RANGER II SFA

A 3:1 Randomized Trial Comparing the Boston Scientific RANGER™ Paclitaxel Coated Balloon vs Standard Balloon Angioplasty for the Treatment of Superficial Femoral Arteries (SFA) and Proximal Popliteal Arteries (PPA)

Clinical Investigation Plan Version AE
October 15, 2018

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CLINICAL INVESTIGATION PLAN

Study Reference Number **S2062**

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Investigational Sites	A list of investigational sites is provided in the Manual Of Operations. A list of investigational sites for Japanese sites only, is provided as a separate attachment to the protocol.
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 investigational sites.

Original Release: June 30, 2016

Current Version: October 15, 2018

Revision History

Revision	Release Date	Template number and version	Section	Change	Reason for Change
AA-Initial	June 30, 2016	90702637 Rev./Ver. AG	NA	NA	NA
vAB	September 19, 2016	90702637 Rev./Ver. AG	Title page	Added IDE number	New information
			Title page	Updated address for BSC European representative	Administrative Change
			Title page	Deleted New Zealand BSC office	Administrative Change
			Synopsis & Exclusion 9.3	Added platelet count exclusion	Test to ensure subject safety
			Synopsis, Statistic Sections 8.3, 12,1,2, 12,2 and 12,4,2	Interim analysis to occur with 75% of enrolled subjects instead of 50% of subjects	Revisions to address FDA comments on IDE submission.
			Synopsis and Secondary Endpoint	Change: Deleted Thrombosis endpoint	Endpoint not required for balloon study
			TOC	Updated	Updated to match amended changes
			Introduction	Added prevalence information for subject >65 yrs. of age	New Supportive information
			4.1.2	FIM Study enrolled 105 instead of 105 subjects	Correction
			10.1, Table 11-1 and 21	Added language to allow sites to include SOC testing completed within 30 days prior to index procedure that aligns with protocol-required baseline testing	Practical testing
			11.10 Follow up visits	Added PK testing	Clarification
			16 Device Accountability	Removed Equipment Accountability	No additional equipment is sent to the sites
			16 Device Accountability	Entered name of Device management vendors: Cenduit and Fisher	New Information
			19.5 Risk Minimization	Added: No treatment of pregnant or breast feeding females nor men intending to father children	Clarification

Revision	Release Date	Template number and version	Section	Change	Reason for Change
			19.519.5 Risk Minimization	Added birth control/pregnancy prevention for at least 90 days after index procedure	Clarification
			26 Bibliography	Added reference #5 related to prevalence	New Information
			26 Bibliography	Updated numbering of references	Formatting
vAC	May 11, 2017	90702637 Rev./Ver. AH	Whole document	Updated to current BSC protocol template 90702637 Rev/Ver AH	Update
			Contact Information	Updated study contacts	Update
			2.0 Protocol Synopsis	Revised number of potential centers from 70 to 80. Clarified Exclusion #2 that cardiac events (e.g. STEMI, unstable angina) within 6 months is an exclusion criteria. Reworded Exclusion #15 for clarification and added example (in-stent restenosis).Clarified contralateral and ipsilateral iliac only lesions may be treated at index. Removed full CMP at screening and 12 month follow-up. Revised statistical methods.	Clarification & Update
			5.2 Device Labeling of Investigational Devices	Updated investigational device label information	Update
			7. Trial Endpoints	Clarified unsuccessful randomized angioplasty treatment and ITT population.	Clarification
			8.1 Pharmacokinetic Sub-study	Clarified the PK sub-study is planned for the U.S. only.	Clarification
			8.2 Required medication therapy	Clarified all enrolled subjects (RCT: Ranger DCB, Standard PTA and PK sub-study) should follow the protocol-required antiplatelet regimen.	Clarification

Revision	Release Date	Template number and version	Section	Change	Reason for Change
				Clarified a subject is exempt from the antiplatelet requirements if the randomized angioplasty treatment is unsuccessful.	
			8.3 Scale & Duration	Revised number of potential centers from 70 to 80. Clarified unsuccessful randomized angioplasty treatment and ITT population. Revised number of patients enrolled in the U.S. to approximately 50%.	Update
			8.4 Treatment Assignment	Clarified unsuccessful randomized angioplasty treatment and ITT population.	Clarification
			8.7 Non-target lesions	Clarified contralateral and ipsilateral iliac only lesions may be treated at index.	Update
			9.3 Exclusion Criteria	Clarified Exclusion #2 that cardiac events (e.g. STEMI, unstable angina) within 6 months is an exclusion criteria. Reworded Exclusion #15 for clarification and added example (in-stent restenosis).	Clarification
			Table 11.1 Data Collection Schedule	Removed full CMP at screening and 12 month follow-up and replaced with only serum creatinine at screening.	Update
			11.4 Pre-procedure Assessments	Removed full CMP at screening and replaced with only serum creatinine at screening.	Update
			11.7.1 Treatment of Non-target Lesions	Clarified contralateral and ipsilateral iliac only lesions may be treated at index.	Update
			11.7.3 Enrollment	Clarified unsuccessful randomized angioplasty treatment and ITT population.	Clarification
			11.7.4 Treatment of Target Lesion(s)	Clarified a major (≥Grade D) flow-limiting dissection at pre-dilatation would exclude the patient. Removed specification of pre-dilatation of optimal sized balloon of "reference size of artery".	Update

Revision	Release Date	Template number and version	Section	Change	Reason for Change
			11.10 Follow-Up Visits	Clarified unsuccessful randomized angioplasty treatment and ITT population.	Clarification
			12. Statistical Considerations	Updated statistical methods throughout.	Update
			13.3 Core Laboratories	Added Covance as PK sub-study core lab	Update
			27.2 Definitions	Added P1 Segment definition	Clarification
vAD	November 7, 2017	90702637 Rev./Ver. AH	Appendix A	Added RANGER Long Balloon Sub Study. For use in selected centers in the EU and New Zealand	Update
vAE	October 15, 2018	90702637 Rev./Ver. AJ	2.0 Protocol Synopsis	Clarified PK blood draw timing is based on last Ranger DCB removal	Clarification
			8.3 Scale and Duration	Clarified PK blood draw timing is based on last Ranger DCB removal	Clarification
			Figure 8-2 Ranger II SFA PK Substudy Design	Clarified PK blood draw timing is based on last Ranger DCB removal	Clarification
			Table 11-1 Data Collection Table	Respiratory rate data collection not required if not local standard of care. Clarified PK blood draw timing is based on last Ranger DCB removal	Update & Clarification
			11.4 Pre-procedure Assessments	Respiratory rate data collection not required if not local standard of care	Update
			11.9 Post-procedure/Pre-Discharge	Respiratory rate data collection not required if not local standard of care. Clarified PK blood draw timing is based on last Ranger DCB removal	Update & Clarification
			Table 11-2 Blood Draw Schedule for Analysis of Paclitaxel Pharmacokinetics	Clarified PK blood draw timing is based on last Ranger DCB removal	Clarification
			11.10 Follow-up Visits	Corrected reference from “occluded stent” to “occluded lesion”. Respiratory rate data collection not required if not local standard of care	Correction & Update

Revision	Release Date	Template number and version	Section	Change	Reason for Change
			11.12 Missed or Late Visit	Clarified that access to a patient locator service may be provided, but will not be required	Clarification
			13.2. Data Retention	Data retention period for using as part of use-results evaluation was clarified/corrected in accordance with current regulation.	Correction & Update
			Appendix A	Corrected Follow-up Schedule required timepoints for Rutherford Classification in the Long Balloon Substudy Synopsis. Clarification that 12 month DUS patency data will be provided for Long Balloon Substudy subjects	Correction & Clarification

2. Protocol Synopsis

<table>
<tr><td colspan="2">RANGER II SFA: A 3:1 Randomized Trial Comparing the Boston Scientific <u>RANGER</u>™ Paclitaxel Coated Balloon vs Standard Balloon Angioplasty for the Treatment of <u>S</u>uperficial <u>F</u>emoral <u>A</u>rteries (SFA) and Proximal Popliteal Arteries (PPA)</td></tr>
<tr><td>Trial Objective(s)</td><td>To evaluate the safety and effectiveness of the Ranger™ Paclitaxel Coated Balloon for treating lesions located in the superficial femoral and proximal popliteal arteries (SFA/PPA).</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The Ranger drug coated balloon (DCB) is indicated for percutaneous transluminal angioplasty (PTA), after successful pre-dilatation, of de novo or restenotic lesions up to 180 mm in length located in native superficial femoral and proximal popliteal arteries (SFA/PPA) with reference vessel diameters of 4-8 mm.</td></tr>
<tr><td>Test Device</td><td>Ranger™ Paclitaxel Coated PTA Balloon Catheter (Ranger DCB)</td></tr>
<tr><td>Control Device</td><td>Standard Percutaneous Angioplasty (PTA) Balloon: Balloon Angioplasty</td></tr>
<tr><td>Device Sizes</td><td>I. Ranger™ Paclitaxel Coated PTA Balloon Catheter (Test Device)
The working catheter length is 135 cm for all diameters with two exceptions: The 4 mm diameter balloons (80 mm and 100 mm length balloons) are only available with a working shaft length of 80 cm.

The Ranger DCB balloons (test device) are provided by the Sponsor.

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="5">Balloon Length (mm)</th></tr>
<tr><th>30</th><th>40</th><th>60</th><th>80</th><th>100</th></tr>
<tr><td rowspan="5">Balloon Diameter (mm)</td><td>4.0</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>5.0</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>6.0</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>7.0</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>8.0</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td></tr>
</table>

II. Standard PTA (Control Device)
Standard PTA (non-scoring) device size (diameter, balloon and catheter lengths) utilization is determined by the research investigator. Standard PTA balloons (non-scoring) are commercially available balloons that the investigative sites utilize from their inventory.

Note: Drug coated balloons must be overlapped to cover targeted lesion(s) as specified in the inclusion criteria.</td></tr>
<tr><td>Trial Design</td><td>The clinical trial is a global, prospective, multicenter, single-blind, superiority, 3:1 (Ranger DCB vs. Standard PTA) controlled randomized</td></tr>
</table>

	clinical trial (RCT) evaluating the safety and effectiveness of the Ranger DCB in subjects with claudication and/or rest pain and with a positive diagnostic finding of *de novo*, non-stented and non-atherectomy-treated or restenotic lesion(s) in the SFA and/or PPA. Pharmacokinetic Substudy Concurrently, a human pharmacokinetics (PK) investigation (substudy) of this trial is also planned. This substudy is a prospective, multicenter, non-randomized study arm (Ranger DCB), conducted at multiple pre-specified investigational sites designed to evaluate the levels of paclitaxel in the systemic circulation of subjects at multiple time points after treatment with the Ranger DCB. Although an investigative center can participate in both the RCT and PK trial arms, a subject can either be enrolled in the RCT study arm or the PK sub-study, but not both.
Blinding / Unblinding	The RANGER II SFA trial is conducted as single blind. Subjects will be blinded to treatment assigned and treatment received. All subjects must remain blinded until completion of all 12 month follow-up visits (primary endpoint). Packaging of the investigational Ranger DCB and control PTA devices differ. Therefore the Investigator and staff performing the procedure will not be blinded to the assigned treatment arm or resulting treatment. Trial center personnel will be trained not to disclose the treatment assignment to the subject in order to minimize the potential unblinding of the subjects. The Duplex Ultrasound (DUS) Core Laboratory personnel, Angiography Core Laboratory personnel, and Clinical Events Committee (CEC) will remain blinded to each subject's treatment assignment through primary endpoint. Those involved in data analysis for the Sponsor will remain blinded until the primary endpoint interim analysis.
Planned Number of Subjects	Up to 396 subjects may be enrolled in this trial. At least 376 subjects will be enrolled into the randomized arm of the trial to yield: • 282 subjects to receive treatment with the Ranger DCB; investigational test device • 94 subjects to receive treatment with Standard PTA; control device From 12 to 20 subjects will receive treatment with the Ranger DCB for the non-randomized PK substudy. Approximately 25% of those enrolled into the PK substudy will have long lesions (≥100 mm) treated with the Ranger DCB.

Planned Number of Investigational Sites / Countries	Up to 80 trial centers worldwide may enroll subjects into the RANGER II SFA global pivotal DCB trial. Countries that may participate include centers located in Australia, Canada, European Union, Japan, New Zealand and the United States. Approximately 10 trial centers may enroll subjects into the PK substudy.
Primary Safety Endpoint	The primary safety endpoint assesses the occurrence of Major Adverse Events (MAE) defined as all-cause death through 1 month, target limb major amputation through 12 months, and/or target lesion revascularization (TLR) through 12 months post-index procedure. This safety endpoint is designed to demonstrate that the Ranger DCB 12-month MAE-free rate is non-inferior to the control group.
Primary Effectiveness Endpoint	The primary effectiveness endpoint assesses the primary lesion patency within 12 months post-index procedure. Primary effectiveness is defined as a binary endpoint determined by duplex ultrasound (DUS) peak systolic velocity ratio (PSVR) ≤ 2.4 in the absence of clinically-driven TLR. This effectiveness endpoint is designed to demonstrate that the 12-month primary patency for the Ranger DCB treated test group is superior to the control group. **Notes**: • Lesion patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment. • PSVR >2.4 suggests >50% stenosis. The treated segment will be assessed for patency as a single segment regardless of the number of tandem lesions within the ballooned segment.
Secondary Endpoints	• Technical success defined as successful delivery, balloon inflation and deflation and retrieval of the intact trial device without burst below the rated burst pressure (RBP) • Procedural success defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core laboratory evaluation (if core laboratory assessment is not available then the site-reported estimate is used) • Clinical success defined as procedural success without procedural complications (i.e. death, major target limb amputation, thrombosis of the target lesion, or clinically-driven TLR) prior to discharge • Major Adverse Events (MAE) through 60 months. MAEs are defined as all-cause death post-index procedure, TLR, and major target limb amputation • Death of any cause within 30 days, 6, 12, 24, 36, 48 and 60 months • TVR rates at 6, 12, 24, 36, 48 and 60 months • TLR rates at 6, 12, 24, 36, 48 and 60 months

	• Rate of Primary and Secondary sustained clinical improvement as assessed by changes in Rutherford Classification from baseline at 1, 6, 12, 24 and 36 months post-procedure • Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1, 6, 12, 24 and 36 months post-procedure • Duplex-defined binary restenosis (PSVR > 2.4) of the target lesion at 1, 6, 12, 24 and 36 months • Walking Improvement (distance) at 6 months and 12 months as assessed by changes in the Six Minute Hall Walk Test (6MWT) from baseline • Walking Improvement and Patient Utility Values assessed at 1, 6, 12, 24 and 36 months as assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D™ from baseline • Changes in healthcare utilization over time • PK parameters calculated for subjects in the PK substudy
Method of Assigning Patients to Treatment	Subjects presenting with claudication or ischemic rest pain, an angiographically significant lesion in the superficial femoral and/or proximal popliteal artery and a patent outflow artery to the foot are considered for the trial. If after consenting, meeting inclusion criteria and none of the exclusion criteria, confirmed angiographically significant lesion in the superficial femoral and/or proximal popliteal artery and successful protocol-defined pre-dilatation, subjects are randomized 3:1 to either a Ranger DCB (test) or a Standard PTA balloon (control). In the PK substudy, subjects will not be randomized; all subjects will be treated with the Ranger DCB. Subjects are considered enrolled when the Ranger DCB or Standard PTA is introduced into the subject's vasculature. **Note**: If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be entered into this trial (no randomization nor enrollment) The subject should be cared for and followed outside of the trial based on the physician's treatment plan. **Note**: If the balloon angioplasty attempt with the assigned treatment device (the test device Ranger DCB or control device Standard PTA) is not successful, follow-up through the 1 month visit only will occur as part of the Intent to Treat (ITT) population. Data for assessment of MAE will be collected for these subjects. No other testing or follow up is required.
Follow-up Schedule	Follow-up visits will occur pre-discharge, at Day 7, 1 month, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months post-index

	procedure. Office or clinic visits are required for testing during each protocol required follow-up visit, with the exception of the 48 and 60 month visits. These two visits can be conducted in the office/clinic or by phone to obtain MAE and medication data. Planned procedures and testing include the following: • Physical Exam at screening, pre-discharge, 1 month, 6 month, 12 month, 24 month and 36 month • Angiogram at time of index procedure and during any subsequent revascularization procedure (up to12 months post index procedure) • Duplex Ultrasound at 1 month, 6 month, 12 month, 24 month and 36 month • Rutherford Classification at screening, 6 month, 12 month, 24 month and 36 month • Resting ABI exam at screening, 1 month, 6 month, 12 month, 24 month and 36 month • Exercise Testing (6MWT) at screening, 6 month and 12 month • Questionnaires (WIQ and EQ5D) at screening, 1 month, 6 month, 12 month, 24 month and 36 month • Lab tests: - Complete Blood Count (CBC) containing WBC, RBC and PLT at screening - PK substudy subjects: venous blood drawn at screening, 10 min, 30 min, 1 hr., 3 hr., 6 hr., 24 or 48 hr. after last Ranger DCB balloon removal, Day 7 and Day 30 post index procedure - Pregnancy testing (serum or urine) within 24hrs prior to index procedure if of child bearing age • Medication compliance at screening, procedure, pre-discharge, 1 month, 6 month, 12 month, 24 month, 36 month, 48 month and 60 month • Adverse event monitoring at procedure, pre-discharge, 1 month, 6 month, 12 month, 24 month, 36 month, 48 month and 60 month
Study Duration	The trial will be considered complete (with regard to the primary endpoint) after all subjects have completed the 12 month follow-up visit, were discontinued prior to the 12 month follow-up visit, have died, or the last 12 month follow-up visit window is closed. The trial will be considered complete (with regard to all subject follow-up) after all subjects have completed the 60 month (5 year) follow-up visit, were discontinued prior to the 60 month (5 year) follow-up visit, have died, or the last 60 month (5 year) follow-up visit window is closed.

Required Medication Therapy	Anti-platelet therapy is recommended throughout the length of the trial participation. Investigators must prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice. Antiplatelet medication and peripheral artery disease (PAD) medication usage will be collected and reported for compliance throughout the trial. Minimum protocol requirements: • Anti-coagulation therapy administered prior to and during the procedure should be consistent with current clinical practice. • A minimum of 30 days of dual antiplatelet therapy for non-stented subjects and a minimum of 3 months (90 days) dual antiplatelet therapy for stented subjects post index procedure. Minimum recommendation: • Antiplatelet monotherapy is recommended for administration throughout the 5 year follow-up (trial completion). **Note**: A subject is exempt from the above-mentioned antiplatelet requirements if he/she requires Coumadin or other similar anti-coagulant due to known comorbidities and in the opinion of the investigator, the combination of antiplatelet and anticoagulant could put the subject at an unreasonable risk of bleeding.
Inclusion Criteria	Enrollment into the RANGER II SFA trial is limited to the following inclusion criteria: 1. Subject (or Legal Guardian) is willing and able to provide consent before any study-specific tests or procedures are performed and agree to attend all required follow-up visits; 2. Subject at least 20 years of age; 3. Chronic symptomatic lower limb ischemia defined as Rutherford classification 2, 3, or 4; 4. Target lesion is in the native SFA and/or PPA down to the P1 segment; 5. Patent popliteal and infrapopliteal arteries, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot; 6. Reference vessel diameter ≥ 4 mm and ≤ 8 mm by visual estimate (Use of a radiopaque ruler is recommended); and 7. Angiographic evidence that target lesion consists of a single de novo, non-stented and non-atherectomy treated or restenotic lesion (or tandem lesions or a combination lesion as defined below) that is: a. ≥ 70% -99% stenotic with total lesion length up to180 mm by visual estimate. Use of a radiopaque ruler is recommended.

	b. Occluded with total lesion length ≤ 100 mm by visual estimate. Use of a radiopaque ruler is recommended. c. If lesion is restenotic, most recent PTA treatment must be > 3 months prior to enrollment **Notes**: Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) are eligible provided that the combined total lesion length is ≤180 mm. Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria: • Separated by a gap of ≤ 30 mm (3 cm) • Total combined lesion length meets requirements (Angiographic inclusion criteria (7) including 30 mm gap); • Able to be treated as a single lesion.
Exclusion Criteria	Patients are not permitted to enroll into the RANGER II SFA trial if they meet any of the following exclusion criteria: 1. Life expectancy, documented in the Investigator's opinion, of less than 12 months; 2. Hemorrhagic stroke or cardiac event (e.g. STEMI, unstable angina) within 6 months prior to enrollment; 3. Known allergies or sensitivities to heparin, aspirin, other anticoagulant/antiplatelet therapies, and/or paclitaxel; 4. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated; 5. Chronic renal insufficiency with serum creatinine > 2.0 mg/dL within 30 days of index procedure or treatment with dialysis; 6. Platelet count <80,000 mm^3 or >600,000 mm^3 or history of bleeding diathesis; 7. Receiving immunosuppressive therapy; 8. Septicemia at the time of enrollment; 9. Any major (e.g., cardiac, peripheral, abdominal) intervention (including in the contralateral SFA/PPA) planned within 30 days post index procedure; 10. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of enrollment; 11. Failure to successfully cross the target lesion with a guidewire (successful crossing means tip of the crossing device is distal to the target lesion in the absence of flow-limiting dissections or perforations); 12. Failure to successfully pre-dilate the target vessel;

	13. Patient has lesion that requires the use of adjunctive primary treatment modalities (i.e. laser, atherectomy, scoring/cutting balloon, other debulking devices, etc.) during the index procedure; 14. History of major amputation in the target limb; 15. Target lesion or vessel has ever been previously treated with stent (e.g. in-stent restenosis) or surgery. Target lesion or vessel has been treated with atherectomy or a DCB in the past 12 months; 16. Pregnant or breast feeding; 17. Presence of aneurysm in the target vessel; 18. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to enrollment; 19. Patient has significant inflow disease which cannot be treated prior to the target lesion treatment; 20. Patient has perforated targeted vessel as evidenced by extravasation of contrast media; 21. Patient has severe calcification that renders the lesion undilatable; 22. Current participation in another investigational drug or device clinical trial that has not completed the primary endpoint at the time of randomization/enrollment or that clinically interferes with the current trial endpoints. **Note**: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies.
Multiple Interventions During Index Procedure	Contralateral & Ipsilateral Limb Lesions Using the same access site, iliac lesion(s) in the contralateral and ipsilateral limb may be treated during the index procedure under the following conditions: • Treatment with a commercially (non-drug coated) available device occurs prior to randomization of the target SFA/PPA lesion(s); • Treatment of the lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation) and If the above criteria are not met, the subject may not be randomized into the trial but may be rescreened for eligibility after 30 days. **Note**: Provisional stenting of the target lesion with bare-metal stents can be completed in cases where adequate results could not be obtained after using post-dilatation balloons; such as in the case of remaining residual stenosis[≥ 50%] or major [≥ Grade D] flow-limiting dissection after post-dilatation.
Statistical Methods	

Adaptive Sequential Testing Hypotheses Strategy	The primary effectiveness and safety hypotheses will be tested simultaneously in an adaptive group sequential manner at the overall significance level of one-sided 2.5%. The Lan-DeMets alpha spending function by Power Family Method with Rho=2 will be used to determine the interim and the final type I error adjustment. With a minimum of 75% of 12-month required subjects planned to be assessed in the interim analysis, the adjusted type I error will be distributed as 1.41% for the interim analysis (i.e. 75%) and 1.92% for the final analysis (i.e. 100%). The actual interim and final alpha adjustments will be calculated based on the alpha spending function when the exact interim proportion is observed (e.g. >75%). Note: when Rho=2, the alpha adjustments are between Pocock's method (Rho=1) and O'Brien-Fleming's method (Rho=3).
Primary Effectiveness Statistical Hypothesis	The primary effectiveness hypothesis to be tested is that 12-month primary patency in subjects treated with Ranger DCB is superior to subjects treated with Standard PTA at an overall one-sided significance level of 2.5%.
Primary Effectiveness Statistical Test Method Parameters	The Chi-Square Test will be used to assess the hypothesis of superiority in proportions: H_0: Pt - Pc ≤ 0 H_1: Pt - Pc > 0 where Pt and Pc are the 12-month primary patency for the Ranger DCB and Standard PTA, respectively.
Primary Safety Statistical Hypothesis	The primary safety hypothesis to be tested is that 12-month MAE-free rate in subjects treated with Ranger DCB is as safe as the subjects treated with Standard PTA at an overall one-sided significance level of 2.5%.
Primary Safety Statistical Test Method	The Chi-Square Test will be used to assess the hypothesis of non-inferiority in proportions: H_0: Pt - Pc $\leq \Delta$ H_1: Pt - Pc $> \Delta$ where Pt and Pc are the 12-month MAE-free rates for the Ranger DCB and Standard PTA, respectively, and Δ (delta) is the non-inferiority margin of -10%.
Success Criteria for the RCT	<u>Success Criteria for the Interim Analysis</u> <u>(for example, 75% subjects to be assessed at the interim analysis)</u> Ranger DCB will be concluded to be superior to Standard PTA for device effectiveness in the interim analysis if the one-sided lower 98.59% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month primary patency is greater than zero.

	Ranger DCB will be concluded to be as safe as Standard PTA if the one-sided lower 98.59% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month MAE-free is greater than -0.1. The study success will be concluded as both primary effectiveness and primary safety endpoints being achieved in the interim analysis. <u>Success Criteria for the Final Analysis</u> <u>(all subjects to be assessed at the final analysis when the interim analysis is not able to be concluded)</u> If for any reason the final analysis is required to demonstrate superiority, Ranger DCB will be concluded to be superior to Standard PTA for device effectiveness in the final analysis if the one-sided lower 98.08% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month primary patency is greater than zero. Ranger DCB will be concluded to be as safe as Standard PTA if the one-sided lower 98.08% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month MAE-free is greater than -0.1. As required, the study success will be concluded as both primary effectiveness and primary safety endpoints being achieved in the final analysis.

Sample Size Parameters	The overall sample size for RCT is driven by the primary effectiveness endpoint.
	
	<u>Primary Effectiveness Endpoint</u>
	• Power ≥ 85%
	• One-sided overall significance level (alpha) = 2.5%
	• Lan-DeMets alpha spending function with Power Family Method (Rho=2) is used for adjusted alphas for the interim and final assessments:
	  - One interim assessment for a minimum of 75% subjects to be assessed
	  - The final assessment for the overall subjects
	• Expected Standard PTA 12-month primary patency = 52.5%
	• Ranger DCB to demonstrate 20% treatment effect
	• Allocation (Ranger DCB vs. Standard PTA) = 3:1
	• Attrition rate in 12 months = 15%
	• N = 320 (total) evaluable subjects are required at 12 months (240 in Ranger DCB and 80 in the Standard PTA)
	• N = 376 (total) subjects to be randomized prior to the procedure (282 in Ranger DCB and 94 in Standard PTA)

	Primary Safety Endpoint • 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 for the interim analysis and/or for the final analysis as needed • Expected Standard PTA 12-month MAE-free = 75% • Expected Ranger DCB 12-month MAE-free rate = 90% • Non-inferiority margin (Δ) = -10%(clinically meaningful) The sample size is driven by the primary effectiveness endpoint to provide at least 94% power to assess the primary safety endpoint.
Sample Size and Statistical Method for PK Substudy	In order to support the stated objectives for the PK substudy, the sample size for this substudy will be 12 to 20 subjects in addition to the RCT. Descriptive statistics will be presented to describe the PK substudy results.
Core Laboratories	The following core laboratories will be established for the central assessment of key data collected during the trial: • Angiography: to assess angiograms taken during the index procedure and during any subsequent revascularization procedure (up to12 months post index procedure) • Ultrasound: to assess ultrasounds taken during the follow-up periods (1 month, 6 months, 12 months, 24 months and 36 months follow-up visits) • Pharmacokinetics: to assess paclitaxel levels at baseline and at defined time points.

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4. Introduction

Peripheral Arterial Disease (PAD) is the third leading cause of cardiovascular morbidity after myocardial infarction (MI) and stroke. Current estimates state that there are over 8 million US and 200 million global patients with PAD[1, 2] with an age–adjusted prevalence ranging from 12 to 20 percent[3, 4]. The prevalence of PAD among individuals age 65-69 years is 10.08% for women and 10.33% for men with advances to 18.38% for women and 18.83% for men by age 85-89 years[5]. Less than twenty percent of patients with PAD have typical symptoms of intermittent claudication such as leg muscle discomfort on exertion that is relieved by rest, or critical limb ischemia (CLI) (i.e., rest pain, ulceration or gangrene); whereas, another third have atypical exertional leg symptoms. In very serious cases, this blocked blood flow can lead to leg amputation.

PAD is a progressive disease of the circulatory system; excluding the heart and brain. Atherosclerosis is a build-up of plaque in the circulatory system. Over time, plaque hardens narrowing the arteries and limiting oxygen-rich blood flow to parts of the body. Treatment includes lifestyle interventions, medical treatment to prevent cardiovascular events as well as surgery and endovascular interventions. The majority of the patients remain stable or improve in response to lifestyle modification. But there are also patients who do not improve with this conservative management. They need revascularisation procedures to restore or improve their peripheral circulation. Notably, the risk of cardiovascular morbidity and mortality is equally high in patients with PAD, regardless of the presence of symptoms[6]. Non-revascularized lower extremity PAD is the most common cause of lower extremity amputation[7].

Endovascular Treatment of PAD in the SFA/PPA

In general, the debate for state-of-the-art therapy in SFA disease involves endovascular intervention versus bypass surgery. Historically, surgery is generally reserved for resting pain and critical limb ischemia. However, surgical therapy carries significant morbidity, including wound infection, MI and even death. In addition, up to 17 percent of the post-bypass surgery patients do not experience satisfactory clinical improvement[8]. Over the past decade, percutaneous catheter-based techniques have improved such that acute procedural success is high even in complex anatomy. Patency rates have also increased with the use of atherectomy devices and drug-eluting stents (DES). Often, patients with PAD have comorbidities that increase the risk of cardiovascular complications with surgical procedures. These factors have led to the adoption of an endovascular first strategy with surgical management reserved for selected patients[2, 9].

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

The femoropopliteal segment is a challenging vascular territory and has been among the least effective of all endovascular procedures in terms of long-term patency[10,11,12]. The SFA is the longest artery in the human body and is located between two major flexion points, the knee and the hip. The relatively small vessel lumen, in conjunction with a high plaque burden, slow flow, and a high frequency of primary occlusions, contributes to considerable technical difficulties. In

recent years, however, improvements in device technology and the skill-sets of the interventionalists have facilitated the treatment of complex lesions, including long-segment chronic occlusions with or without moderate calcification. In fact, the current evolution towards treating more complex femoropopliteal lesions as seen in the renewed TransAtlantic Inter-Society Consensus (TASC) II recommendations clearly reflects the continuous evolutions in femoropopliteal stent design[15]. In most cases, the progression of atherosclerotic flow-limiting lesions in the blood vessels of the legs frequently involves the infra-popliteal arteries, resulting in a worsening diagnosis of CLI.

In the past, balloon angioplasty alone was the treatment of choice for the femoropopliteal artery segment[14]. Percuteous transluminal angioplasty (PTA) is a procedure that can open up a blocked blood vessel using a small, flexible plastic tube, or catheter, with a "balloon" at the end of it. When the tube is in place, it inflates to open the blood vessel, or artery, so that blood flow is restored. The TASC working group suggested that primary success rates were above 90% with a very low rate of complications (< 4%)[14,15]. However, within one year, patency failure rates above 70% were observed after balloon angioplasty in lesions longer than 10 cm[15,16].

The application of self-expanding nitinol stent technology seemed to improve the safety and durability of stenting in the SFA[10, 17, 18, 19]. The theoretical basis for improved performance with the use of nitinol stents is due to the unique properties of nitinol such as flexibility, persistent radial force when oversized to a vessel, and ability for crush recovery in these high flexion and torsion force areas in the femoropopliteal arteries. In addition, self-expanding nitinol stents are not as prone to external compression as are balloon-expandable stents. Moreover, due to its smaller arterial diameter and complex nature, the femoropopliteal segment does not respond well to rigid stents. As such, the most flexible nitinol stent is needed to mitigate stent fracture that often occurs in the femoropopliteal arteries.

Although above the knee use of nitinol bare metal stents (BMS) is safe and feasible, it is evidently associated with significant neointimal hyperplasia and early restenosis [20, 21] which may be due to the chronic external forces on the vessel/stent interface resulting in a chronic stimulus for restenosis[22]. Therefore, the interest of investigators turned towards the pharmaceutical ingredients such as paclitaxel and everolimus to suppress neointimal growth and restenosis after stent deployment. DES technology was developed to prevent early thrombosis and late luminal loss to potentially improve long-term patency rates for SFA[23].

The use of drug coated balloon (DCB) treatment has emerged as a therapeutic alternative in the treatment of PVD/PAD in the superficial femoral and proximal popliteal arteries (SFA/PPA). In many European countries, DCBs have been utilized to treat PAD since 2003. Based on the results of the following three clinical trials, two DCBs are approved for use in the United States. LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) was a prospective, single blind (to patient), randomized (1:1) trial comparing LLL in femoropopliteal lesions treated with the Lutonix DCB versus an uncoated balloon. Demographic, peripheral vascular disease, and lesion characteristics were matched, with mean lesion length of 8.1 ± 3.8 cm and 42% total occlusions. At 6 months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 ± 1.13 mm) than for the control group (1.09 ± 1.07 mm; p = 0.016). Composite 24-month major adverse events were 39% for the DCB group, including 15 target lesion revascularizations, 1 amputation, and 4 deaths versus 46% for uncoated balloon group, with 20 target lesion revascularizations, 1 thrombosis, and 5 deaths. Pharmacokinetics showed

biexponential decay with peak concentration (C_{max}) of 59 ng/ml and total observed exposure (AUC_{all}) of 73 ng h/ml. For successful DCB deployment excluding 8 malfunctions, 6-month late lumen loss was 0.39 mm and the 24-month target lesion revascularization rate was 24%[24].

The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT) 2 trial was a prospective, multicenter, randomized, controlled trial. Between July 20, 2011, and July 10, 2012, 543 patients were enrolled at 54 sites in the United States and Europe. A total of 56 patients were enrolled in the roll-in phase, 11 patients with predilatation results indicating flow-limiting dissection or clinically significant residual stenosis were excluded from randomization but were treated according to the standard of care and followed for 30 days (standard-practice subgroup), and 476 patients were randomly assigned, in a 2:1 ratio, to undergo angioplasty with a drug-coated balloon (316 patients) or standard angioplasty (160). With respect to the primary composite safety end point, the proportion of patients free from perioperative death from any cause or free at 12 months from index-limb amputation, index-limb reintervention, and index-limb–related death was 83.9% in the drug-coated–balloon group versus 79.0% in the standard-angioplasty group, which met the prespecified criterion for noninferiority (P=0.005 for noninferiority). The proportion of patients who had primary patency at 12 months (the primary efficacy end point) was significantly greater with the drug-coated balloon than with the standard angioplasty balloon (65.2% vs. 52.6%, P=0.02)[25].

The IN.PACT SFA Trial is a prospective, multicenter, single-blinded, randomized trial in which 331 patients with intermittent claudication or ischemic rest pain due to superficial femoral and/or popliteal peripheral artery disease (PAD) were randomly assigned in a 2:1 ratio to treatment with DCB or PTA. One year (12 mth) data results are as follows: The DCB resulted in higher primary patency vs. PTA (82.2% vs. 52.4%; *P*<.001). The rate of clinically-driven target lesion revascularization was 2.4% in the DCB arm compared with 20.6% in the PTA arm (*P*<.001). There was a low rate of vessel thrombosis in both arms (1.4% after DCB and 3.7% after PTA (*P*=.10)). There were no device- or procedure-related deaths and no major amputations[26].

4.1. Clinical Program Development

4.1.1. Ranger DCB Platform

The Ranger DCB is a paclitaxel-coated Percutaneous Transluminal Angioplasty (PTA) balloon catheter developed as a collaborative effort between BSC and Hemoteq AG [HTQ, Wuerselen, Germany]. This co-development relationship leverages BSC's extensive Sterling™ catheter experience and HTQ's coating expertise for DCBs. The Ranger DCB is based on BSC's well characterized Sterling PTA balloon catheters. These catheters are coated with the paclitaxel (active ingredient) drug that is formulated with the excipient acetyltributyl citrate (ATBC) to effectively deliver paclitaxel to the vessel wall. Paclitaxel has been widely used for both stent and DCB applications as a safe and effective drug to inhibit neointimal proliferation and thereby reduce the rate of restenosis.

In some countries, the Ranger Paclitaxel-Coated PTA balloon catheter is CE Marked and indicated for Percutaneous Transluminal Angioplasty (PTA) in the peripheral vasculature, including iliac and infrainguinal arteries.

The justification of the leveraged data regulatory strategy for Ranger DCB's current indicated use is based on the following:

- The safety and performance of PTA balloon catheters in the revascularization of peripheral artery disease have been demonstrated with over 20 years of clinical experience with these devices.
- The safety and performance of the predicate device: Sterling PTA balloon catheter in the treatment of the peripheral vasculature is established via the extensive market experience with these devices. Field experience with the catheters demonstrates a favorable and reliable safety profile.
- The Ranger experience since CE-mark certification in July, 2014, demonstrates a favorable and reliable safety profile.
- The usefulness of paclitaxel in the treatment of peripheral arterial disease has been clinically established. Review of the literature demonstrates that paclitaxel is safe in peripheral applications and effective when delivered from a stent or a DCB platform. Both paclitaxel-coated drug-eluting stents[27] and paclitaxel-coated PTA balloons[28, 29, 30, 31] showed superiority to plain balloon angioplasty in the treatment of peripheral vascular disease in prospective, randomized clinical trials.

4.1.2. First In Man Feasibility Trial

The first-in-man clinical feasibility trial with the Ranger DCB completed the enrollment of 105 subjects from centers located in Germany, Austria, and France in October 2015. The trial design was a prospective, randomized; multicenter controlled (2:1 Ranger DCB vs uncoated balloon) clinical trial of the Ranger™ Paclitaxel-Coated PTA Balloon Catheter in comparison to uncoated PTA balloons in femoropopliteal lesions. The objective of the trial was to prove the superior performance of the Ranger DCB for angioplasty in femoropopliteal artery lesions when compared to non-coated balloons at six months post-procedure when comparing Late Lumen Loss (LLL). The primary endpoint was in-segment late lumen loss of the treated segment, as observed by core lab analyzed angiography at six months post-procedure. Subject eligibility criteria included clinically significant symptomatic limb ischemia defined as Rutherford classification 2, 3, or 4, and de novo, non-stented and non-atherectomy treated or restenotic lesions (≥70% stenosis) located in the native superficial femoral artery or proximal popliteal artery with a total lesion length ≥ 20 mm and ≤ 150 mm. The trial's Clinical Study Report (CSR) with results will be provided with the investigational device exemption submission.

5. Device Description

5.1. Ranger™ Paclitaxel Coated PTA Balloon Catheter

The Ranger Paclitaxel-Coated PTA balloon catheter (Figure 1) is an Over-the-Wire (OTW) Percutaneous Transluminal Angioplasty (PTA) balloon catheter with a semi-compliant balloon coated with a formulation of paclitaxel (drug) and ATBC (excipient).

The Ranger catheter is designed to inhibit restenosis by delivering drug to diseased arterial tissue.

The Ranger DCB catheter has a coaxial shaft design. The outer lumen is used for inflation of the balloon, and the wire lumen permits the use of guide wires 0.014 in (0.36 mm) or 0.018 in (0.46 mm) to facilitate advancement of the catheter. The balloon is designed to provide an inflatable segment of known diameter and length at recommended pressures. The Ranger DCB catheter includes a tapered tip to facilitate advancement of the catheter to and through the stenosis.

The Ranger DCB catheter has two radiopaque marker bands (one proximal and one distal) which, in conjunction with fluoroscopy, aid in the placement of the balloon. The working lengths of the Ranger DCB catheters are 80 cm and 135 cm. The proximal portion of the Ranger DCB catheter include one female Luer-lock port connected to the inflation lumen, and one female Luer-lock port for the guidewire lumen.

In addition, the Ranger DCB catheter is equipped with a balloon protector and a loading tool. The balloon protector is provided to help protect the coated balloon during transportation and is removed prior to use. The loading tool is provided to help protect the drug coating prior to sheath insertion and minimize the potential handing of the coated balloon by the operator. An image of the Ranger Paclitaxel-Coated PTA Balloon Catheter is below (**Figure 5-1**).

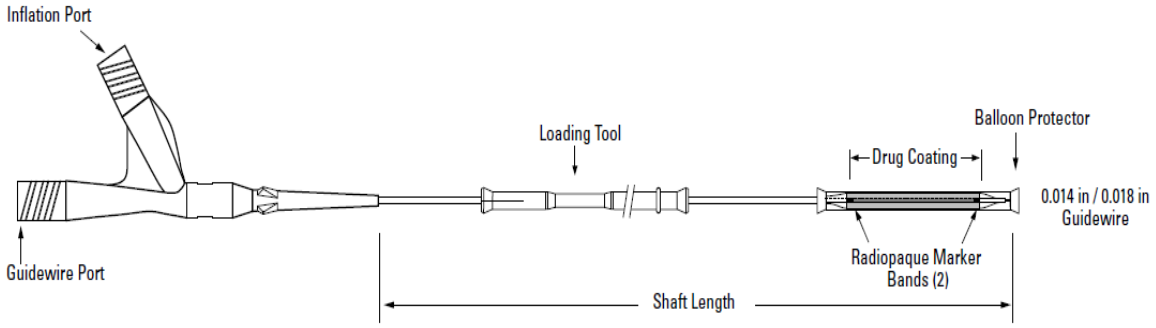

Figure 5-1: Ranger Paclitaxel-Coated PTA Balloon Catheter with Balloon Protector and Loading Tool

Technical characteristics of the device component of the Ranger DCB are identical to BSC's globally approved PTA balloon catheters: Sterling. Key device characteristics of the Ranger DCB are summarized in **Table 5-1**.

Table 5-1: Ranger DCB Characteristics

Characteristic	Description
Guidewire compatibility	0.014 in. (0.36 mm) or 0.018 in. (0.46 mm)
Working lengths (cm)	80 cm and 135 cm
Balloon diameters (mm)	4.0, 5.0, 6.0, 7.0, 8.0
Balloon lengths (mm)	30, 40, 60, 80, 100
Balloon type	Semi-compliant
Nominal pressure	6 atm

The Ranger DCB is available in a variety of diameters and balloon lengths. Device sizes intended for use in this global trial are exhibited in **Table 5-2**. The shaft lengths utilized for this trial is 135 cm for all diameters with two exceptions: The 4 mm diameter balloons (80 mm and 100 mm length balloons) are only available with a working shaft length of 80 cm. **Table 5-3** exhibits the dose of paclitaxel for each balloon by length and diameter. **Table 5-4** exhibits the Ranger DCB balloon compliance chart.

Table 5-2: Ranger DCB Device Sizes

		Balloon Length (mm)				
		30	**40**	**60**	**80**	**100**
Balloon Diameter (mm)	**4.0**	X	X	X	X	X
	5.0	X	X	X	X	X
	6.0	X	X	X	X	X
	7.0	X	X	X	X	X
	8.0	X	X	X	X	

Table 5-3: Paclitaxel Dose per Balloon Diameter and Length

		Balloon Length (mm)				
		30	**40**	**60**	**80**	**100**
Balloon Diameter (mm)	**4.0**	782 µg	1043 µg	1564 µg	2086 µg	2607 µg
	5.0	975 µg	1301 µg	1951 µg	2601 µg	3251 µg
	6.0	1100 µg	1467 µg	2200 µg	3108 µg	3889 µg
	7.0	1283 µg	1711 µg	2714 µg	3626 µg	4538 µg
	8.0	1468 µg	1957 µg	2935 µg	3913 µg	

Table 5-4: Ranger DCB Compliance Chart

Pressure		**Mean Balloon Diameter (mm)** (Balloon Lengths: mm)						
		4.0	**5.0**	**6.0**		**7.0**		**8.0**
atm	**kPa**	(all lengths)	(all lengths)	(30 - 60)	(80 - 100)	(30 - 40)	(60 - 100)	(all lengths)
6*	**608**	4.01	5.02	6.01	6.22	6.92	7.13	7.92
7	**709**	4.09	5.11	6.09	6.32	7.02	7.25	8.03
8	**811**	4.15	5.19	6.17	6.40	7.11	7.35	8.12
9	**912**	4.20	5.25	6.24	6.47	7.18	7.43	8.19
10	**1013**	4.25	5.31	6.29	6.53	7.25	7.49	8.25
11	**1115**	4.29	5.36	6.35	6.57	7.31	7.56	8.31
12**	**1216**	4.34	5.41	6.39	6.62	7.36	7.61	8.37
13	**1317**	4.37	5.45	6.43	6.67	7.41	7.66	
14**	**1419**	4.40	5.49	6.48	6.72	7.46	7.73	

*6 = Nominal all sizes
**12 = RBP for 8.0 mm
**14 = RBP for 4.0 mm to 7.0 mm

5.1.1. Drug Components Description

The balloon coating consists of paclitaxel (PTx) and the excipient, acetyltributyl citrate (ATBC). PTx is a widely utilized drug in both stent and drug-coated balloon applications for reducing the rate of neointimal proliferation and thereby the rate of restenosis. The drug to excipient formulation ratio is 80:20 PTx/ATBC. The resulting drug dose density (total weight of drug per unit of balloon surface area) on the coated balloon is 2 µg/mm^2.

Paclitaxel (PTx) is the active pharmaceutical ingredient on the Ranger DCB. Paclitaxel is a white powder, isolated from a spectrum of TAXUS species and hybrids. It is a terpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol, and a molecular formula of $C_{47}H_{51}NO_{14}$ as shown in **Figure 5-2** below. It is highly lipophilic and insoluble in water, but is freely soluble in methanol, ethanol, chloroform, ethyl acetate, and dimethyl sulfoxide.

The principal mechanism by which PTx inhibits neointimal growth is through the stabilization of microtubules by preventing deploymerization during the final G2/M phase of cell division.

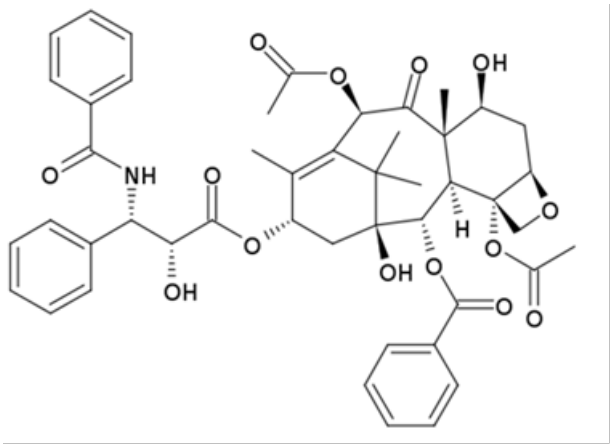

Figure 5-2: Chemical Structure of Paclitaxel

The coating utilizes the inactive ingredient acetyltributyl Citrate (ATBC) as an excipient to facilitate the release and transfer of paclitaxel into the arterial wall. ATBC is a carboxylic acid ester with a molecular weight of 402.48 g/mol. ATBC is a colorless, slightly viscous liquid with very faint sweet herbaceous odor. The chemical structure of ATBC is provided in **Figure 5-3**.

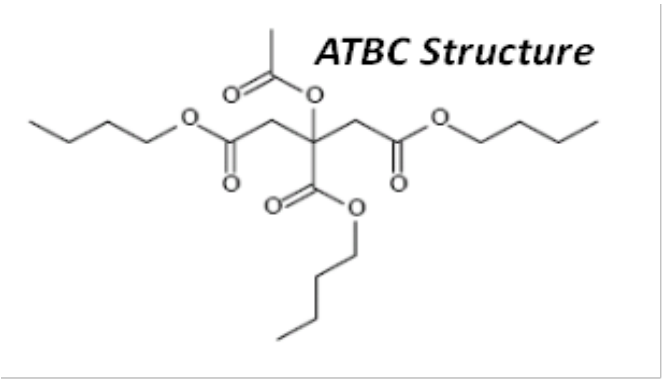

Figure 5-3: Chemical Structure of Acetyltributyl Citrate (ATBC)

Studies have shown that paclitaxel inhibits neointimal hyperplasia by disrupting normal microtubule function, thereby inhibiting smooth muscle cell migration, proliferation, and extracellular matrix secretion thus supporting short-term local delivery of paclitaxel for inhibiting restenosis in the SFA[25, 28]. Subjects with PAD will require treatment options that best fit their individual clinical presentation. No one therapy technique can treat all subjects. Although effective treatment with drug coated balloons has been proven, more research is needed.

5.2. Device Labeling of Investigational Device

A copy of the Directions for Use (DFU) for the Ranger DCB will be included in the Manual of Operations. The trial device is labeled on the front, back and bottom spine of the outer carton, and on the inside sterile pouch. Packaging will include peelable, self-adhesive labels for each unit shipped. The labeling will include the following information.

- Product Name
- Universal Part Number (UPN)/Catalog Number
- Serial number
- GTIN
- Lot number
- Balloon dimensions (balloon diameter and length in mm), and working catheter length (in cm)
- Expiration (use by) date

The following statements appear on the Ranger DCB product labeling:

Caution: Investigational Device. Limited by United States law to Investigational Use.

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

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

The Ranger DCB should be stored at room temperature, in a dry and dark place.

5.3. Control Device

Standard PTA (non-scoring) balloons are the control device for the global trial. The standard PTA device size (diameter, balloon and catheter lengths) utilization is determined by the research investigator.

6. Trial Objectives

The objective of the RANGER II SFA global pivotal trial is to evaluate the safety and effectiveness of the RANGER™ Paclitaxel Coated Balloon for treating superficial femoral and proximal popliteal arteries (SFA/PPA) lesions up to 180 mm.

7. Trial Endpoints

The primary and secondary endpoints will be evaluated on an intent-to-treat analysis and a per-treatment analysis. If the balloon angioplasty with the assigned treatment device (the test device Ranger DCB or control device Standard PTA) is not successfully deployed, the subject will be followed through the 1 month follow-up visit only as part of the ITT population. Data to assess 1 month MAE rate will be collected for these subjects. No other testing is required.

7.1. Primary Endpoints

7.1.1. Primary Safety Endpoint

The primary safety endpoint assesses the occurrence of Major Adverse Events (MAE) defined as all-cause death through 1 month, target limb major amputation through 12 months, and/or target lesion revascularization (TLR) through 12 months post-index procedure. This safety endpoint is designed to demonstrate that the Ranger DCB 12-month MAE-free rate is non-inferior to the control group.

7.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint assesses the primary lesion patency within 12 months post-index procedure. Primary effectiveness is defined as a binary endpoint determined by (DUS) peak systolic velocity ratio (PSVR) ≤ 2.4 in the absence of clinically-driven TLR. This effectiveness endpoint is designed to demonstrate that the 12-month primary patency for the Ranger treated test group is superior to the control group.

Notes:

- Lesion patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment.

- PSVR >2.4 suggests >50% stenosis.[32]
- The treated segment will be assessed for patency as a single segment regardless of the number of tandem lesions within the ballooned segment.

7.2. Secondary Endpoints

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

- Technical success defined as successful delivery, balloon inflation and deflation and retrieval of the intact trial device without burst below the rated burst pressure (RBP)
- Procedural success defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core laboratory evaluation (if core laboratory assessment is not available then the site-reported estimate is used)
- Clinical success defined as procedural success without procedural complications (i.e. death, major target limb amputation, thrombosis of the target lesion, or clinically-driven TLR) prior to discharge
- Major Adverse Events (MAE) through 60 months. MAEs are defined as all-cause death post-index procedure, TLR, and major target limb amputation
- Death of any cause within 30 days, 6, 12, 24, 36, 48 and 60 months
- TVR rates at 6, 12, 24, 36, 48 and 60 months
- TLR rates at 6, 12, 24, 36, 48 and 60 months
- Rate of Primary and Secondary sustained clinical improvement as assessed by changes in Rutherford Classification from baseline at 1, 6, 12, 24 and 36 months post-procedure
- Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1, 6, 12, 24 and 36 months post-procedure
- Duplex-defined binary restenosis (PSVR > 2.4) of the target lesion at 1, 6, 12, 24 and 36 months
- Walking Improvement (distance) at 6 months and 12 months as assessed by changes in the Six Minute Hall Walk Test (6MWT) from baseline
- Walking Improvement and Patient Utility Values assessed at 1, 6, 12, 24 and 36 months as assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D™ from baseline
- Changes in healthcare utilization over time
- PK parameters calculated for subjects in the PK substudy

8. Trial Design

The RANGER II SFA clinical trial is a global, prospective, multicenter, single-blind, superiority, 3:1 (Ranger DCB vs. Standard PTA) controlled randomized clinical trial (RCT) evaluating the safety and effectiveness of the Ranger DCB in subjects with claudication and/or rest pain and with a positive diagnostic finding of de novo, non-stented and non-atherectomy-treated or restenotic lesion(s) in the SFA and/or PPA.

8.1. Pharmacokinetic Substudy

Concurrently, a human pharmacokinetics (PK) investigation (substudy) of this trial is also planned in the U.S. This substudy is a prospective, multicenter, non-randomized substudy arm (Ranger DCB), conducted at multiple pre-specified investigational sites. This substudy is designed to evaluate the levels of paclitaxel in the systemic circulation of subjects at multiple time points after treatment with the Ranger DCB.

Although an investigative center can participate in both the RCT and PK trial arms, a subject can either be enrolled in the RCT study arm or the PK sub-study, but not both."

8.2. Required Medication Therapy

There is risk of acute, sub-acute, or late thrombosis, vascular complications, and/or bleeding events. It is strongly advised that the treating physician follow the Inter-Society Consensus (TASC II) Guidelines recommendations (or other applicable country guidelines) for antiplatelet therapy pre – and post –procedure to reduce the risk of thrombosis. Anti-platelet therapy is recommended throughout the length of the trial participation. Investigators must prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice.

Antiplatelet medication and peripheral artery disease (PAD) medication usage will be collected and reported for compliance throughout the trial.

Minimum protocol requirements:

- Anti-coagulation therapy administered prior to and during the procedure should be consistent with current clinical practice[33].
- A minimum of 30 days of dual antiplatelet therapy for non-stented subjects and a minimum of 3 months (90 days) dual antiplatelet therapy for stented subjects post index procedure.

Minimum recommendation:

- Antiplatelet monotherapy is recommended for administration throughout the 5 year follow-up (trial completion).

All enrolled subjects (RCT: Ranger DCB, Standard PTA and PK sub-study) should follow the above-mentioned antiplatelet requirements.

A subject is exempt from the above-mentioned antiplatelet requirements if he/she requires Coumadin or other similar anti-coagulant due to known comorbidities and in the opinion of the investigator, the combination of antiplatelet and anticoagulant could put the subject at an unreasonable risk of bleeding.

A subject is also exempt from the above-mentioned antiplatelet requirements if the randomized angioplasty treatment is unsuccessful.

8.3. Scale and Duration

The RANGER II SFA trial plans to enroll up to 396 subjects. At least 376 of the subjects will be enrolled into the randomized arm of the trial to yield:

- 282 subjects to receive treatment with the Ranger DCB; investigational test device and
- 94 subjects to receive treatment with Standard PTA; control device

From 12 to 20 subjects will receive treatment with the Ranger DCB for the non-randomized PK substudy. Approximately 25% of those enrolled into the PK substudy will have long lesions (≥100 mm) treated with the Ranger DCB.

Up to 80 study centers worldwide may enroll subjects into the RANGER II SFA pivotal trial. Countries that may participate include centers located in Australia, Canada, European Union, Japan, New Zealand and the United States.

Approximately 10 study centers may enroll subjects into the PK substudy.

All subjects will be screened according to the protocol inclusion and exclusion criteria. Subjects meeting all inclusion criteria and no exclusion criteria will be randomized in a 3:1 allocation to either Ranger DCB or Standard PTA, respectively.

For subjects undergoing successful balloon deployment, clinical follow up assessments are required at the following time points: pre-discharge, Day 7, 1 month, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months post index procedure. Office or clinic visits are required for testing during each protocol required follow-up visit, with the exception of the 48 and 60 month visits. These two visits can be conducted in the office/clinic or by phone to obtain MAE and medication data.

Subjects for whom the deployment of the randomly assigned balloon is unsuccessful (the test device Ranger DCB or control device Standard PTA) will be included in the Intent to Treat (ITT) population and followed for MAEs through 1 month.

In addition, for those enrolled into the PK substudy, PK sampling from venous blood are required at the following time points: pre-Ranger DCB deployment, 10 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 24 or 48 hours after last Ranger DCB removal, Day 7 and Day 30 post index procedure.

The enrollment is estimated to take up to 20 months to complete after the first patient is enrolled. Approximately fifty percent (50%) of the subjects enrolled will come from the United States. The trial will be considered complete (with regard to the primary endpoint) after all enrolled subjects have completed the 12 month follow-up visit, were discontinued prior to the 12 month follow-up visit, have died, or the last 12 month follow-up visit window is closed.

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

It is estimated that it will take approximately 7 years to complete the entire trial.

Figure 8-1 and **Figure 8-2** exhibit the RCT and PK substudy designs, respectively.

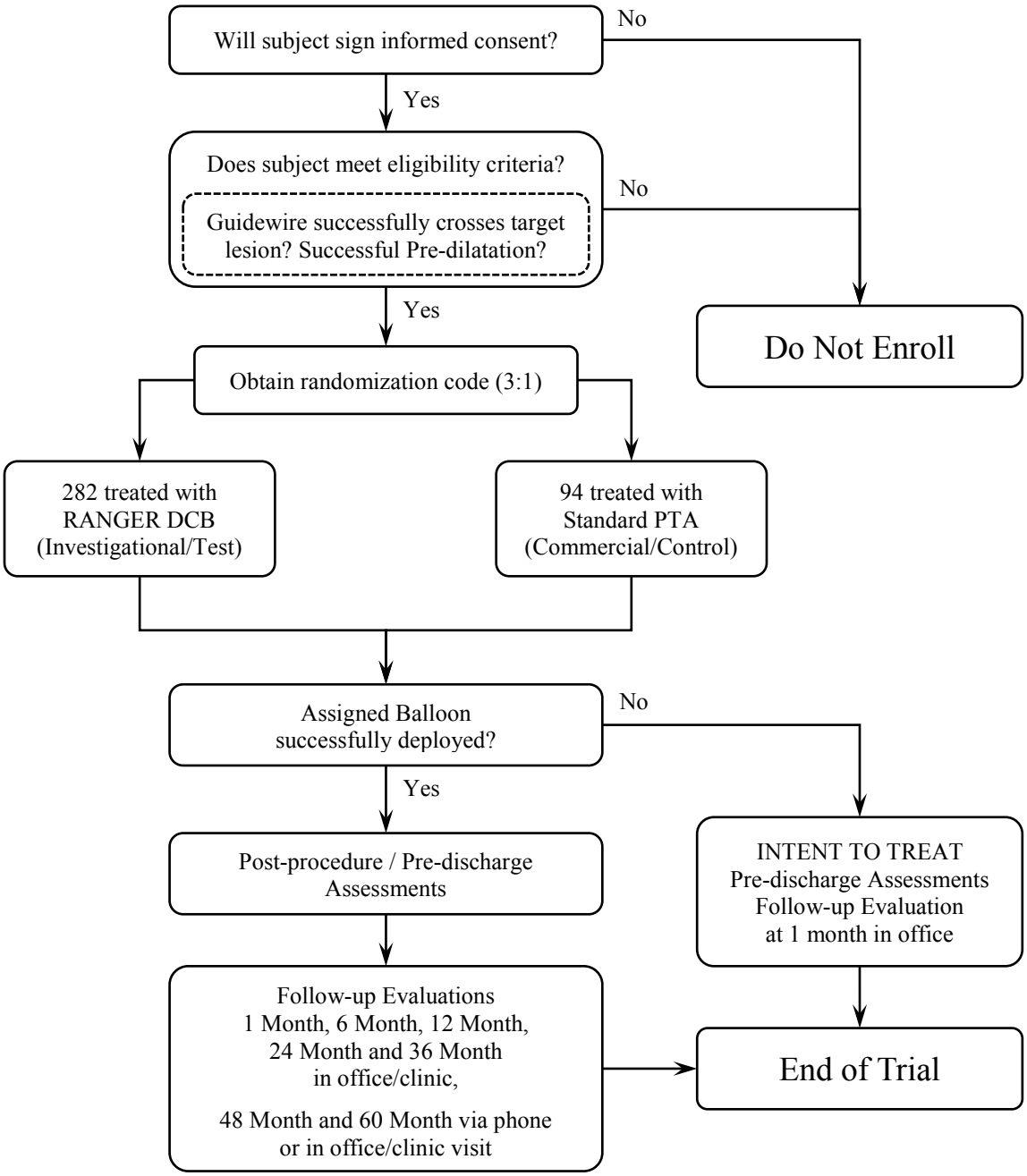

Figure 8-1: RANGER II SFA Randomized Control Study Design

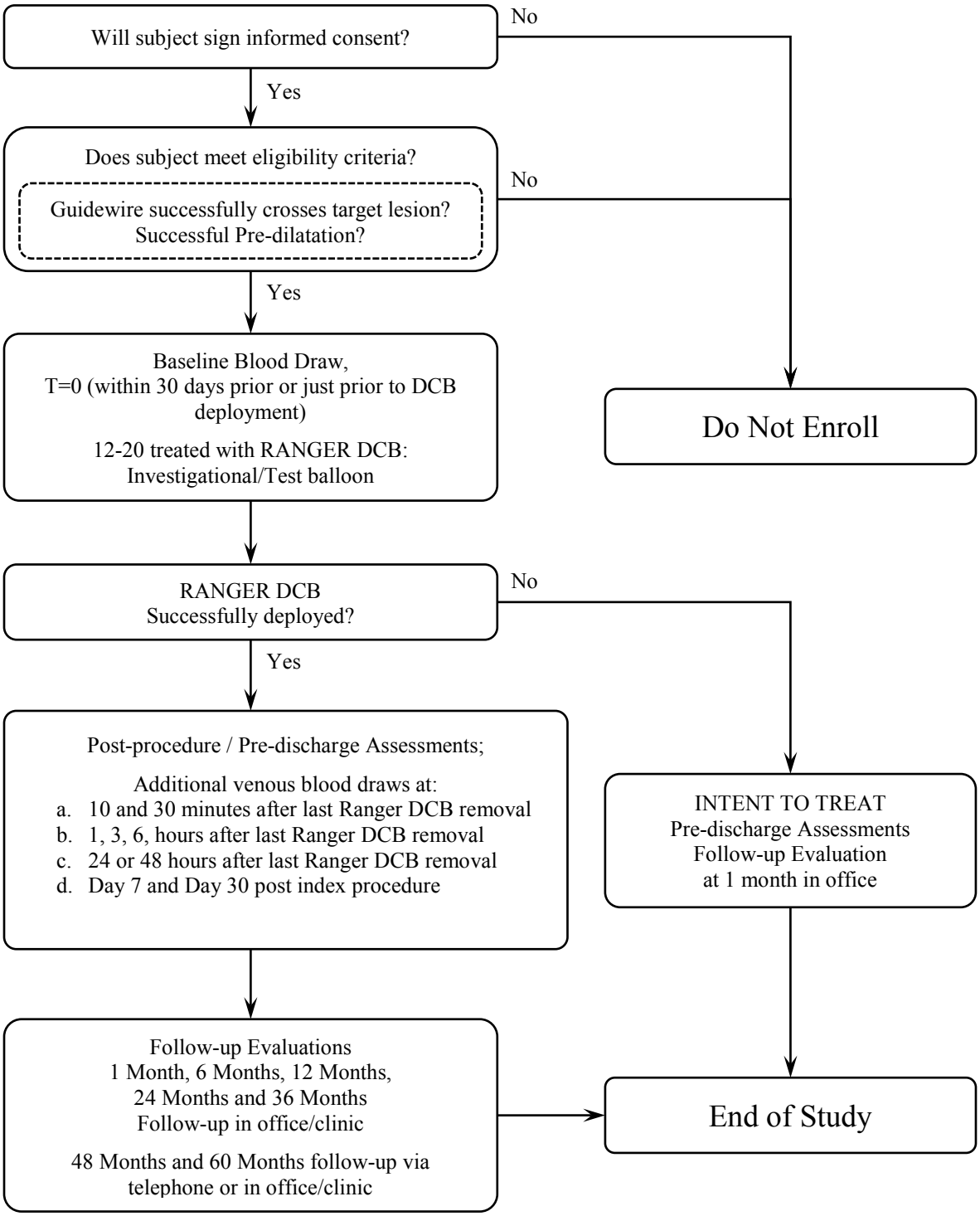

Figure 8-2: RANGER II SFA PK Substudy Design

8.4. Treatment Assignment

Subjects presenting with claudication or ischemic rest pain, an angiographically significant lesion in the superficial femoral and/or proximal popliteal artery and a patent outflow artery to the foot are considered for the RANGER II SFA trial.

If after consenting, meeting inclusion criteria and none of the exclusion criteria, confirmed angiographically significant lesion in the superficial femoral and/or proximal popliteal artery and successful protocol-defined pre-dilatation, subjects are randomized 3:1 to either a Ranger DCB (test) or a Standard PTA balloon (control). Randomization will be stratified by site. After the guidewire successfully crosses the target lesion and successfully pre-dilates the target lesion, a randomization custom function within the Rave EDC database will be used to assign subjects to the test or control treatment group.

In the PK substudy, subjects will not be randomized; all subjects will be treated with the Ranger DCB.

Subjects are considered enrolled when the Ranger DCB or Standard PTA is introduced into the subject's vasculature.

Note: If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be entered into this trial (no randomization nor enrollment) The subject should be cared for and followed outside of the trial based on the physician's treatment plan.

Note: If the balloon angioplasty with either the test device (Ranger DCB) or control device (Standard PTA) is not successfully deployed, follow-up through the 1 month visit only will occur as part of the ITT population. Data for assessment of MAE will be collected for these subjects. No other testing or follow up is required.

8.5. Blinding and Unblinding

The RANGER II SFA trial is conducted as single blind. Subjects will be blinded to treatment assigned and treatment received. All subjects must remain blinded until completion of all 12 month follow-up visits (primary endpoint).

Packaging of the investigational Ranger DCB and control PTA devices differ. Therefore the Investigator and staff performing the procedure will not be blinded to the assigned treatment arm or resulting treatment.

Study center personnel will be trained not to disclose the treatment assignment to the subject in order to minimize the potential unblinding of the subjects.

The DUS Core Laboratory personnel, Angiography Core Laboratory personnel, and Clinical Events Committee (CEC) will remain blinded to each subject's treatment assignment through primary endpoint.

Those involved in data analysis for the Sponsor will remain blinded until the primary endpoint interim analysis.

8.6. Target Lesions

The RANGER II SFA trial is designed to treat lesions located in the superficial femoral and/or proximal popliteal arteries (SFA/PPA). These arteries are located in the lower extremities above the knee. The arteries, with a reference vessel diameter (RVD) of ≥ 4 mm and ≤ 8 mm by visual estimate (use of a radiopaque ruler is recommended), must show angiographic evidence of a single de novo, non-stented and non-atherectomy-treated or restenotic lesion (or tandem lesions or a combination lesion as defined below) that is:

- ≥ 70% -99% stenotic with total lesion length up to180 mm by visual estimate. Use of a radiopaque ruler is recommended.
- Occluded with total lesion length ≤ 100 mm by visual estimate. Use of a radiopaque ruler is recommended.
- If lesion is restenotic, most recent PTA treatment must be > 3 months prior to enrollment

Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) are eligible provided that the total combined lesion length is ≤180 mm.

Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria:

- Separated by a gap of ≤ 30 mm (3 cm)
- Total combined lesion length meets requirements (Angiographic inclusion criteria (7) including 30 mm gap); and
- Able to be treated as a single lesion

The Ranger DCB must be overlapped to cover targeted lesion(s) as specified in the inclusion criteria.

Provisional stenting of the target lesion with bare-metal stents can be completed in cases where adequate results could not be obtained after using post-dilatation balloons; such as in the case of remaining residual stenosis[≥ 50%] or major [≥ Grade D] flow-limiting dissection after post-dilatation.

8.7. Non-target Lesions

Multiple interventions using the same access site may occur at the time of the index procedure. Using the same access site, iliac lesion(s) in the contralateral and ipsilateral limb may be treated during the index procedure under the following conditions:

- Treatment with a commercially (non-drug coated) available device occurs prior to randomization of the target SFA/PPA lesion(s);
- Treatment of the lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation)

If the above criteria are not met, the subject may not be randomized into the trial but may be rescreened for eligibility after 30 days.

8.8. Justification for the Trial Design

The RANGER II SFA trial will evaluate the safety and effectiveness of the Ranger DCB balloon for the treatment of atherosclerotic lesion(s) in native SFA and/or PPA vessels compared with Standard PTA balloons. Standard PTA balloons have been utilized to treat atherosclerotic lesions in these arteries for more than 20 years. There are many documented studies that show effectiveness and safety with use of commercially available Standard PTA balloons. Further, the two DCBs, approved for use in the United States (US) have patency rates that differ significantly. This significant patency variance makes it extraordinarily difficult to ascertain which of the two approved US DCBs to compare with the Ranger DCB. Therefore a randomized controlled trial was required by the US Food and Drug Administration.

9. Subject Selection

9.1. Trial Population and Eligibility

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

9.2. Inclusion Criteria

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

Table 9-1: Inclusion Criteria

Inclusion Criteria	1. Subject (or Legal Guardian) is willing and able to provide consent before any study-specific tests or procedures are performed and agree to attend all required follow-up visits; 2. Subject at least 20 years of age; 3. Chronic symptomatic lower limb ischemia defined as Rutherford classification 2, 3, or 4; 4. Target lesion is in the native SFA and/or PPA down to the P1 segment; 5. Patent popliteal and infrapopliteal arteries, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot; 6. Reference vessel diameter ≥ 4 mm and ≤ 8 mm by visual estimate (Use of a radiopaque ruler is recommended); 7. Angiographic evidence that target lesion consists of a single de novo, non-stented and non-atherectomy treated or restenotic lesion (or tandem lesions or a combination lesion as defined below) that is: a. ≥ 70% -99% stenotic with total lesion length up to180 mm by visual estimate. Use of a radiopaque ruler is recommended.

	b. Occluded with total lesion length ≤ 100 mm by visual estimate. Use of a radiopaque ruler is recommended. c. If lesion is restenotic, most recent PTA treatment must be > 3 months prior to enrollment **Notes:** Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) are eligible provided that the total combined lesion length is ≤180 mm. Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria: • Separated by a gap of ≤ 30 mm (3 cm) • Total combined lesion length meets requirements (Angiographic inclusion criteria (7) including 30 mm gap); and • Able to be treated as a single lesion.

9.3. Exclusion Criteria

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

Table 9-2: Exclusion Criteria

Exclusion Criteria	1. Life expectancy, documented in the Investigator's opinion, of less than 12 months; 2. Hemorrhagic stroke or cardiac event (e.g. STEMI, unstable angina) within 6 months prior to enrollment; 3. Known allergies or sensitivities to heparin, aspirin, other anticoagulant/antiplatelet therapies, and/or paclitaxel; 4. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated; 5. Chronic renal insufficiency with serum creatinine > 2.0 mg/dL within 30 days of index procedure or treatment with dialysis; 6. Platelet count <80,000 mm^3 or >600,000 mm^3 or history of bleeding diathesis; 7. Receiving immunosuppressive therapy; 8. Septicemia at the time of enrollment; 9. Any major (e.g., cardiac, peripheral, abdominal) intervention (including in the contralateral SFA/PPA) planned within 30 days post index procedure;

	10. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of enrollment; 11. Failure to successfully cross the target lesion with a guidewire (successful crossing means tip of the crossing device is distal to the target lesion in the absence of flow-limiting dissections or perforations); 12. Failure to successfully pre-dilate the target vessel; 13. Patient has lesion that requires the use of adjunctive primary treatment modalities (i.e. laser, atherectomy, scoring/cutting balloon, other debulking devices, etc.) during the index procedure; 14. History of major amputation in the target limb; 15. Target lesion or vessel has ever been previously treated with stent (e.g. in-stent restenosis) or, surgery. Target lesion or vessel has been treated with atherectomy or a DCB in the past 12 months; 16. Pregnant or breast feeding; 17. Presence of aneurysm in the target vessel; 18. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to enrollment; 19. Patient has significant inflow disease which cannot be treated prior to the target lesion treatment; 20. Patient has perforated targeted vessel as evidenced by extravasation of contrast media; 21. Patient has severe calcification that renders the lesion undilatable; 22. Current participation in another investigational drug or device clinical trial that has not completed the primary endpoint at the time of randomization/enrollment or that clinically interferes with the current trial endpoints. **Note**: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies.

Abbreviations: STEMI- ST elevation myocardial infraction

10. Subject Accountability

10.1. Point of Enrollment

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

If the subject is found to meet the eligibility criteria during the angiographic phase of the procedure, the subject will be considered eligible to be enrolled. After the Investigator successfully crosses the target lesion with the guidewire and successfully pre-dilates the target lesion, a randomization custom function within the Rave EDC database will be used to assign RCT subjects to the test or control treatment group. Subjects are considered enrolled when the Ranger DCB or Standard PTA is introduced into the subject's vasculature.

Testing (including CBC, platelets, ABI, and Rutherford Classification) completed as a part of the subject's standard of care, within 30 days of the index procedure and that meets the study (inclusion/exclusion) criteria, are not required to be repeated after consenting is complete.

10.2. Withdrawal

All subjects enrolled in the clinical trial (including those withdrawn from the clinical trial or lost to follow-up) shall be accounted for and documented.

While trial withdrawal is discouraged, subjects may choose to withdraw from the trial at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional trial follow-up, nor will they be replaced (the justified sample size considers an estimated allowance for attrition). The reason for withdrawal will be recorded (if given) in all cases of withdrawal. The Investigator may discontinue a subject from participation in the trial if the Investigator feels that the subject can no longer fully comply with the requirements of the trial or if any of the trial procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

10.3. Enrollment Controls

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

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

11. Trial Methods

11.1. Data Collection

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

Table 11-1: Data Collection Schedule

Procedure/Assessment	Pre-procedure[2]	During Index Procedure	Pre-Discharge	Day 1 or 2[6]	Day 7 (±1 days)	1-month (30±7 days)	6-month (182±30 days)	12-month (365±30 days)	24-month (730±30 days)	36-month (1095±30 days)	48-month[5] (1460 ± 30 days) (office/clinic visit or telephone)	60-month[5] (1825 ± 30 days) (office/clinic visit or telephone)
Informed Consent[1]	X											
Confirm Inclusion/Exclusion	X	X										
Demographics and Medical History, Height and Weight	X											
Pregnancy Test[2]	X											
Physical Exam[3]	X		X			X	X	X	X	X		
Complete Blood Count (CBC) and platelet count	X											
Serum Creatinine	X											
ABI Measurements	X					X	X	X	X	X		
Rutherford Classification	X					X	X	X	X	X		
Walking Impairment Questionnaire (WIQ)	X					X	X	X	X	X		
EQ-5D Questionnaire	X					X	X	X	X	X		
6 Minute Walk Test (6MWT)	X						X	X				
Angiogram[4]		X										
Randomization/Enrollment		X										
PK venous draw	X	X[6]	X	X	X	X						
Duplex Ultrasound[4]						X	X	X	X	X		
Medication Assessment	X	X	X			X	X	X	X	X	X	X
Adverse Events Assessment		X	X			X	X	X	X[7]	X[7]	X[7]	X[7]

[1] Subject's consent obtained and informed consent form signed prior to obtaining any study-specific tests or procedures. Testing (CBC, platelets, ABI, and Rutherford Classification) completed as a part of the subject's standard of care, within 30 days of the index procedure and that meets the study (inclusion/exclusion) criteria, are not required to be repeated.

[2] Performed within 30 days of procedure, except urine or blood pregnancy test required for females of childbearing potential performed within 24 hrs. of procedure

[3] Physical exam includes obtaining Vital signs (B/P, HR, RR*), Rutherford Classification and ABI at 1 mth, 6 mth, 12 mth, 24 mth and 36 mth follow up visits. Pre-discharge: Vital signs only. * Respiratory rate is not mandatory if not local standard of care.

[4] Angiograms and Ultrasounds will be sent to the respective core lab for analysis.

[5] The 48 month and 60 month visit may be conducted in the office/clinic or by telephone.

[6] PK venous draw at screening, 10 min, 30 min, 1 hr., 3 hr., 6 hr., 24 or 48 hr. after last Ranger DCB removal, Day 7 and Day 30 post index procedure.

[7] Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

11.2. Trial Candidate Screening

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

11.3. Informed Consent

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

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

Refer to section 10.1 for definition of point of enrollment

11.4. Pre-Procedure Assessments – Within 30 Days Prior to Index Procedure

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

- Demographics and medical history obtained
- Physical assessment including:
  - Vital Signs: Blood pressure (B/P), Heart rate (HR), Respiratory rate (RR)*
  - Weight and height
  - Rutherford Classification
  - Ankle-Brachial Indices (ABI) measurements

  *Respiratory rate data collection is not mandatory if not local standard of care
- Laboratory tests
  - Complete blood count (CBC) with platelets
  - Serum Creatinine
  - PK baseline
- 6 Minute Walk Test
- Administer Questionnaire Assessments
  - Walking Impairment Questionnaire (WIQ)
  - EQ-5D

11.5. Pre-Procedure Assessments – Within 24 hrs. prior to index procedure

A pregnancy test for females of childbearing potential with analysis per local practice (serum or urine) is required within 24 hours prior to the index procedure.

11.6. Pre-Procedure Requirement

Anti-platelet therapy is recommended throughout the length of trial participation. Investigators must prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice.

Antiplatelet medication and peripheral artery disease (PAD) medication usage will be collected and reported for compliance throughout the trial.

Anti-coagulation therapy administered prior to and during the procedure should be consistent with current clinical practice.

Note: A subject is exempt from the above-mentioned antiplatelet requirement if he/she requires Coumadin or other similar anti-coagulant due to known comorbidities and in the opinion of the investigator, the combination of antiplatelet and anticoagulant could put the subject at an unreasonable risk of bleeding.

11.7. Index Procedure

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

The start of the index procedure is defined as the time the guide (catheter or sheath) is inserted.

11.7.1. Treatment of Non-target Lesions

Multiple interventions may occur using the same access site at the time of the index procedure. Using the same access site iliac lesion(s) in the contralateral and ipsilateral limb may be treated during the index procedure under the following conditions:

- Treatment with a commercially (non-drug coated) available device occurs prior to randomization of the target SFA/PPA lesion(s);
- Treatment of the lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation)

If the above criteria are not met, the subject may not be randomized into the trial but may be rescreened for eligibility after 30 days.

11.7.2. Angiographic Imaging of Target Lesion(s)

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

Refer to the BIDMC Angiographic Core Lab Protocol for Angiographic Film Acquisition. This manual is located in the RANGER II SFA manual of operations and has detailed trial requirements.

A few key steps are below:

- Obtain both pre-procedure (2 views) and post-procedure (2 views) utilizing the standard DICOM 3. The first frame of the series should be unmasked.
- A ruler or radiopaque marking tape with centimeter markings should be used as the calibration source to determine the image calibration. The core lab will need to observe the ruler for analysis.
- Perform run-off vessel images demonstrating patency to the foot. This imaging should be taken once at the beginning (pre-procedural views), and once at the end of the procedure, after all target lesions have been treated (post-procedural views).
- For the most accurate analysis of lesions, it is necessary to have matching projection angles in the pre-procedural and post-intervention angiographic projections.

Angiographic images must be sent to the BIDMC Angiographic Core Laboratory for evaluation. If the core lab is unable to analyze the angiogram, then site reported assessment is used.

11.7.3. Enrollment

Prior to enrollment, a subject must meet all of the clinical and angiographic inclusion criteria and none of the clinical and angiographic exclusion criteria.

If the subject is found to meet the eligibility criteria during the angiographic phase of the procedure, the subject will be considered eligible to be enrolled. After the Investigator successfully crosses the target lesion with the guidewire and successfully pre-dilates the target lesion, a randomization custom function within the Rave EDC database will be used to assign randomized subjects to the Ranger DCB (test) or Standard PTA (control treatment group). The Ranger DCB balloons are provided by the Sponsor. Standard PTA balloons are commercially available balloons that the investigative sites utilize from their inventory. Subjects are considered enrolled when the Ranger DCB or Standard PTA is introduced into the subject's vasculature.

If the balloon angioplasty attempt with the assigned treatment device (the test device Ranger DCB or control device Standard PTA) is not successful, follow-up through the 1 month visit only will occur as part of the ITT population. Data for assessment of MAE will be collected for these subjects. No other testing or follow up is required.

11.7.4. Treatment of Target Lesion(s)

The Directions For Use (DFU) for the Ranger DCB is located in the Manual of Operations. Prior to use of the device, the treating physician must carefully read and be familiar with the entire DFU. The Ranger DFU must be followed for deploying the investigational DCB.

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

Ranger DCB Procedure:

Optimal target lesion/vessel preparation is required. Successful pre-dilatation of the target lesion(s) with optimally sized balloon(s) is required before DCB deployment. Successful pre-

dilatation occurs when the selected balloon opens vessel entry at nominal pressure without major (≥ Grade D) flow-limiting dissection or need for intervention (i.e. stenting).

Note: If major dissection occurs at this step, subject should not be enrolled into the trial. No follow up is required.

Record the following information on pre-dilatation balloon(s) used:

- Maximum balloon diameter (mm) inflated
- Maximum pressure (atmospheres) inflated
- Maximum length of time (seconds) inflated

The recommended Ranger DCB inflation time is three (3) minutes to ensure apposition to the arterial wall and to reduce the chance of vessel recoil. Post-dilatation may be performed at the discretion of the Investigator.

Record the following information on post-dilatation balloon(s), if utilized:

- Maximum balloon diameter (mm) inflated
- Maximum pressure (atmospheres) inflated
- Maximum length of time (seconds) inflated

Peri-procedure dissections should be treated conservatively, with low pressure prolonged balloon inflation, or with provisional stenting of the target lesion with bare-metal stents. Bare metal stents can be utilized in cases where adequate results could not be obtained after using post-dilatation balloons; such as in the case of remaining residual stenosis [≥ 50%] or major [≥ Grade D] flow-limiting dissection after post-dilatation.

Haziness, lucency, or filling defects within or adjacent to the ballooned area, and angiographic complications such as distal thromboemboli or no reflow, should also be treated per standard practice. All angiographic complications that occur should be documented by angiography and submitted to the BIDMC Angiographic Core Laboratory for analysis.

For subjects randomized to the Standard PTA (non-scoring), treatment with commercially available Standard PTA (control) balloons should be completed according to each individual device labelling.

11.7.5. Post-procedure Angiogram

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

11.8. End of the Index Procedure

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

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

11.9. Post-procedure/Pre-Discharge

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

- Physical Exam: Vital signs only (B/P, HR and RR*)

  *Respiratory rate data collection is not mandatory if not local standard of care
- Medication assessment
- Adverse Event (AE) assessment
- Pharmacokinetic (PK) venous blood should be obtained at 10 min, 30 min, 1 hr., 3 hr., 6 hr., 24 or 48 hr. after last Ranger DCB balloon removal for subjects enrolled into the PK sub-study

Assessment of Whole Blood Paclitaxel Levels

The PK profile of the Ranger DCB will be analyzed for subjects enrolled in the PK substudy. Nine (9) venous blood samples will be drawn according to the schedule shown in **Table 11-2**.

Treatment of the SFA/PPA with a drug coated or uncoated balloon is most often performed as an out-patient procedure and sampling time points greater than 5 hours post-procedure will require most subjects to return to the research site for blood draws.

To encourage all enrolled PK subjects to comply with the PK sampling schedule after release from the hospital/facility, the research team will allow the subject to choose to return for either the 24 hours or 48 hour time point. The day 7 and day 30 time points will be scheduled for all PK subjects.

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

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

Instructions for blood sample collection, storage, and shipment are provided in the PK core laboratory Instruction Manual. This manual is located in the Manual of Operations.

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

Day		Blood Draw Schedule
Before balloon treatment		Within 30 Days prior to index procedure
After balloon treatment	Day 0	10 minutes (±5 minutes) after last Ranger DCB balloon removal
		30 minutes (±10 minutes) after last Ranger DCB balloon removal
		1 hour (±10 minutes) after last Ranger DCB balloon removal
		3 hours (±10 minutes) after last Ranger DCB balloon removal
		6 hours (±10 minutes) after last Ranger DCB balloon removal
	Day 1-2 *	24 hours (±4 hours) **OR** 48 hours (±4 hours) after last Ranger DCB balloon removal
	Day 7	Day 7 (±1 Day)
	Day 30	Day 30 (±7 Days)

*Either draw blood on Day 1 (24 hr) or Day 2 (48 hr) for each subject

Bioanalytical Method

The blood samples collected from patients at the specified time points will be analyzed for levels of paclitaxel using HPLC/GC with UV/Fluorescence/MS/MS detection by Covance Core Lab.

Pharmacokinetics Parameters

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

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

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

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

11.10. Follow-up Visits

RANGER II SFA trial is a single blind trial. Subjects will be blinded to treatment assigned and treatment received. All subjects (excluding subjects in the PK substudy) must remain blinded until completion of all 12 month follow-up visits (primary endpoint).

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

All randomized and enrolled subjects who receive a test or control balloon, Ranger DCB or Standard PTA, will continue to be evaluated at 1 month, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months after the index procedure.

Subjects enrolled in the PK substudy who receive the RANGER DCB will have blood drawn at 24 or 48 hours, Day 7 and Day 30 as well as complete protocol required assessments at 1 month, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months after the index procedure.

Subjects who underwent advancement of the Ranger DCB or Standard PTA into the body but deployment was unsuccessful, will be considered enrolled under Intent to Treat population and will be followed for safety through the 1-month follow-up visit only. Data for assessment of MAE will be collected for these subjects; other testing is not required.

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

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

Requirements of each follow-up evaluation are described below.

11.10.1. Day 7 Follow-up Visit (±1 Day)

Ranger DCB Successful Angioplasty	Unsuccessful Angioplasty (Intent to Treat)
PK substudy: venous Blood Draw	None

11.10.2. 1 Month Follow-up Visit (±7 Days)

Ranger DCB or Standard PTA Successful Angioplasty	Unsuccessful Angioplasty (Intent to Treat)
Physical Exam: • Vital signs (B/P, HR, RR*) • ABI measurement • Rutherford Classification WIQ Questionnaire EQ-5D Questionnaire DUS PK substudy: venous blood draw AE assessment** Medication assessment	AE assessment

* Respiratory rate data collection is not mandatory if not local standard of care.

** Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

11.10.3. Duplex Ultrasound Assessment of Target Lesion(s)

DUS are utilized to assess the primary effectiveness endpoint of the RANGER II SFA trial. The primary effectiveness endpoint assesses the primary lesion patency within 12 months post-index procedure.

Primary effectiveness is defined as a binary endpoint determined by (DUS) peak systolic velocity ratio (PSVR) ≤ 2.4 in the absence of clinically-driven TLR.

Clinically-driven TLR is defined as any re-intervention at the target lesion due to recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥ 20% or > 0.15 when compared to post-procedure baseline ABI/TBI in the treated segment. TBI allowed in cases of incompressible vessels).

This effectiveness endpoint is designed to demonstrate that the 12-month primary patency for the Ranger DCB treated test group is superior to the control group.

Lesion patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment. PSVR >2.4 suggests >50% stenosis.

It is imperative that the DUS examinations be completed according to the VASCORE Vascular Core Lab protocol. The DUS protocol will be located in the Manual of Operations.

11.10.4. 6 Month Follow-up Visit (±30 Days)

Ranger DCB or Standard PTA Successful Angioplasty	Unsuccessful Angioplasty (Intent to Treat)
Physical Exam • Vital signs (B/P, HR, RR*) • ABI measurement • Rutherford Classification WIQ Questionnaire EQ-5D Questionnaire 6 Minute Walk Test DUS AE assessment** Medication assessment	Not Applicable

* Respiratory rate data collection is not mandatory if not local standard of care.

** Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

11.10.5. 12 Month Follow-up (±30 Days)

Ranger DCB or Standard PTA Successful Angioplasty	Unsuccessful Angioplasty (Intent to Treat)
Physical Exam • Vital signs (B/P, HR, RR*) • ABI measurement • Rutherford Classification WIQ Questionnaire EQ-5D Questionnaire 6 Minute Walk Test DUS AE assessment** Medication assessment	Not Applicable

* Respiratory rate data collection is not mandatory if not local standard of care.

** Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

11.10.6. 24 Month and 36 Month Follow-up (±30 Days)

Ranger DCB or Standard PTA Successful Angioplasty	Unsuccessful Angioplasty (Intent to Treat)
Physical Exam • Vital signs (B/P, HR, RR*) • ABI measurement • Rutherford Classification WIQ Questionnaire EQ-5D Questionnaire DUS AE assessment** Medication assessment	Not Applicable

* Respiratory rate data collection is not mandatory if not local standard of care.

** Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

11.10.7. 48 Month and 60 Month Follow-up (±30 Days): The 48 and 60 month visits can occur in office/clinic or by phone.

Ranger DCB or Standard PTA Successful Angioplasty	Unsuccessful Angioplasty (Intent to Treat)
AE assessment* Medication assessment	Not Applicable

* Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

11.11. Trial Completion

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

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

11.12. Missed or Late Visits

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

A minimum of 3 attempts (i.e., 2 phone calls followed by a certified letter, or other traceable letter, if necessary) should be made to contact the subject or subject's next of kin for each missed

follow-up visit and this information should be documented in the source. Missed or late visits will be recorded as Protocol Deviations. For subjects who miss their 12 Month follow-up visit (primary endpoint), BSC may provide sites access to a patient locator service (if allowed by the site's IRB/IEC/REB). A subject will be considered lost to follow-up after the subject misses 2 consecutive annual follow-up visits without due cause. No subject will be considered lost to follow-up prior to the 24 Month follow-up visit in order to make every effort to collect evaluable data for the primary endpoint.

11.13. Source Documents

It is preferable that original source documents (see **Section 27.2** for definition) are maintained, when available. Where copies of the original source document as well as printouts of original electronic source documents are retained, it is required that the copies be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

12. Statistical Considerations

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

12.1. Primary Endpoints

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

The primary effectiveness and safety hypotheses are planned for being tested simultaneously in an adaptive group sequential manner at the overall significance level of one-sided 2.5%. The Lan-DeMets alpha spending function with Power Family Method will be used to determine the interim and the final type I error adjustment.

For the PK sub-study, the sample size determination is arbitrary and the analysis is based on observation. There is no primary endpoint for the PK substudy.

12.1.1. Primary Effectiveness Endpoint

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

12.1.1.1. Effectiveness Hypotheses

The primary effectiveness hypothesis to be tested is that 12-month primary patency in subjects treated with Ranger DCB is superior to subjects treated with Standard 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 Ranger DCB vs. Standard 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 ≤ 0

H_1: Pt - Pc > 0 (superior)

where Pt and Pc are the 12-month primary patency for Ranger DCB and Standard PTA, respectively.

12.1.1.2. Effectiveness Sample Size

The overall sample size is driven by the primary effectiveness endpoint. Approximately 376 subjects are planned to be enrolled in the RCT. The sample size justification for the RCT is based on the following assumptions.

- Power $\geq$ 85%
- One-sided overall significance level (alpha) = 2.5%
- Lan-DeMets alpha spending function with Power Family Method:
  - One assessment for a minimum of 75% subjects to be assessed subjects to be assessed
  - The final assessment for the overall subjects
- Expected Standard PTA 12-month primary patency = 52.5%
- Ranger DCB to demonstrate 20% treatment effect
- Allocation (Ranger DCB vs. Standard PTA) = 3:1
- Attrition rate in 12 months = 15%
- N = 320 (total) evaluable subjects are required at 12 months (240 in Ranger DCB and 80 in the Standard PTA)
- N = 376 (total) subjects to be randomized prior to the procedure (282 in Ranger DCB and 94 in Standard PTA)

12.1.1.3. Effectiveness Statistical Methods

A Chi-Square Test for the difference in 12-month primary patency will be used to assess the effectiveness hypotheses.

12.1.2. Primary Safety Endpoints

The 12-month MAE-free rate is selected to be assessed for the primary safety composite endpoint. The safety goal is designed to demonstrate that Ranger DCB is non-inferior to Standard PTA in terms of MAE-free rate through 12 months post-procedure.

12.1.2.1. Safety Hypotheses

The primary safety hypothesis to be tested is that 12-month MAE-free rate in subjects treated with Ranger DCB is as safe as the subjects treated with Standard 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 RANGER DCB vs. Standard PTA as opposed to the alternative hypothesis (H_1) states that there is a marginal treatment effect. The hypotheses inequalities are shown below:

H_0: Pt - Pc $\leq \Delta$

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

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

12.1.2.2. 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 for the interim analysis and/or for the final analysis as needed
- Expected Standard PTA 12-month MAE-free = 75%
- Expected Ranger DCB 12-month MAE-free rate = 90%
- Non-inferiority margin (Δ) = -10%*

The sample size is driven by the primary effectiveness endpoint to provide at least 94% power to assess the primary safety endpoint.

* The margin of -10% is clinically meaningful for the safety endpoint per physicians' consensus. Due to the interim alpha adjustment, the observed Ranger DCB will require to outperform the Standard PTA such that the lower confidence bound of the observed difference within the margin to claim a success. For an example of 75% subjects to be assessed for the interim analysis, the margin of -10% will require the observed MAE-free rate of 79.4% in Ranger DCB when the Standard PTA is observed as 75% to demonstrate non-inferiority at interim alpha level of one-sided 1.41%.

12.1.2.3. Safety Statistical Methods

A Chi-Square Test will be used to assess the hypothesis of for the difference in 12-month MAE-free rate will be used to assess the safety hypotheses.

12.2. Success Criteria

The following success criteria are defined for the RCT. For the group sequential design, a minimum of 75% evaluable subjects are required for the interim analysis. Since the Lan-DeMets alpha spending function is continuous, the confidence levels and adjusted alpha levels will depend on the actual observed proportion of subjects (e.g. >75%). Without loss of generality, an example of 75% subjects is described below.

12.2.1. Success Criteria for the Interim Analysis

For example, exact 75% subjects are to be assessed at the interim analysis.

Ranger DCB will be concluded to be superior to Standard PTA for device effectiveness in the interim analysis if the one-sided lower 98.59% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month primary patency is greater than zero.

Ranger DCB will be concluded to be as safe as Standard PTA if the one-sided lower 98.59% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month MAE-free is greater than -0.1.

The study success will be concluded as both primary effectiveness and primary safety endpoints being achieved in the interim analysis.

12.2.2. Success Criteria for the Final Analysis

All subjects are to be assessed at the final analysis when the interim analysis is not able to be concluded.

If for any reason, the final analysis is required to prove superiority, Ranger DCB will be concluded to be superior to Standard PTA for device effectiveness in the final analysis if the one-sided lower 98.08% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month primary patency is greater than zero.

Ranger DCB will be concluded to be as safe as Standard PTA if the one-sided lower 98.08% confidence bound on the difference between treatment groups (Ranger DCB – Standard PTA) in 12-month MAE-free is greater than -0.1.

As required, the study success will be concluded as both primary effectiveness and primary safety endpoints being achieved in the final analysis.

12.3. General Statistical Methods

12.3.1. Analysis Sets

The intention-to-treat (ITT) analysis set will be the primary analysis set for assessing superiority of Ranger DCB to the Standard PTA in the RCT. The per-protocol and/or the as-treated analysis sets will be assessed in RCT for reference. However per-protocol analysis will be performed only when the ITT and the per-protocol analysis sets are not identical. As-treated analysis will be performed as deemed necessary.

All subjects who sign the informed consent form (ICF) and are randomized in the RCT will be included in the ITT analysis set, regardless of whether the subjects receive the assigned treatment.

For per-protocol analysis, only randomized subjects who meet the eligibility criteria and receive the assigned treatment will be included in the per-protocol analysis set. For subjects who do not receive randomized devices will be excluded from the per-protocol analysis set.

For as-treated analysis, all subjects who actually receive either Ranger DCB or Standard PTA at procedure will be included in the as-treated analysis set. For subjects who do not receive Ranger DCB or PTA will be excluded from the as-treated analysis set.

12.3.2. Randomization Scheme

Randomization to treatments will be stratified by study site. A computer generated random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatments in a 3:1 ratio of Ranger DCB to Standard PTA. This list will be specific to the subject's site. Random permuted blocks of varying sizes will be employed to ensure approximate balance of treatment allocation within each site.

12.3.3. Control of Systematic Error/Bias

Selection of subjects will be made from the Investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria and have signed the protocol-specific ICF will be eligible for enrollment in the trial. Consecutively eligible subjects should be enrolled into the trial to minimize selection bias. Trial subjects will be randomly assigned to a treatment group within the investigational site. In determining subject eligibility for the trail, the investigator's assessment of imaging will be used. However, BIDMC Angiographic Core Laboratory will independently analyze the angiograms and the data obtained from the core laboratory will be utilized for analyses.

An independent CEC composed of medical experts will adjudicate safety assessments, as defined in the CEC Charter. In addition, an independent data reviewer (IDR) is responsible for the oversight review of the aggregate safety data, as defined in the IDR charter. The IDR will not participate in the trial and who have no affiliation with BSC.

12.3.4. Number of Subjects per Investigative Site

Study sites will not be allowed to randomize more than 10% (N=37) 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=76) of the total number of randomized subjects.

12.4. Baseline Data Analyses

Baseline covariates will be summarized for RCT and PK sub-study. Subject baseline demographics and clinical characteristics, site-reported and core lab reported lesion characteristics, procedure assessment, device information, and medication compliance will be summarized using descriptive statistics. The analysis unit may be (but will not be limited to) by subject, lesion, procedure, or device.

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.

12.4.1. Secondary Endpoint Assessments

Secondary assessments may refer to (but not limited to) technical/procedural success, safety/effectiveness endpoints, any type of AE rates, distribution of Rutherford classification, hemodynamic improvement, walking improvement at time points that data is collected (refer to **Section 7.2**). All additional assessments are observational.

12.4.2. Interim Analyses

One interim analysis is planned for the purpose of early declaring device effectiveness and safety. The interim analysis data will be used as submission for approval. The RCT will proceed to the study end for all planned number of subjects regardless of the interim result. The Lan-DeMets alpha spending function with Power Family Method is pre-specified for the type I error adjustment to determine the interim and the final significance levels to retain the overall significance level under one-sided 2.5%. Both levels are adaptive based on accumulating study data in the interim. However a minimum of 75% of 12-month required subjects for the interim analysis is recommended.

Without loss of generality, for 75% of subjects to be assessed in the interim analysis, the adjusted type I error will be distributed (i.e. spending) as 1.41% and 1.92% for the interim and the final analyses respectively. Due to the nature of continuous function, the adjusted alphas will be based on the observed interim proportion (e.g. >75%).

The primary effectiveness and primary safety endpoints will be tested simultaneously at the same significance level for the interim analysis and/or for the final analysis as needed.

12.4.3. Subgroup Analyses

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

- Region (e.g. by US/OUS, by country, by site)
- Race
- Gender (male vs. female)
- Age (≥ 65 and < 65)
- Diabetic status (medically-treated vs. non-diabetic)
- Lesion characteristics (vessel diameter/lesion length)
- Balloon matrix (balloon diameter/length)
- Adjunctive devices used (e.g. provisional stents)

- 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 efficacy assessment at two-sided significance level of 0.15 will be performed for the following subgroups:

- Region (e.g. US/OUS)
- Gender (male vs. female)

12.4.4. Justification of Pooling

The poolability analysis regarding the primary effectiveness and/or safety endpoint across sites as well as between US and OUS 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.

12.4.4.1. Site Poolability

Due to the 3:1 randomization scheme using random permuted blocks (i.e. blocks of 4 and 8) employed within each site, ideally there will be 3 Ranger DCB subjects for every 1 Standard PTA subject. Therefore the poolability method is described as below.

The sites with enrollment of 8 subjects or more are reported individually.

The sites with enrollment of 7 or less subjects are pooled into super-sites according to their geographical closeness so that the combined super-sites would have 8 or more enrolled subjects. If a super-site has 8 or more subjects and at least 2 subjects in each treatment group, the pooling of this super-site should stop and the pooling of the next super-site should start.

12.4.4.2. US vs. OUS Poolability

The focus is mostly on the applicability of OUS data to the US population. If the treatment effect is significantly different between US and OUS, possible/plausible explanation is required and/or potential bias needs to be addressed.

12.4.5. Missing Data, Drop-Outs, and Protocol Deviation Handling

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

- Ensure that site personnel are properly trained on the data that is required to be collected and the importance of planning for the follow-up visits.

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

12.4.6. Sensitivity Analyses for Missing Outcome Data

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

12.4.7. Multivariable Analyses

Univariate and multivariable analyses will be performed as post-hoc analysis after unblinding 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.

12.4.8. 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).

12.4.9. Changes to Planned Analyses

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

13. Data Management

13.1. Data Collection, Processing, and Review

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

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

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

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

13.2. Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential trial documents and source documentation that support the data collected on the trial subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years (at least 3 years in Japan) have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

In Japan, BSC must maintain necessary essential documents for 5 years from the date of the marketing application approval (or during the period of use-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 3 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

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

- BIDMC Angiographic: to assess angiograms taken during the index procedure and during any subsequent revascularization procedure (up to12 months post index procedure).

- VASCORE Vascular Ultrasound: to assess DUS taken during the follow-up period (1 month, 6 month, 12 month, 24 month, and 36 month visits).
- COVANCE Pharmacokinetics: to assess baseline paclitaxel levels and at defined time points.

14. Amendments

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

15. Deviations

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

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

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

16. Device Accountability

The investigational devices shall be securely maintained, controlled, and used only in this clinical trial. The Medidata RAVE EDC will be used to track subjects and the device management vendor, Cenduit LLC, will track device allocations throughout the trial enrollment.

The sponsor's device management vendor shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSC or designated facility/equipment to the investigation sites until return or disposal.

Records shall be kept by the device management vendor, Fisher Clinical Services, to document the physical location and conditions of storage of all investigational devices.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the Ranger DCB (test) devices, which shall include the following

- Date of receipt

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

17. Compliance

17.1. Statement of Compliance

This trial will be conducted in accordance with ISO 14155 Clinical Investigation of Medical Devices for Human Subjects-GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The trial shall not begin until the required approval/favorable opinion from the IRB/IEC/REB and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/IEC/REB or regulatory authority shall be followed, if appropriate.

17.2. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the trial 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/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

- Prior to beginning the trial, sign the Clinical Study documenting his/her agreement to comply with the Investigator responsibilities as described in such Agreement, if applicable.
- Prior to beginning the trial, sign the Investigator Brochure Signature Page, if applicable and Protocol Signature page documenting his/her agreement to conduct the trial in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the trial and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical trial 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 trial 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 SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical trial in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical trial, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical trial.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with

identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

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

17.3. Institutional Review Board/ Ethics Committee

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

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

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

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

17.4. Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this trial will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these

confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this trial. Trial data collected during this trial may be used by BSC for the purposes of this trial, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this trial will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the trial 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.

17.4.1. 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 implant, testing required by the protocol during the index procedure. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC investigational device.

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- 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

17.5. Insurance

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

18. Monitoring

Monitoring will be performed during the trial, according to the trial Monitoring Plan, to assess continued compliance with the current, approved protocol/amendments and applicable regulations. In addition, 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. Pre-defined thresholds for protocol deviation and compliance once met or exceeded, can also trigger increased monitoring frequency and/or the implementation of corrective action plans at clinical sites. For the RANGER II SFA trial, source documents include, at a minimum but are not limited to, the ICF; patient medical records, including nursing records and

catheterization laboratory records; imaging records; laboratory results; reports of SAEs; and device accountability logs. Data documented in the eCRF relevant to device deficiencies, relationship of AE to trial device(s), index procedure, antiplatelet medication; and the anticipated assessment of ADEs, may be considered source data for the trial.

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

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

19. Potential Risks and Benefits

19.1. Anticipated Adverse Events and Risks Associated with Use of the Ranger DCB

The following anticipated adverse events (AE) have been identified for this trial.
These adverse events include but are not limited to, the following:

- Allergic reaction (device, contrast medium, medications)
- Arrhythmias
- Arteriovenous fistula
- Death
- Hematoma
- Hemodynamic instability
- Hemorrhage
- Pseudoaneurysm
- Sepsis/infection
- Thromboembolic episodes
- Vascular thrombosis
- Vessel injury (e.g., dissection, perforation, rupture)
- Vessel occlusion
- Vessel spasm

19.2. Risks Associated with the Trial Device(s) Unique to Paclitaxel

Certain side effects and discomforts have been reported in subjects that have received paclitaxel in intravenous forms as part of chemotherapy treatment. These subjects may have other comorbid conditions and/or have received concomitant medications that may also contribute to the reported side effects. Under these circumstances the dose is delivered throughout the body by the blood and in doses hundreds of times higher than the total amount on the coated balloon for use in the proposed clinical trial. Potential adverse events that may be unique to the paclitaxel drug coating include but are not limited to the following:

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

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

19.3. Risks associated with Participation in the Clinical Trial

There may be additional risks linked to the procedure, and follow-up testing which are unforeseen at this time. All testing planned for the first year of follow-up is standard of care in the United States. Follow up assessments after the first year are included to monitor the long term effectiveness and safety profile of the SFA/PPA treatment. These additional requirements should not create additional risk to the subject.

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

- Ecchymosis
- Hematoma
- Infection/inflammation
- Pain

19.4. Possible Interactions with Concomitant Medical Treatments

In addition to the aforementioned risks associated with the treatment of drug coated balloons and the use of paclitaxel, the use of prolonged dual antiplatelet therapy after the index procedure may

increase the risk of bleeding. Refer to the local package insert for further information on drug interactions and side effects associated with paclitaxel or antithrombotic/antiplatelet medications.

19.5. Risk Minimization Actions

Additional risks may exist. Do not utilize in pregnant or breastfeeding women, or in men intending to father children, as this product has not been tested in this population. Birth control/pregnancy prevention should be utilized for up to ninety (90) days after the index procedure.
Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

19.6. Anticipated Benefits

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

19.7. Risk to Benefit Rationale

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

20. Safety Reporting

20.1. Reportable Events by investigational site to Boston Scientific

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

- All Adverse Events (reporting ends after 12 month follow up visit for non-serious, non-device related and non-procedure related Adverse Events)
- All Serious Adverse Events
- All Device Related Adverse Events/Device Related Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

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

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

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

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. For centers in Austria, cancer must always be reported as a Serious Adverse Event. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 20.2-1 for AE definitions).

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

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

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

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

20.2. Definitions and Classification

Adverse event definitions for the RANGER II SFA trial are provided in Table 20.2-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 (2015). In addition, country-specific definitions may apply per local reporting requirements.

Table 20-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3(2015)*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. **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 14155-2011* *Ref: MEDDEV 2.7/3(2015)*	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 intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3(2015)*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, as defined by either: - a life-threatening illness or injury, or - a permanent impairment of a body structure or a body function, or - in-patient hospitalization or prolongation of existing hospitalization, or - medical or surgical intervention to prevent life-threatening illness, or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3(2015)*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *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 14155-2011* *Ref: MEDDEV 2.7/3(2015)*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3(2015)*	An Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

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

20.3. Relationship to Trial Device(s)

The Investigator must assess the relationship of the AE to the trial device or procedure. See criteria in **Table 20-2.**

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

Classification	Description
Not Related	Relationship to the device or procedure can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the device or the procedure; • 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 not expected to be affected by the device or procedure; the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely Related	The relationship with the use of the device or procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the device or procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible related.

Classification	Description
Probably Related	The relationship with the use of the device or procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or with procedure beyond reasonable doubt when: • 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 device use/application or procedure; • the event involves a body-site or organ that - the device or procedure are applied to; - the device or procedure 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 (e.g. 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 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/procedure and the event.

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

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

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

20.4. Investigator Reporting Requirements

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

Table 20-4: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies* (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	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
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the trial
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	• At request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the trial
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) **Note**: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiencies CRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the trial
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • ADE Reporting required through the end of the study • AE reporting required through the 12 month follow-up

Abbreviations: AE=adverse event; CRF=case report form; UADE=unanticipated adverse device effect
* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

20.5. Boston Scientific Device Deficiencies

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

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

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

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

- Packaging or labeling deficiency
- Difficulty advancing or tracking device

20.6. Reporting to Regulatory Authorities/IRBs/ECs/REB Investigators

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

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

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

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

21. Informed Consent

Subject participation in this clinical 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 the use of any investigational devices, study-required procedures and/or testing, or data collection. Testing (including CBC, platelets, ABI, and Rutherford Classification) completed as a part of the subject's standard of care, within 30 days of

the index procedure and that meets the study (inclusion/exclusion) criteria, are not required to be repeated after consenting is complete.

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

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

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

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

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

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

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an

addendum to the ICF. In addition to new significant information during the course of a 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/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

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

22. Committees

22.1. Executive Committee

An Executive Committee composed of BSC Clinical Management and selected Global and National Principal Investigators has been developed. 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. As appropriate the Executive Committee may request participation of RANGER II SFA Investigators on the committee.

22.2. Safety Monitoring Process

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

22.3. Clinical Events Committee (CEC)

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

- All Deaths
- TLR
- TVR
- Target limb amputations

CEC members will be blinded to a subject's treatment assignment through primary endpoint of all participating subjects. Responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

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

22.4. Independent Data Review (IDR)

The independent data reviewer (IDR) provides external oversight and review for potential safety concerns. The IDR is a physician expert in peripheral interventional therapy who is not participating in the clinical trial and is independent to BSC.

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

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

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

23. Suspension or Termination

23.1. Premature Termination of the Trial

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

23.1.1. Criteria for Premature Termination of the Trial

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

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the trial.
- 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.

23.2. Termination of Trial Participation by the Investigator or Withdrawal of IRB/EC/REB Approval

Any investigator, or IRB/ EC in the RANGER II SFA Trial may discontinue participation in the trial or withdrawal 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.

23.3. 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 sites by Boston Scientific. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB 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 BSC.

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

23.4. Criteria for Suspending/Terminating a Study Center

BSC reserves the right to stop the inclusion of subjects at a trial site at any time after the trial initiation visit if no subjects have been enrolled for a period beyond 2 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

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

24. Publication Policy

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

- All authorship and contributorship requirements as described above must be followed.

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

25. Reimbursement and Compensation for Subjects

25.1. Subject Reimbursement

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

25.2. Compensation for Subject's Health Injury

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

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27. Abbreviations and Definitions

27.1. Abbreviations

Abbreviations are shown in **Table 27-1**.

Table 27-1: Abbreviations

Abbreviation	Terminology
ABI	Ankle Brachial Index
ACC/AHA	American College of Cardiology/American Heart Association
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
CE	Conformité Européenne (meaning European Conformity)
CEC	Clinical Events Committee
CIN	Contrast-Induced Nephropathy
CRA	Clinical Research Associate
CRF	Case Report Form
CVA	Cerebrovascular Accident
DCB	Drug Coated Balloon
DFU	Directions for Use
DUS	Duplex Ultrasound
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IEC	Institutional Ethics Committee
ITT	Intent to Treat
IRB	Institutional Review Board
MAE	Major Adverse Event

Abbreviation	Terminology
OUS	Outside United States
PMDA	Pharmaceutical Medical Device Agency
PPA	Proximal Popliteal Artery
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
RBP	Rated Burst Pressure
REB	Research Ethic Board
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
TBI	Tibial Brachial Index
TLR	Target Lesion Revascularization
TM	Transmetatarsal
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
UPN	Universal Product Number
US	United States

27.2. Definitions

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

Table 27-2: Definitions

Term	Definition
AMPUTATION	• Major Amputation: amputation of the lower limb at the ankle level or above. • 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.
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including but not limited to, sinus arrhythmia, premature beats, heart block, ventricular or atrial fibrillation, ventricular tachycardia, or atrial flutter.
ASSISTED PRIMARY PATENCY	Percentage (%) of lesions without clinically-driven TLR and those with clinically-driven TLR (not due to complete occlusion or by-pass) that reach endpoint without restenosis.
BLEEDING COMPLICATION	Includes, but is not limited to, intracranial hemorrhage, GI bleeding, hematoma, bleeding at percutaneous catheterization site, and/or retroperitoneal bleeding. Bleeding that requires surgery qualifies as an SAE.
CALCIFICATION	Readily apparent densities seen within the artery wall and site of lesion as an x-ray-absorbing mass.
CEREBRO-VASCULAR ACCIDENT (CVA)	CEREBRO-VASCULAR ACCIDENT / STROKE An acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging trial or autopsy showing infarction.
CLINICAL DETERIORATION	Downgrade in Rutherford classification of 1 or more categories as compared to pre-procedure.

Term	Definition
COMPLETE BLOOD COUNT (CBC)	A blood test used to measure several components and features of blood, including: Red Blood Cells, White Blood Cells, Hemoglobin, Hematocrit and Platelets.
COMPLICATION	An undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the investigational product(s).
DEATH	All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, an unexpected death in subjects with coexisting potentially fatal non-cardiac diseases (e.g. Cancer, infection) should be classified as cardiac. All death events will be submitted to 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.

Term	Definition
DISTAL EMBOLIZATION	Migration of a filling defect, or thrombus, to distally occlude the target vessel or one of its branches.
EQ-5D™	Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.
END OF INDEX PROCEDURE (TIME)	The end of the index procedure is defined as the time the guide (catheter or sheath) is removed (post final angiography).
HEMATOMA	A localized swelling filled with blood resulting from a break in a blood vessel.
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.
HYPOTENSION	Systolic blood pressure < 80 mmHg lasting more than 30 minutes or requiring intervention (e.g. pacing, IABP, intra venous vasopressors to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.
INTIMAL FLAP	An extension of the vessel wall into the arterial lumen.
LESION LENGTH	Measured as the distance from the proximal shoulder to the distal shoulder of the lesion, in the view that demonstrates the stenosis in its most elongated projection.
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 clinical site or Angiographic Core Laboratory at any point during the procedure. ***Clinical perforation*:** perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant hemodynamic compromise, abrupt closure, or death.
PRIMARY PATENCY	Percentage (%) of lesions that reach endpoint without a hemodynamically significant stenosis on DUS and without clinically-driven TLR or, bypass of the target lesion.

<table>
<tr><th>Term</th><th colspan="3">Definition</th></tr>
<tr><td>PRIMARY SUSTAINED CLINICAL IMPROVEMENT</td><td colspan="3">Endpoint determined to be a success when there is an improvement in Rutherford classification of one or more categories as compared to pre-procedure without the need for repeat TLR.</td></tr>
<tr><td>PROCEDURAL SUCCESS</td><td colspan="3">Procedural success defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core laboratory evaluation (if core laboratory assessment is not available then the site-reported estimate is used)</td></tr>
<tr><td>PSEUDO-ANEURYSM</td><td colspan="3">An encapsulated hematoma in communication with an artery.</td></tr>
<tr><td>PRODUCT NON-CONFORMITY</td><td colspan="3">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.</td></tr>
<tr><td>P1 SEGMENT</td><td colspan="3">The P1 segment (above the knee popliteal artery) is from the Hunter’s canal to the proximal edge of the patella. Target lesion must be in the native SFA and/or PPA down to the P1 segment to the edge of the patella.</td></tr>
<tr><td>REPEAT INTERVENTION (PERCUTANOUS AND/OR SURGERY)</td><td colspan="3">Either repeat percutaneous transluminal angioplasty (PTA) or artery bypass surgery, performed subsequently to the subject leaving the cath lab after the index procedure.</td></tr>
<tr><td>REFERENCE VESSEL DIAMETER (RVD) OF NORMAL ARTERY SEGMENT</td><td colspan="3">Angiographic measurement of the artery proximal and/or distal to the lesion intended for treatment.</td></tr>
<tr><td>RESTENOSIS</td><td colspan="3">DUS systolic velocity ratio (SVR) > 2.4 suggest stenosis >50%.</td></tr>
<tr><td>RUTHERFORD / BECKER CLASSIFICATION</td><td colspan="3"><table>
<tr><th>Category</th><th>Clinical Description</th><th>Objective Criteria</th></tr>
<tr><td>0</td><td>Asymptomatic</td><td>Normal Treadmill /stress test</td></tr>
<tr><td>1</td><td>Mild claudication</td><td>Completes treadmill exercise; ankle pressure (AP) after exercise but at least 20 mm Hg lower than resting value</td></tr>
<tr><td>2</td><td>Moderate claudication</td><td>Between categories 1 and 3</td></tr>
<tr><td>3</td><td>Severe claudication</td><td>Cannot complete treadmill exercise and AP after exercise < 50 mm Hg</td></tr>
<tr><td>4</td><td>Ischemic rest pain</td><td>Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording (PVR); toe pressure (TP) < 30 mm Hg</td></tr>
</table></td></tr>
</table>

Term	Definition		
	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal edema	Resting AP < 60 mm Hg, ankle or metatarsal (MT) PVR flat or barely pulsatile; TP < 40 mm Hg
	6	Major tissue loss – extending above TM level	Same as Category 5
SECONDARY SUSTAINED CLINICAL IMPROVEMENT	Endpoint determined to be a success when there is an improvement in Rutherford classification of one or more categories as compared to pre-procedure including those subjects with repeat TLR.		
SOURCE DATA	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies).		
SOURCE DOCUMENT	Original documents, data or records. Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.		
START OF INDEX PROCEDURE (TIME)	The start of the index procedure is defined as the time the guide (catheter or sheath) is inserted.		
SUCCESSFUL PRE-DILATATION	Successful pre-dilatation occurs when the selected balloon opens vessel entry at nominal pressure without major (≥ Grade D) flow-limiting dissection or need for intervention (i.e. stenting).		
TARGET LESION	A target lesion is identified as a clinical trial lesion intended to be treated with a clinical trial device during the index procedure.		
TARGET LESION REVASCULARIZATION (TLR)	Any surgical or percutaneous intervention to the target lesion(s) after the index procedure. Clinically-driven TLR A target lesion revascularization will be considered clinically-driven by CEC if the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥20% or ≥ 0.15 when compared to post-procedure baseline ABI/TBI in the treated segment. TBI allowed in cases of incompressible vessels.)		

Term	Definition
TARGET VESSEL	Target vessel is defined as the vessel containing the target lesion(s). If the target lesion is entirely within the right superficial femoral artery, then the target vessel is the right superficial femoral artery. If the target lesion extends from the right superficial femoral artery into the right proximal popliteal artery, then both the right superficial femoral artery and right proximal popliteal artery would be considered part of the target vessel.
TARGET VESSEL REVASCULARIZATION (TVR)	Any surgical or percutaneous intervention to the target vessel(s) after the index procedure. Clinically-driven TVR: A target vessel revascularization will be considered as clinically-driven by CEC if the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥20% or ≥ 0.15 when compared to post-procedure baseline ABI/TBI in the treated segment. TBI allowed in cases of incompressible vessels.)

Term	Definition
TRANSATLANTIC INTER-SOCIETAL CONSENSUS (TASC) LESION GUIDELINES	Type A lesion: • Single stenosis ≤ 10 cm in length. • Single occlusion ≤ 5 cm in length. Type B lesion: • Multiple lesions (stenoses or occlusions), each ≤ 5 cm • Single stenosis or occlusion ≤ 15cm not involving the infra geniculate popliteal artery • Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass • Heavily calcified occlusion ≤ 5cm in length • Single popliteal stenosis Type C lesion: • Multiple stenoses or occlusions totaling > 15 cm with or without heavy calcification • Recurrent stenoses or occlusions that need treatment after two endovascular interventions Type D lesion: • Chronic total occlusions of the CFA or SFA (> 20 cm, involving the popliteal artery) • Chronic total occlusion of the popliteal artery and proximal trifurcation vessels
TECHNICAL SUCCESS	Successful delivery, balloon inflation and deflation and retrieval of the intact trial device without burst below the rated burst pressure (RBP)
THROMBUS (ANGIOGRAPHIC)	Discrete, mobile intraluminal filling with defined borders with/without associated contrast straining; these are classified as either absent or present.
UNSUCCESSFUL ANGIOPLASTY	Unsuccessful deployment of assigned balloon
VASCULAR COMPLICATION	An occurrence of hematoma > 5 cm, pseudoaneurysm, arteriovenous (AV) fistula, or need for vascular surgical repair.
VESSEL PATENCY	Freedom from more than 50% stenosis based on DUS peak systolic velocity ratio (PSVR) comparing data within the treated segment to the proximal normal arterial segment. A PSVR > 2.4 suggests >50% stenosis. All DUS readings are assessed by an independent core lab.

Term	Definition
WALKING IMPAIRMENT QUESTIONNAIRE (WIQ)	The WIQ is a functional-assessment questionnaire that evaluates walking ability with regard to speed, distance and stair climbing ability as well as the reasons that walking ability might be limited. Range of scores is between 0% and 100% with 100% being the best and 0% being the worst score.

Appendix A: RANGER Long Balloon Substudy

1. RANGER Long Balloon Substudy Synopsis

<table>
<tr><th colspan="2">RANGER Long Balloon Substudy to RANGER II SFA</th></tr>
<tr><td>Substudy Objective(s)</td><td>To evaluate the safety and effectiveness of the Boston Scientific Corporation (BSC) Ranger™ Paclitaxel Coated Balloon in the 120, 150 and 200 mm lengths for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions.</td></tr>
<tr><td>Indication(s) for Use</td><td>The Ranger Paclitaxel Coated Balloon is intended to be used for Percutaneous Transluminal Angioplasty (PTA) in the peripheral vasculature, including iliac and infrainguinal arteries.</td></tr>
<tr><td>Test Device</td><td>Ranger Paclitaxel Coated PTA Balloon Catheter (Ranger DCB)</td></tr>
<tr><td>Device Sizes</td><td>The working catheter length is 90 cm and 150 cm for all diameters.
The Ranger DCB Long Balloons (test device) are commercially available in Europe and New Zealand (CE Mark #0344, received on 12 July 2017).
<table>
<tr><th colspan="2"></th><th>Balloon Length (mm)</th><th></th><th></th></tr>
<tr><th colspan="2"></th><th>120</th><th>150</th><th>200</th></tr>
<tr><td rowspan="5">Balloon Diameter (mm)</td><td>4.0</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>5.0</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>6.0</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>7.0</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>8.0</td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Substudy Design</td><td>A non-blinded, non-randomized, Long Balloon substudy run concurrent to the RANGER II SFA Global Pivotal Trial in Europe and New Zealand in order to meet DEKRA’s Post-Market Clinical Follow-up (PMCF) Requirement.
Although an investigative center can participate in both the RCT and Long Balloon trial arms, a subject can either be enrolled in the RCT study arm or the RANGER Long Balloon substudy, but not both.</td></tr>
<tr><td>Blinding / Unblinding</td><td>All subjects in the RANGER Long Balloon substudy will be treated with the Ranger DCB. Therefore, all subjects, Investigators, trial center personnel, Duplex Ultrasound (DUS) Core Laboratory personnel, Angiography Core Laboratory personnel, and Clinical Events Committee (CEC) will not be blinded to the assigned treatment arm.</td></tr>
</table>

Planned Number of Subjects	A minimum of 50 subjects will be treated with the Ranger DCB in the RANGER Long Balloon substudy, with at least 20 subjects treated with the 200 mm balloon.
Planned Number of Investigational Sites / Countries	Up to 12 trial centers in Europe and New Zealand may enroll subjects into the RANGER Long Balloon substudy.
Primary Safety Endpoint	The primary safety endpoint assesses the occurrence of Major Adverse Events (MAE) defined as all-cause death through 1 month, target limb major amputation and/or target lesion revascularization (TLR) at 6 and 12 months post-index procedure. It is expected that the MAE-free rate will be similar to the rates observed by the RANGER II SFA group observed in the RCT. The MAE-free rate as well as its individual components will be reported separately for this subgroup.
Primary Effectiveness Endpoint	The primary effectiveness endpoint assesses primary lesion patency at 6 months as determined by duplex ultrasound (DUS). Primary effectiveness is defined as a binary endpoint determined by duplex ultrasound (DUS) peak systolic velocity ratio (PSVR) ≤ 2.4 in the absence of clinically-driven TLR. **Notes**: • Lesion patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment. • PSVR >2.4 suggests >50% stenosis. The treated segment will be assessed for patency as a single segment regardless of the number of tandem lesions within the ballooned segment.
Secondary Endpoints	• Technical success defined as successful delivery, balloon inflation and deflation and retrieval of the intact trial device without burst below the rated burst pressure (RBP) • Procedural success defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core laboratory evaluation (if core laboratory assessment is not available then the site-reported estimate is used) • Clinical success defined as procedural success without procedural complications (i.e. death, major target limb amputation, thrombosis of the target lesion, or clinically-driven TLR) prior to discharge • Major Adverse Events (MAE) through 12 months. MAEs are defined as all-cause death post-index procedure, TLR, and major target limb amputation

	• Death of any cause within 30 days, 6, 12 months • TVR rates at 6, 12 months • TLR rates at 6, 12 months • Rate of Primary and Secondary sustained clinical improvement as assessed by changes in Rutherford Classification from baseline at 1, 6, 12 months post-procedure • Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1, 6, 12 months post-procedure • Duplex-defined binary restenosis (PSVR > 2.4) of the target lesion at 1, 6, 12 months
Method of Assigning Patients to Treatment	In the RANGER Long Balloon substudy, subjects will not be randomized; all subjects will be treated with the Ranger DCB. Subjects are considered enrolled when the Ranger DCB is introduced into the subject's vasculature. **Note**: If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be entered into this substudy. The subject should be cared for and followed outside of the trial based on the physician's treatment plan. **Note**: If the balloon angioplasty attempt with the assigned treatment device (the test device Ranger DCB) is not successful, follow-up through the 1 month visit only will occur as part of the Intent to Treat (ITT) population. Data for assessment of MAE will be collected for these subjects. No other testing or follow up is required.
Follow-up Schedule	Follow-up visits for the RANGER Long Balloon substudy will occur at pre-discharge, 1 month, 6 months, and 12 months post-index procedure. Office or clinic visits are required for testing during each protocol required follow-up visit. Planned procedures and testing include the following: • Physical Exam at screening, pre-discharge, 1 month, 6 month, and 12 month • Angiogram at time of index procedure and during any subsequent revascularization procedure (up to12 months post index procedure) • Duplex Ultrasound at 1 month, 6 month, and 12 month • Rutherford Classification at screening, 1 month, 6 month, and 12 month • Resting ABI exam at screening, 1 month, 6 month, and 12 month

	• Lab tests:
	  - Complete Blood Count (CBC) containing WBC, RBC and PLT at screening
	  - Serum creatinine at screening
	  - Pregnancy testing (serum or urine) within 24 hrs prior to index procedure if of child bearing age
	• Medication compliance at screening, procedure, pre-discharge, 1 month, 6 month, and 12 month,
	• Adverse event monitoring at procedure, pre-discharge, 1 month, 6 month, and 12 month

Study Duration	The Long Balloon substudy primary endpoint will be considered complete after all subjects have completed the 6 month follow-up visit, were discontinued prior to the 6 month follow-up visit, have died, or the last 6 month follow-up visit window is closed. The RANGER Long Balloon substudy will be considered complete after all subjects have completed the 12 month follow-up visit, were discontinued prior to the 12 month follow-up visit, have died, or the last 12 month follow-up visit window is closed.
Required Medication Therapy	Anti-platelet therapy is recommended throughout the length of the trial participation. Investigators must prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice. Antiplatelet medication and peripheral artery disease (PAD) medication usage will be collected and reported for compliance throughout the trial. Minimum protocol requirements: • Anti-coagulation therapy administered prior to and during the procedure should be consistent with current clinical practice. • A minimum of 30 days of dual antiplatelet therapy for non-stented subjects and a minimum of 3 months (90 days) dual antiplatelet therapy for stented subjects post index procedure. Minimum recommendation: • Antiplatelet monotherapy is recommended for administration throughout the 12 month follow-up (trial completion). **Note**: A subject is exempt from the above-mentioned antiplatelet requirements if he/she requires Coumadin or other similar anti-coagulant due to known comorbidities and in the opinion of the investigator, the combination of antiplatelet and anticoagulant could put the subject at an unreasonable risk of bleeding.

Inclusion Criteria	Enrollment into the RANGER Long Balloon substudy is limited to the following inclusion criteria: 1. Subject (or Legal Guardian) is willing and able to provide consent before any study-specific tests or procedures are performed and agree to attend all required follow-up visits; 2. Subject at least 20 years of age; 3. Chronic symptomatic lower limb ischemia defined as Rutherford classification 2, 3, or 4; 4. Target lesion is in the native SFA and/or PPA down to the P1 segment; 5. Patent popliteal and infrapopliteal arteries, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot; 6. Reference vessel diameter ≥ 4 mm and ≤ 8 mm by visual estimate (Use of a radiopaque ruler is recommended); and 7. Angiographic evidence that target lesion consists of a single de novo, non-stented and non-atherectomy treated or restenotic lesion (or tandem lesions or a combination lesion as defined below) that is: a. ≥ 70% -99% stenotic with total lesion length up to180 mm by visual estimate. Use of a radiopaque ruler is recommended. b. Occluded with total lesion length ≤ 150 mm by visual estimate. Use of a radiopaque ruler is recommended. c. If lesion is restenotic, most recent PTA treatment must be > 3 months prior to enrollment **Notes**: Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) are eligible provided that the combined total lesion length is ≤180 mm. Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria: • Separated by a gap of ≤ 30 mm (3 cm) • Total combined lesion length meets requirements (Angiographic inclusion criteria (7) including 30 mm gap); and • Able to be treated as a single lesion.
Exclusion Criteria	Patients are not permitted to enroll into the RANGER Long Balloon substudy if they meet any of the following exclusion criteria:

	1. Life expectancy, documented in the Investigator's opinion, of less than 12 months; 2. Hemorrhagic stroke or cardiac event (e.g. STEMI, unstable angina) within 6 months prior to enrollment; 3. Known allergies or sensitivities to heparin, aspirin, other anticoagulant/antiplatelet therapies, and/or paclitaxel; 4. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated; 5. Chronic renal insufficiency with serum creatinine > 2.0 mg/dL within 30 days of index procedure or treatment with dialysis; 6. Platelet count <80,000 mm^3 or >600,000 mm^3 or history of bleeding diathesis; 7. Receiving immunosuppressive therapy; 8. Septicemia at the time of enrollment; 9. Any major (e.g., cardiac, peripheral, abdominal) intervention (including in the contralateral SFA/PPA) planned within 30 days post index procedure; 10. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of enrollment; 11. Failure to successfully cross the target lesion with a guidewire (successful crossing means tip of the crossing device is distal to the target lesion in the absence of flow-limiting dissections or perforations); 12. Failure to successfully pre-dilate the target vessel; 13. Patient has lesion that requires the use of adjunctive primary treatment modalities (i.e. laser, atherectomy, scoring/cutting balloon, other debulking devices, etc.) during the index procedure; 14. History of major amputation in the target limb; 15. Target lesion or vessel has ever been previously treated with stent (e.g. in-stent restenosis) or surgery. Target lesion or vessel has been treated with atherectomy or a DCB in the past 12 months; 16. Pregnant or breast feeding; 17. Presence of aneurysm in the target vessel; 18. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to enrollment; 19. Patient has significant inflow disease which cannot be treated prior to the target lesion treatment;

	20. Patient has perforated targeted vessel as evidenced by extravasation of contrast media; 21. Patient has severe calcification that renders the lesion undilatable; 22. Current participation in another investigational drug or device clinical trial that has not completed the primary endpoint at the time of randomization/enrollment or that clinically interferes with the current trial endpoints. **Note**: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies.
Multiple Interventions During Index Procedure	Contralateral & Ipsilateral Limb Lesions Using the same access site, iliac lesion(s) in the contralateral and ipsilateral limb may be treated during the index procedure under the following conditions: • Treatment with a commercially (non-drug coated) available device occurs prior to enrollment of the target SFA/PPA lesion(s); • Treatment of the lesion(s) is deemed an angiographic success without clinical sequelae (success is measured as <30% residual stenosis by visual estimation) and If the above criteria are not met, the subject may not be enrolled into the substudy but may be rescreened for eligibility after 30 days. **Note**: Provisional stenting of the target lesion with bare-metal stents can be completed in cases where adequate results could not be obtained after using post-dilatation balloons; such as in the case of remaining residual stenosis [≥ 50%] or major [≥ Grade D] flow-limiting dissection after post-dilatation.
Statistical Methods: Descriptive statistics will be used in the RANGER Long Balloon substudy.	
Sample Size and Statistical Method for Long Balloon substudy	In order to support the stated objectives for the RANGER Long Balloon substudy, the sample size for this substudy will be a minimum of 50 subjects; 20 subjects will be treated with a 200 mm Long Balloon. Descriptive statistics will be presented to describe the Long Balloon substudy results.
Core Laboratories	The following core laboratories will be established for the central assessment of key data collected during the trial: • Angiography: to assess angiograms taken during the index procedure and during any subsequent revascularization procedure (up to 12 months post index procedure)

	• Ultrasound: to assess ultrasounds taken during the follow-up periods (1 month, 6 months, and 12 months)

2. RANGER Long Balloon Substudy

2.1. Objectives

To evaluate the safety and effectiveness of the Boston Scientific Corporation (BSC) Ranger™ Paclitaxel Coated Balloon in the 120, 150 and 200 mm lengths for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions.

2.2. Design

The RANGER Long Balloon substudy is a non-blinded, non-randomized, single arm, substudy run concurrent with the RANGER II SFA Global Pivotal Clinical Trial. The substudy will be conducted in Europe and New Zealand in order to meet DEKRA's Post-Market Clinical Follow-up (PMCF) Requirement.

2.2.1. Scale and Duration

A minimum of 50 subjects will be enrolled in the RANGER Long Balloon substudy.

All subjects will receive treatment with test device (Ranger DCB) in the RANGER Long Balloon substudy; 20 subjects will receive treatment with the 200mm test device. The RANGER Long Balloon substudy will be conducted at the RANGER II SFA Global Pivotal Trial sites in Europe and New Zealand. The Ranger Long Balloons are commercially available in Europe and New Zealand. The Directions for Use (DFU) will be followed.

Clinical follow-up will be required at the following time points: pre-discharge, 1 month, 6 months, and 12 months post index procedure. Testing required at these at these visits are described in section 11.10 of the RANGER II SFA Global Pivotal Protocol.

The enrollment period will run concurrent with the RANGER II SFA Global Pivotal Trial. Figure 2-1 shows the schematic of the RANGER Long Balloon substudy design.

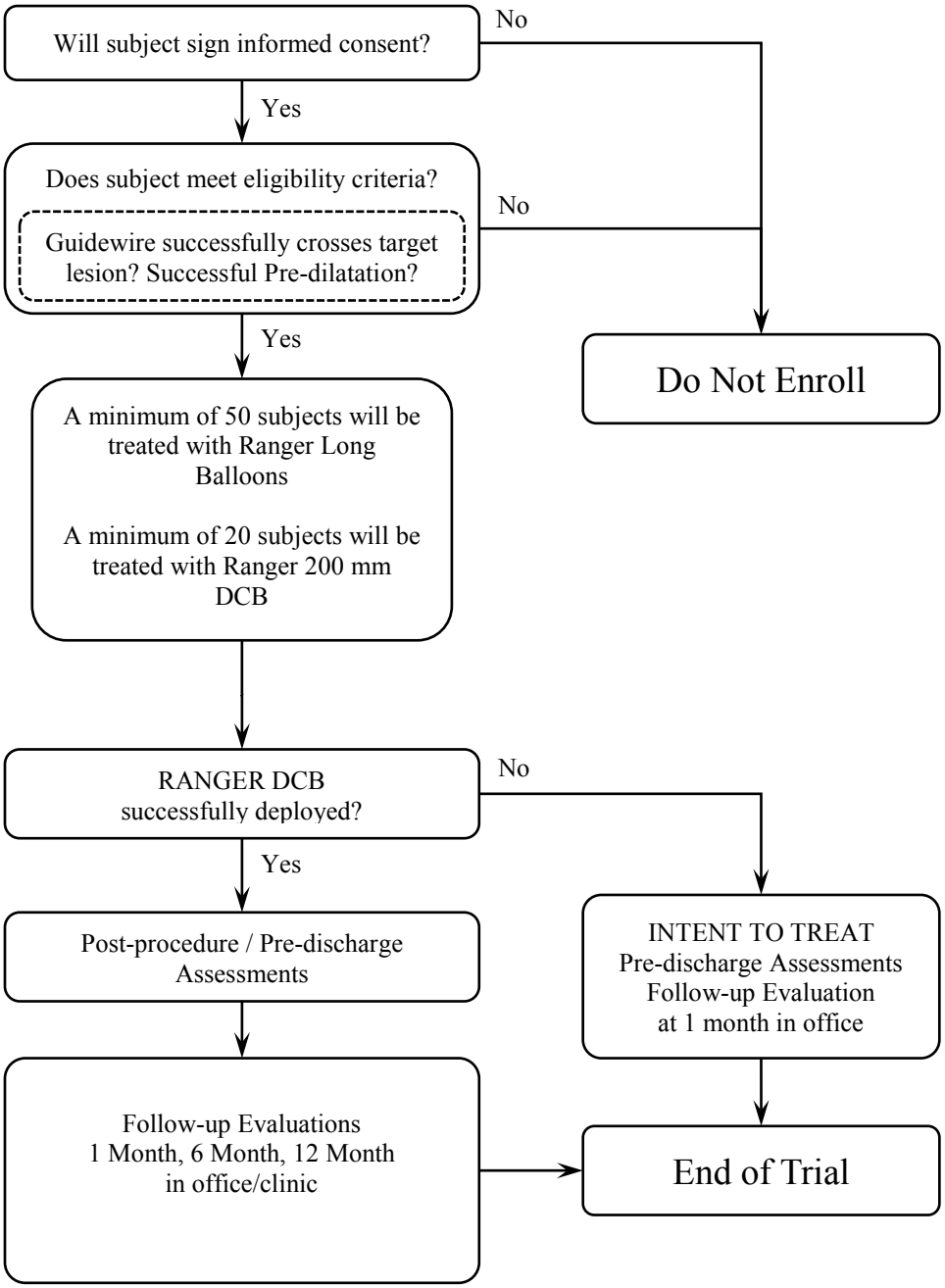

Figure 2-1: RANGER Long Balloon Substudy

2.2.2. Treatment Assignment

Once the subject has signed the Ethics Committee (IEC/REB) approved study informed consent form (ICF), and has met all clinical inclusion and no clinical exclusion criteria, the subject will be considered eligible to be enrolled in the RANGER Long Balloon substudy. Subjects cannot be simultaneously enrolled in the RCT and the RANGER Long Balloon substudy.

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

All subjects enrolled in the RANGER Long Balloon substudy will be treated with a commercial available Ranger DCB.

2.2.3. Device Description

The Ranger DCB is available in a variety of diameters and balloon lengths. Device sizes intended for use in this RANGER Long Balloon substudy are summarized below in Table 2-2. The shaft lengths utilized for the Long Balloon sizes in this substudy are 90 cm and 150 cm for diameters 4-7 mm. The Ranger DCB Long Balloons are commercially available in Europe and New Zealand (CE Mark #0344, received on 12 July 2017).

Table 2-2: Ranger DCB Long Balloon Device Sizes

		Balloon Length (mm)		
		120	**150**	**200**
Balloon Diameter (mm)	**4.0**	X	X	X
	5.0	X	X	X
	6.0	X	X	X
	7.0	X	X	X
	8.0			

2.3. Multiple Interventions Using Same Access Site During Index Procedure

Target Limb

The target lesion may include two or more tandem lesions, provided that the entire segment of tandem lesions is ≤ 180 mm and can be covered with Ranger DCB(s) according to the Directions for Use (DFU).

3. Subject Selection

3.1. Study Population and Eligibility

Clinical and angiographic inclusion criteria and exclusion for the RANGER Long Balloon substudy are included in Table 3-1 and 3-2. Inclusion and exclusion criteria identical to that of RANGER II SFA Global Pivotal Protocol (Sections 9.2 and 9.3) except for the CTO length in the RANGER Long Balloon substudy are ≤ 150 mm. Prior to enrollment, a subject must meet all of the clinical and angiographic inclusion criteria and none of the clinical and angiographic exclusion criteria.

Table 3-1: RANGER Long Balloon Substudy Inclusion Criteria

Inclusion Criteria	1. Subject (or Legal Guardian) is willing and able to provide consent before any study-specific tests or procedures are performed and agree to attend all required follow-up visits; 2. Subject at least 20 years of age; 3. Chronic symptomatic lower limb ischemia defined as Rutherford classification 2, 3, or 4; 4. Target lesion is in the native SFA and/or PPA down to the P1 segment; 5. Patent popliteal and infrapopliteal arteries, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot; 6. Reference vessel diameter ≥ 4 mm and ≤ 8 mm by visual estimate (Use of a radiopaque ruler is recommended); 7. Angiographic evidence that target lesion consists of a single de novo, non-stented and non-atherectomy treated or restenotic lesion (or tandem lesions or a combination lesion as defined below) that is: a. ≥ 70% -99% stenotic with total lesion length up to180 mm by visual estimate. Use of a radiopaque ruler is recommended. b. Occluded with total lesion length ≤ 150 mm by visual estimate. Use of a radiopaque ruler is recommended. c. If lesion is restenotic, most recent PTA treatment must be > 3 months prior to enrollment **Notes:** Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) are eligible provided that the total combined lesion length is ≤180 mm. Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria:

	• Separated by a gap of ≤ 30 mm (3 cm) • Total combined lesion length meets requirements (Angiographic inclusion criteria (7) including 30 mm gap); and • Able to be treated as a single lesion.

Table 3-2: RANGER Long Balloon Substudy Criteria

Exclusion Criteria	1. Life expectancy, documented in the Investigator's opinion, of less than 12 months; 2. Hemorrhagic stroke or cardiac event (e.g. STEMI, unstable angina) within 6 months prior to enrollment; 3. Known allergies or sensitivities to heparin, aspirin, other anticoagulant/antiplatelet therapies, and/or paclitaxel; 4. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated; 5. Chronic renal insufficiency with serum creatinine > 2.0 mg/dL within 30 days of index procedure or treatment with dialysis; 6. Platelet count <80,000 mm^3 or >600,000 mm^3 or history of bleeding diathesis; 7. Receiving immunosuppressive therapy; 8. Septicemia at the time of enrollment; 9. Any major (e.g., cardiac, peripheral, abdominal) intervention (including in the contralateral SFA/PPA) planned within 30 days post index procedure; 10. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of enrollment; 11. Failure to successfully cross the target lesion with a guidewire (successful crossing means tip of the crossing device is distal to the target lesion in the absence of flow-limiting dissections or perforations); 12. Failure to successfully pre-dilate the target vessel; 13. Patient has lesion that requires the use of adjunctive primary treatment modalities (i.e. laser, atherectomy, scoring/cutting balloon, other debulking devices, etc.) during the index procedure; 14. History of major amputation in the target limb;

	15. Target lesion or vessel has ever been previously treated with stent (e.g. in-stent restenosis) or, surgery. Target lesion or vessel has been treated with atherectomy or a DCB in the past 12 months; 16. Pregnant or breast feeding; 17. Presence of aneurysm in the target vessel; 18. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to enrollment; 19. Patient has significant inflow disease which cannot be treated prior to the target lesion treatment; 20. Patient has perforated targeted vessel as evidenced by extravasation of contrast media; 21. Patient has severe calcification that renders the lesion undilatable; 22. Current participation in another investigational drug or device clinical trial that has not completed the primary endpoint at the time of randomization/enrollment or that clinically interferes with the current trial endpoints. **Note**: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies.

Abbreviations: STEMI- ST elevation myocardial infraction

3.2. Subject Accountability

Subject accountability is as described in Section 10 of the RANGER II SFA Global Pivotal Protocol.

3.3. Substudy Methods

The RANGER Long Balloon substudy will follow the RANGER II SFA Global Pivotal Protocol for all aspects of study execution including but not limited to Data Management (section 13), Deviations (section 15), Compliance (section 17) monitoring (section 18) and Safety Reporting (section 20), with the exception of Device Accountability (section 16) as commercial devices will be used in this substudy.

3.4. Data Collection

Subjects enrolled in the RANGER Long Balloon substudy will follow the Data Collection schedule as summarized in Table 3-3. Clinical follow-up will be required at the following time points: pre-discharge, 1 month, 6 months, and 12 months post index procedure. The Data Collection schedule in the RANGER Long Balloon substudy is the same as the RANGER II SFA Global Pivotal Protocol (section 11.1) with the exception of the following tests that are not required:

- Walking Impairment Questionnaire (WIQ)
- EQ-5D Questionnaire

- 6 Minute Walk Test (6MWT)

Table 3-3-: RANGER Long Balloon Substudy Data Collection

Procedure/Assessment	Pre-procedure	During Initial Procedure	Pre-Discharge	1-month	6-month	12-month
Informed Consent	X					
Confirm Inclusion/Exclusion	X	X				
Demographics and Medical History, Height and Weight	X					
Pregnancy Test	X					
Physical Exam	X		X	X	X	X
Complete Blood Count (CBC) and platelet count	X					
Serum Creatinine	X					
Ankle Brachial Index Measurements	X			X	X	X
Rutherford Classification	X			X	X	X
Angiogram		X				
Enrollment		X				
Duplex Ultrasound				X	X	X
Medication Assessment	X	X	X	X	X	X
Adverse Events Assessment		X	X	X	X	X

4. Statistical Considerations

The RANGER Long Balloon Substudy is an observational substudy. The non-statistically driven performance goal will be compared against the observed 6-month and 12-month primary patency in the evaluable long balloon subjects.

4.1. Primary Endpoint

The sample size determination for the RANGER Long Balloon substudy is arbitrary and not statistically driven.

4.1.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint assesses 6-month primary patency as determined by duplex ultrasound (DUS). Lesion patency is defined as freedom from greater than 50% stenosis in the

absence of clinically-driven TLR. Primary effectiveness is defined as a binary endpoint determined by duplex ultrasound (DUS) peak systolic velocity ratio (PSVR) ≤ 2.4 in the absence of clinically-driven TLR.

Statistical Methods

The non-statistically driven performance goal will be compared against the observed 6-month primary patency in the evaluable long balloon subjects. If the observed 6-month primary patency is greater than or equal to 50%, the RANGER DCB will be considered to have acceptable effectiveness performance in the long balloon population.

4.1.2. Primary Safety Endpoint

The primary safety endpoint assesses the occurrence of Major Adverse Events (MAE) defined as all-cause death through 1 month, target limb major amputation and/or target lesion revascularization (TLR) at 6 and 12 months post-index procedure.

It is expected that the MAE-free rate will be similar to the rates observed by the RANGER II group observed in the RCT. The MAE-free rate as well as its individual components will be reported separately for this subgroup.

4.2. Additional Endpoints

Secondary endpoints that will be evaluated, but are not necessarily powered to make statistically-based conclusions, will be reported separately for this subgroup including:

- Technical success defined as successful delivery, balloon inflation and deflation and retrieval of the intact trial device without burst below the rated burst pressure (RBP)
- Procedural success defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core laboratory evaluation (if core laboratory assessment is not available then the site-reported estimate is used)
- Clinical success defined as procedural success without procedural complications (i.e. death, major target limb amputation, thrombosis of the target lesion, or clinically-driven TLR) prior to discharge
- Major Adverse Events (MAE) through 12 months. MAEs are defined as all-cause death post-index procedure, TLR, and major target limb amputation
- Death of any cause within 30 days, 6, and 12 months
- TVR rates at 6, and 12 months
- TLR rates at 6, and 12 months
- Rate of Primary and Secondary sustained clinical improvement as assessed by changes in Rutherford Classification from baseline at 1, 6 and 12 months post-procedure
- Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1, 6 and 12 months post-procedure
- Duplex-defined binary restenosis (PSVR > 2.4) of the target lesion at 1, 6 and 12 months

The following endpoints will **not** be collected in the RANGER Long Balloon substudy:

- Walking Improvement (distance) at 6 months and 12 months as assessed by changes in the Six Minute Hall Walk Test (6MWT) from baseline
- Walking Improvement and Patient Utility Values assessed at 1, 6 and 12 months as assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D™ from baseline