continuum) will be reported as an AE.

New wound development on the index limb will be reported as an AE. Images will be collected for all new wounds and submitted for the study.

Serious adverse device-effects that are still ongoing at the end of the subject's participation in the trial will be followed up for resolution status and this information will be provided to Boston Scientific for the purpose of regulatory agency reporting for the trial.

19.2. *Definitions and Classification*

Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 19.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Term	Definition
	NOTE 1: This includes events related to the investigational medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational medical device **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. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *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.

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the risk assessment. **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 assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **Note 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

19.3. *Relationship to Study Device(s)(Investigational Device and Comparator Device) and/or Study Procedure*

The investigator must assess the relationship of the reportable AE to the study device, or procedure.

Table 19.3-1: Criteria for Assessing Relationship of Trial Device(s) (Investigational Device and Comparator Device) or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: • The event has no temporal relationship with the use of the investigational device or the procedures related to the use of the investigational device; • The event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • 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; • The event involves a body-site or an organ that cannot be affected by the device or procedure; • The event can be attributed to another cause (eg, an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors); • The event does not depend on a false result given by the investigational device used for diagnosis, when applicable; • 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.

Classification	Description
Unlikely Related *Ref: MEDDEV 2.7/3*	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 *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship *Ref: MDCG 2020-10/1*	The event is associated with the investigational device or comparator or with procedures beyond reasonable doubt when: • The event is a known side effect of the product category the device belongs to or of similar devices and procedures; • The event has a temporal relationship with investigational device use/application or procedures; • The event involves a body-site or organ that ➢ the investigational device or procedures are applied to ➢ the investigational device or procedures have an effect on; • The event follows a known response pattern to the medical device (if the response pattern is previously known); • 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); • Other possible causes (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • Harm to the subject is due to error in use; • The event depends on a false result given by the investigational device used for diagnosis, when applicable • In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event

The investigator must assess the relationship of an AE to the antiplatelet medication as related or unrelated.

Table 19.3-2: Criteria for Assessing Relationship of Antiplatelet Medication to an 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.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 19.4-1.** An Event Document Checklist included in the MOP specifies the required source documents for events requiring CEC adjudication.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline** (21 CFR Part 812, *MDCG 2020-10/1*)
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. • Terminating at the end of the trial
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event	• At request of sponsor
Serious Adverse Event (SAE)	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the 36 Months Post-Procedure Visit
	Provide all relevant source documentation (de-identified/ pseudonymized) for events to be adjudicated by CEC	• When documentation is available
Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the 36 Months Post-Procedure Visit
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event	• At request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors and inadequacy in information supplied by the manufacturer, including labeling)	Complete Device Deficiency eCRF with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the trial

Event Classification	**Communication Method**	**Communication Timeline** (21 CFR Part 812, *MDCG 2020-10/1*)
Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred or circumstances had been less fortunate is considered a reportable event.	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event	• At request of sponsor
Adverse Event (AE) including Adverse Device Effects (ADE)	Complete AE eCRF, which contains such information as date of AE, treatment of AE, resolution, assessment of seriousness and relationship to the device.	• In a timely manner (eg, Recommended within 10 business days) after becoming aware of the information • ADE reporting required through the 36 Months Post-Procedure Visit • AE reporting required through the 12-month follow-up visit
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event	• At request of sponsor

19.5. *Boston Scientific Device Deficiencies*

Device deficiencies for the DES BTK Vascular Stent System (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 Boston Scientific. If possible, the device(s)/system should be returned to Boston Scientific for analysis. Instructions for returning the investigational device(s) will be provided in the manual of operations and trial training. Device deficiencies should also be documented in the subject's medical records.

Device deficiencies related to a non-BSC comparator device will not be collected. Any non-BSC comparator device malfunction will be reported by the Investigator directly to the manufacturer of that device as a complaint.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency should be recorded as an adverse event on the appropriate eCRF.

Any Device Deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred or circumstances had been less fortunate is considered a reportable event.

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

- Packaging or labeling deficiency
- Difficult or unable to advance over wire
- Difficult or unable to track through anatomy

- Difficult or unable to cross lesion
- Difficult or unable to deploy stent
- Stent damaged
- Stent jump
- Kinked or deformed stent
- Difficult to remove stent delivery system from body
- Stent fracture
- Stent migration

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

Boston Scientific is responsible for reporting adverse event information to all participating principal investigators, IRBs/ECs and regulatory authorities, as applicable.

The principal investigator is responsible for informing the IRB/EC, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

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.

20. Informed Consent

Subject participation in this clinical trial is voluntary. Informed consent is required from each subject or his/her legally authorized representative. The investigator is responsible for ensuring that informed consent is obtained prior to any trial-required procedure or testing, the use of an investigational device, and 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 institutional ethics committee and/or regulatory authority, as applicable. Boston Scientific will provide a template of the ICF to investigators participating in this trial. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC.

Approval of the investigational center's ICF is required by Boston Scientific (or designee) and the governing IRB/EC prior to the first use and any time the ICF is updated during the trial.

The ICF must be in a language understandable to the subject and, when needed, Boston Scientific (or delegate) will assist the investigational center with obtaining ICF translation. Translated ICFs must also have IRB/EC approval prior to their use. Privacy language will be included in the body of the form or as a separate form in compliance with local requirements.

The process of obtaining informed consent will, at minimum, include the following and will be in compliance with all local applicable laws, rules, regulations and guidelines:

- Be conducted by the principal investigator or qualified designee authorized to conduct the process

- Include a description of all aspects of the clinical trial that are relevant to the subject's decision to participate throughout the clinical trial
- Avoid any coercion of or undue influence of a subject to participate
- Will not waive or appear to waive subject's legal rights
- Will 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
- Explain that important new information is to be provided to new and existing subjects throughout the clinical trial

The ICF will 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. The original signed ICF will be retained by the investigational center and a copy of the signed and dated document and any other written information must be given to the person signing the ICF. The subject will receive a signed copy of the ICF and other written information as approved by the IRB/EC.

For individuals 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. In Japan, ICF signature may be replaced by printed name and seals of appropriate individuals.

If the informed consent is obtained the same day the subject begins participation in trial-related procedures, it must be clearly documented in the subject's medical record that consent was obtained prior to participation in any trial-related procedures.

Failure to obtain subject consent will be reported by Boston Scientific to the applicable regulatory authority according to the local requirements (eg, FDA requirement is within 5 working days of learning of such an event).

Any violation of the informed consent process must be reported as a deviation to the sponsor and in compliance with local requirements (ie, regulatory authority, IRB/EC).

If new information becomes available that can significantly affect a subject's future health and medical care, that information will 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 trial, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in principal investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the investigational center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

21. Committees

21.1. *Executive Committee*

An executive committee composed of Boston Scientific clinical management and selected coordinating principal investigator(s) will be convened. This committee will be responsible for the overall conduct of the trial which will include protocol development, trial progress, subject safety, overall data quality and integrity, and timely dissemination of trial results through appropriate scientific sessions and publications. The executive committee may request participation of SAVAL trial investigators on the committee.

21.2. *Safety Monitoring Process*

To promote early detection of safety issues, the independent clinical events committee (CEC) and data monitoring committee (DMC) 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 the Boston Scientific safety group (or designee), which is responsible for coordinating the collection of information for the subject dossier from the 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.

21.3. *Clinical Events Committee*

The CEC is an independent group of individuals with no affiliation with Boston Scientific. 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
- Clinically-driven target lesion revascularization
- Target vessel revascularization
- Target limb major amputations
- Target Lesion stent thrombosis

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 centers.

21.4. *Data Monitoring Committee*

A DMC will be established to review overall trial conduct and safety and will be comprised of, at minimum, 3 members who are independent of Boston Scientific and the trial investigators. The DMC will be comprised of at least 2 independent clinicians and 1

independent statistician with expertise in peripheral endovascular procedures and/or statistical subject matter.

The DMC will be responsible for:

- Assessing the progress of the trial, including safety data
- Evaluating trial conduct (eg, trial deviations) for the impact on the validity and scientific merit of the trial
- Recommending to Boston Scientific whether to continue, modify, or stop the trial
- Provide recommendation for use of overlapping stents for the study (i.e. assessing the first 46 phase A RCT subjects)

Boston Scientific personnel, or delegate, may facilitate the DMC meetings, provide trial progress updates, and answer questions. Boston Scientific personnel will not be voting members or participate in the closed session portion of the meetings.

The frequency for meetings and thresholds will be defined within a DMC charter. Meetings may be more frequent depending on the rate of enrollment, number of AEs, and/or deviations collected and at the request of Boston Scientific. Meetings may be held in-person or via teleconference.

21.5. *Independent Wound Assessment*

Wound assessment data and images will be reviewed by an independent reviewer(s), with expertise in wound care and with no affiliation with Boston Scientific. The independent assessor(s) will be blinded to randomization assignment in phase A.

22. Suspension or Termination

22.1. *Premature Termination of the Study*

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

22.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature trial termination include, but are not limited to, the following:

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC or regulatory authorities to suspend or terminate the clinical investigation.

- An enrollment rate far below expectation that prejudices the conclusion of the trial
- A decision on the part of Boston Scientific to suspend or discontinue development of the device

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

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

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

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

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

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

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

22.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific reserves the right to stop the inclusion of subjects at a trial investigational center at any time after the study initiation visit, if no subjects have been enrolled for a period beyond 3 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of an investigational center’s participation, all study devices and testing equipment, as applicable, will be returned to Boston Scientific unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

23. Study Registration and Results

23.1. *Study Registration*

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

23.2. *Clinical Investigation Report*

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

24. Publication Policy

Boston Scientific requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a Boston Scientific trial or its results. Boston Scientific will submit trial results for publication (regardless of trial outcome) following the conclusion or termination of the trial. Boston Scientific 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 trial results in a timely manner, while maintaining an unbiased presentation of trial outcomes, Boston Scientific personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- Authorship and contributorship requirements as described above must be followed
- Boston Scientific involvement in the publication preparation and the Boston Scientific 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

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

25. Reimbursement and Compensation for Subjects

25.1. *Subject Reimbursement*

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the clinical study agreement.

25.2. *Compensation for Subject's Health Injury*

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

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27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviation	Terminology
ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
CTA	Computerized Tomography Angiography
CE	Conformité Européenne (meaning European Conformity)
CEC	Clinical Events Committee
DES BTK	Drug-eluting stent below the knee
DFU	Directions for Use
DSA	Digital Subtraction Angiography
DUS	Duplex Ultrasound

eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ITT	Intention to Treat
IRB	Institutional Review Board
MAE	Major Adverse Event
PTA	Percutaneous Transluminal Angioplasty
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TBI	Toe Brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect

27.2. *Definitions*

Table 26.2-1: **Definitions**

Term	Definition
Amputation	• Major Amputation: amputation of the lower limb at the ankle level or above. • 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: • 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. • Brachial: The systolic pressure will be measured in both arms, and the highest of both pressures will be used for the ABI calculation.
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.
Calcification	Readily apparent densities seen within the artery wall and site of lesion as an x-ray-absorbing mass.
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).

Term	Definition
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. All death events will be submitted to the CEC and will be categorized as: • 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. • Vascular death: death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause**.** • 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.
Dissection NHLBI Grade Types	Type A- Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material. Type B- Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles. Type C- Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material. Type D- Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow. Type E- Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen. 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.

Term	Definition
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.
Hemodynamic Improvement	Improvement of ABI by ≥ 0.1 or to an ABI ≥ 0.90 as compared to the pre-procedure value without the need for repeat revascularization.
Inflow and Outflow Lesions	Inflow lesion – a lesion located in the iliac artery, SFA and/or popliteal artery, proximal to the target lesion Outflow lesion - a lesion located in the segment of the target vessel distal to the target lesion
Lesion Length	Measured as the distance from the proximal shoulder to the distal shoulder of the lesion, in the view that demonstrates the stenosis in its most elongated projection.
Major Adverse Event	Defined as: • Above the ankle amputation of the index limb • Major re-intervention (new bypass graft, jump/interposition graft, or thrombectomy/thrombolysis) • Perioperative (30 day) mortality
Minimal Lumen Diameter	The vessel diameter as measured at the most narrow point of the lesion.
Occlusion	Lesion with no flow; implies 100% diameter stenosis.
Perforation	Perforations are classified as follows: ***Angiographic perforation*:** perforation detected by the investigational center or angiographic core laboratory at any point during the procedure. ***Clinical perforation*:** perforation requiring additional treatment (eg, covered stent graft or surgery), or resulting in significant hemodynamic compromise, or death.

Term	Definition
Planned Hospitalization	An elective/planned hospitalization (ie, planned prior to enrollment)
Primary Patency	A binary endpoint to be determined via duplex ultrasound (DUS) measuring flow or no flow in the absence of clinically-driven target lesion revascularization or bypass of the target lesion
Procedural Success	Technical success with no MAEs noted within 24 hours of the index procedure.
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.
Re-intervention (Percutaneous and/or Surgery)	Either repeat endovascular treatment or bypass surgery of the index limb, performed subsequently to the subject leaving the procedure room after the index procedure.
Reference Vessel Diameter (RVD) of Normal Arterial Segment	Angiographic measurement of the artery proximal and/or distal to the lesion intended for treatment.
Rutherford/Becker Classification	Category 0 - Asymptomatic Category 1 - Mild claudication Category 2 - Moderate claudication Category 3 - Severe claudication Category 4 - Ischemic rest pain Category 5* - Minor tissue loss - nonhealing ulcer, focal gangrene Category 6 - Major tissue loss – extending above TM level *Lesions must be limited to the forefoot and should be treatable with planned debridement, toe amputations and never exceeding trans metatarsal amputation.

Term	Definition
Source data *Ref: ISO 14155*	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. **Note 1**: This includes source data initially recorded in an electronic format.
Source document *Ref: ISO 14155*	Original or certified copy of printed, optical or electronic document containing source data.
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): • Grade 0: No strut fractures • Grade I: single tine fracture • Grade II: multiple tine fracture • Grade III: stent fracture(s) with preserved alignment of the components • Grade IV: stent fracture(s) with mal-alignment of the components • Grade V: Stent fracture(s) in a trans-axial spiral configuration

Term	Definition
Stent thrombosis	The occurrence of either of the following: 1. Angiographic documentation (or any other imaging modality if angiography not available) of an acute, complete occlusion of a previously successfully treated target lesion and/or 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 target lesion. *Acute* stent thrombosis is defined as occurring ≤ 24 hours following the clinical study procedure. *Subacute* stent thrombosis is defined as occurring > 24 hours to ≤ 30 days following the clinical study procedure. *Late* stent thrombosis is defined as > 30 days to 365 days following the clinical study procedure. *Very late* stent thrombosis is defined as > 365 days following the clinical study procedure.
Target Lesion	The segment of the artery with peripheral arterial disease that meets the characteristics outlined in the protocol to be treated with either the DES BTK test device or the PTA control device.
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: • 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.) • 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.)

Term	Definition
Target Vessel	The vessel(s) containing the target lesion, i.e. Tibial Peroneal Trunk, Anterior Tibial Artery, Posterior Tibial Artery and/or Peroneal Artery.
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: • 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.) • 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.)
Technical Success	Delivery and deployment of the assigned study therapy (stent or PTA) to the target lesion achieving a residual angiographic stenosis no greater than 30% by visual assessment.
Thrombus (angiographic)	Discrete, mobile intraluminal filling with defined borders with/without associated contrast straining; these are classified as either absent or present.
VascuQol	The VascuQol is a 25-item questionnaire used to measure the quality of life in patients with lower limb ischemia. The tool is sub-divided into 5 domains: pain (4 items), symptoms (4 items), activities (8 items), social (2 items), and emotional (7 items).

28. Appendices

28.1. *Appendix A: Affect to Medicare Beneficiaries (US only)*

Critical limb ischemia (CLI) represents the terminal stage of obstructive, atherosclerotic, peripheral arterial disease. Patients affected by critical limb ischemia are the most complex subset of those with peripheral arterial disease and typically bear the long-term pathological consequences of hypertension, hyperlipidemia, diabetes mellitus, and renal failure.[1] When left untreated, CLI caused major amputation in 73% of the patients with rest pain and in 95% of the patients with tissue loss at 1 year.[2] Diabetics with CLI are at particularly high risk for advanced complications; studies indicate that within one year of CLI diagnosis, 40% to 50% of diabetics will experience an amputation.[3] Incidence of CLI increases sharply among Medicare beneficiaries ages 65 to 69 (0.13%) to 85 and older (0.31%). As many as 33% of new CLI Medicare beneficiaries may undergo primary amputation within 1 year after diagnosis.[4]

According to HCUP National Inpatient Sample (NIS) all payer 2014 claims data*, Medicare is the payer for 69% of patients with lower extremity atherosclerosis and 67% of patients treated with Percutaneous transluminal angioplasty and/or peripheral stent**. The subjects eligible for inclusion in the SAVAL trial are likely to align with HCUP patients due to their expected age. Medicare eligible patients are not expected to respond differently to treatment compared to other patients, therefore the results of this trial are likely to be highly generalizable to the Medicare population.

* https://hcupnet.ahrq.gov/#setup

** ICD-9-CM Codes (ICD9), Principal Diagnosis: 440.20 Athscl Extrm Ntv Art Nos, 440.21 Ath Ext Ntv At W Claudct, 440.22 Ath Ext Ntv At W Rst Pn, 440.23 Ath Ext Ntv Art Ulcrtion, 440.24 Ath Ext Ntv Art Gngrene, 440.29 Athrsc Extrm Ntv Art Oth, 440.30 Athscl Extrm Bps Gft Nos, 440.31 Ath Ext Autologs Bps Gft, 440.32 Ath Ext Nonautlg Bps Gft, 440.8 Atherosclerosis Nec, 440.9 Atherosclerosis Nos, 445.02 Atheroembolism, Lower Ext, 444.22 Lower Extremity Embolism (after Oct 1, 2002), 440.4 Chr Tot Occl Art Extrem. Procedures--ICD-9-CM Codes (ICD9): Angio Oth Non-Coronary (after Oct 1, 2011) | Ins Nondrug Noncor Stent (after Oct 1, 2002) | Ins Drug-Elut Non-Cor St (after Oct 1, 2004)

1) Mustapha, JA, Et. Al. Percutaneous Transluminal Angioplasty in Patients With Infrapopliteal Arterial Disease: Systematic Review and Meta-Analysis. Circ Cardiovasc Interv. 2016 May;9(5)]
2) Karnabatidis D, Katsanos K, Siablis D. Infrapopliteal stents: overview and unresolved issues. J Endovasc Ther. 2009;16(suppl 1): 1153- 162
3) Elsayed S, Clavijo LC. Critical limb ischemia. *Cardiol Clin.* 2015;33(1):37-47.
4) Prevalence, incidence, and outcomes of critical limb ischemia in the US Medicare population, Baser, Vasc Dis Manag 2013