Prospective, non-randomized, multicenter clinical study of the Boston Scientific Paclitaxel-Coated PTA Balloon Catheter (Ranger™ and Ranger™ SL (OTW) DCB) in China

RANGER CHINA

CLINICAL PROTOCOL

(S6052)

Sponsored By

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

Original Release: March 23, 2015

Current Version: 1 Jul, 2020

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	March 23, 2015	90702637 Rev./Ver. AE	None	None	Original release
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 2 for Contact information	Change PM from "Jade Jian Shi" to "Yisi Wang"	PM changed
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 7 in Synopsis, Page22 for Section 7.1.2 and 7.2	Change the assessment of primary efficacy endpoint from "DUS" to "CTA"; add additional DUS at 30 days post index procedure to additional endpoints; and delete 30-days and 6-months DUS assessment in additional endpoint	To reflect the changes in study endpoints and the assessment methods
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 26 for Section 8.4.1	Add "the diameter ratio of DCB to the reference vessel should be 1:1 (no less than 1:1), and the recommended length of DCB should include the segment of vessel treated with the study device and the 5 mm proximal and 5 mm distal to the treated segment."	Clarify the requirement of the choice of the device size
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 9 in Synopsis, Page27 for Section 9.2	Change "Target vessel diameter" from" ⩾ 4.0 mm and ⩽ 6.0 mm " to " ⩾ 2.0 mm and ⩽ 8.0 mm"	To accommodate the regulatory requirements to include the use of all sizes of study device
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 10 in Synopsis; Page 28 for Section 9.3	• Adjust the exclusion criteria of platelet count from "< 100,000 /ml or > 600,000 /ml" to"< 80,000 /ml or > 700,000 /ml"; • Add the Angiographic Exclusion Criteria: AE1. Subjects with ipsilateral iliac inflow lesions , and unsuccessful treatment prior to the index procedure (i.e., residual stenosis ≥ 30% post treatment) AE2. Subjects with no patent infrapopliteal artery (i.e., ≥ 50% stenosis) to the foot prior to index procedure. • Add exclusion criteria 20: Subjects who had any major procedures (cardiac, aorta, peripheral) within 30 days prior to the index procedure	To clarify the exclusion criteria and adjust the exclusion criteria range.

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 31 for Form 11.1-1	Adjust the FU visit time and related examinations in form "Data Collection Schedule"	To align with the changes in study endpoints and the assessment methods.
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 9 in Synopsis, Page 34 for Section 11.5.3	Change the required length of clopidogrel use from "4 weeks" to "3 months"	To change the required length of medication therapy
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 34 for Section11.5	Add "Clopidogrel is the first choice, if not tolerated, Ticlopidine could be used" and "After Surgery: In addition to DAPT, the risk of bleeding may be increased by subjects with anticoagulant therapy. If necessary, should choose oral warfarin, and disable a new generation of oral anticoagulants(like rivaroxaban, apixaban or dabigatran"	Clarify the choice of Combined medication
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 11 in Synopsis, Page 35 for Section 11.6.1	• Delete "Prior to treatment of the index lesion, successful (< 30% residual stenosis) treatment of ipsilateral outflow lesions may be performed before or during the index procedure." • Delete "Post Index Procedure: Additional interventions should not be performed within 30 days before or after the index procedure."	Adjust the content according to the in/exclusion criteria.
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 8 in Synopsis, Page 33 for Section 11.4, page 36~37 for Section 11.8~11.11	• Add CTA assessment in screening phase • Allow the 30-day and 6-month follow up may be via phone or in-person interview. • Delete 6-month DUS assessment • Add 3-month DUS assessment • Add 12-month CTA assessment	To align with the primary endpoint change.
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 13 in Synopsis, Page 42 for Section 13.3	Change core lab requirement for "DUS" to "CTA"	To align with the endpoint change
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 42 for Section15	Add PD Classifications	To better define the PDs

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 50 for Section 20.1	Add clarification for safety reporting of Device deficiencies and In-patient hospitalization	To clarify the safety reporting requirements
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 53 for Section 20.3(Table 20.3-1)	Change SAE reporting timeline from within 2 business days to 24 hours	To align with SAE report guideline
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 56 for Section 22.2	Add "Safety Monitoring Process"	To better monitor the safety.
AB	November 11, 2015	90702637 Rev./Ver. AE	Page 61 for Section 26.2	Add definitions related to this study	To add relevant definitions for the study
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 8, Section 2, Primary Endpoint; Page 25, Section 7.1.2	To update "The primary efficacy endpoint " from "primary vessel patency" to "primary lesion patency".	To clarify the primary efficacy endpoint is lesion patency not vessel patency per investigators' requirement.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 11, Section 2, Key Inclusion Criteria; Page 30, Section 9.2;	AI1: • To add "must be overlapped to cover targeted lesion(s)" after "Lesion length ≥ 20 mm and ≤ 200 mm, to be covered by one or two balloon(s)" • To add "The lesion length of total occluded lesion ≤ 100 mm" • To add "For diffuse lesion or multiple tandem lesions (may including a total occluded lesion) in the same target vessel, the total lesion length, including the distance between lesions, must be ⩽ 200 mm, with the separation of ⩽ 30 mm (3 cm) between two adjacent lesions"	• To emphasize the overlapping requirement of two balloons. • To add one specific Inclusion Criteria of total occluded lesion. • To clarify the lesion length of multiple tandem lesion to include the distance limits of two lesions.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 12, Section2, Key Exclusion Criteria, Page 31, Section 9.3	To add "176.8 umol/L" to Exclusion Criteria 13.	• To clarify 2.0 mg/dL serum creatinine equals to 176.82 umol/L

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 12, Section 2 Key Exclusion Criteria; Page 31, 32 , Section 9.3	• To add "(even with successfully treatment during the procedure, these subjects should be excluded from enrollment)" in AE 2. • To add AE3 "Failure to successfully antegrade cross the target lesion with a guidewire (successful crossing is defined as the tip of crossing device is distal to the target lesion in the true lumen without flow-limiting dissection or perforation as evidenced by extravasation of contrast media)" • To combine Exclusion Criteria 23 "Perforated vessel as evidenced by extravasation of contrast media" to AE3	• To specify the angiographic exclusion criteria for subjects with on patent infrapopliteal artery (i.e., ≥ 50% stenosis). • To add AE3 based on the discussion at investigator meeting for total occluded lesions.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 28, Section 8.4	To update the % of residual stenosis after pre-dilating the target lesion and to add "Incremental pre-dilatation technique is recommended, and the diameter of last pre-dilation balloon catheter should not exceed the diameter of DCB catheter."	To clarify the pre-dilatation of the target lesion as discussed in the investigator meeting.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 28, Section 8.4.2	To update "minimize balloon overlap and the number of balloons used" to "the Ranger DCB must overlapped to cover targeted lesion(s), and a 1 cm overlap is recommended" for the lesion required the use of more than one balloon.	To clarify the overlap requirement for the lesion that need use more than one balloon as discussed in the investigator meeting.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 35, Section 11.1 Page 37, Section 11.4	To add "(test results within 30 days prior to the index procedure are acceptable)" for CTA and DUS tests.	To extend the time window of CTA and DUS tests within the acceptable time.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 35, Section 11.1	To add "in-person clinic visit is recommended if subjects have worsen symptoms" to 30-day and 6-month follow up visit."	To add the recommendation to protect subjects' safety.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 44, Section 13.2	Updated the duration of "Data Retention" for investigator from "5years" to "10years"; Update the duration of "Data Retention" for BSC to "until the product/device is no longer in use" .	To be in compliance with China new GCP.

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page 44, Section 13.2	Added "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." Under "Data Retention".	To be consistent with the latest version of BSC global protocol template.
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page 45, Section 17.2	Edited and added some appropriate wordings in the section of "Investigator Responsibilities" according to the new protocol template	To be consistent with the latest version of BSC global protocol template.
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page 46, Section 17.2	Added "and provide analysis report, which includes the causality assessed by both investigator and BSC and decision on study continuance, to IRB/EC per local and/or country requirements"	To be in compliance with China new GCP.
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page 46, Section 17.2	Added the wording of "and potential USADE or UADE" to define the reportable device deficiency	To be consistent with the latest version of BSC global protocol template..
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page 46, Section 17.2	Added wording of "provide all required source documents related to a death event to BSC and the IEC per local requirements."	To be in compliance with China new GCP.
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page 51-52, Section 20.1	Editorial revision in the Safety "Definitions and Classifications" per the new protocol template	To be consistent with BSC global protocol template.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page54, Section 20.1	To add "It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories: • All Serious Adverse Events • All Investigational Device Deficiencies • Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects • New findings/updates in relation to already reported events When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.	To be in consistence with the protocol template.

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				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"	
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page53-54, Section 20.2	Combined and revised "Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event". To include the classification of "Unlikely Related/ Possibly Related/ Probably Related/ Causal Relationship"	To be consistent with BSC global protocol template.
AC	January, 16, 2017	90702637 Rev./Ver. A H	Page 57, Section 20.5	Included the wordings of "According to China local reporting requirements, Boston Scientific Corporation will report all SAEs and device deficiencies that could lead to SAEs to the local Food and Drug Administration and the same level Commission of Health and Family Planning within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sites and IRBs/Ecs in a timely manner."	To be in compliance with China new GCP and latest BSC global protocol template.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 59, Section 22.2	Edited the wordings in the section of "Safety Monitoring Process" and included the wording of "The BSC Medical Safety group includes physicians with expertise in vascular intervention and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above."	To be consistent with BSC global protocol template.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 60, Section 23.1.1	Edited the wordings in the section of "Possible reasons for premature study termination", and add the wording "Note: According to the section 20, even if the study is terminated, all the Aes, SAEs, SADEs and Device Deficiency should be evaluated and reported for the subjects who have received the treatment of study device. (China Medical Device GCP requirement: The reasons and criteria based on biostatistics of study termination are: the statistics method of all the data is missing, data is missing or error (including withdraw	To be in compliance with China new GCP and latest BSC global protocol template.

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				and termination) and unreasonable data handling methods.)"	
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page 61, Section 23.4	To add "According to Section 20, all the ongoing Aes should be evaluated and reported for the subjects who have been treated by study device. And the ongoing Aes should be followed up by investigators continues, unless BSC informed the sites."	To be in compliance with China new GCP and latest BSC global protocol template.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Page66-78, Section 26.2	To edit the wordings in the section of "Definition".	Editorial revision.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.
AC	January, 16, 2017	90702637 Rev./Ver. AH	Header & Footer	Change the Format.	To be in consistence with latest BSC protocol template
AD	July 21, 2017	90702637 Rev./Ver. AH	Page 10, Section 2 Protocol Synopsis, Device Sizes; Page 25, section 5 Device Description	Add new size of Ranger LE DCB	To include the longer sizes of Ranger DCB in this study to meet the clinical needs of treating longer lesions.
AE	December 7，2018	90702637 Rev./Ver. AJ	Page 2 for Contact information	Change PM from "Yisi Wang" to "Jian Wen"	PM changed
AE	December 7，2018	90702637 Rev./Ver. AJ	Page 12，Protocol synopsis, Planned number of subjects; Page 18, Sample size parameters; P30, Scale and duration; P33, study population and eligibility; Page 37, Enrollment controls; Page 46,	Change sample size from 123 to 139	Adjust the sample size according to the updated attrition

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			Sample size.		
AE	December 7，2018	90702637 Rev./Ver. AJ	Page 18, Sample size parameters; Page 45-46, Sample size;	Change attrition rate from 15% to 25%	Adjust the attrition rate according to the realistic follow-up rate.
AE	December 7，2018	90702637 Rev./Ver. AJ	Page 37, Enrollment controls; Page 47, Number of subjects per investigative site	Change the enrollment cap for each study site from 25% to 30%, and adjust the maximum number of patients for each site from 30 to 42 according to the cap and total sample size	Adjust the enrollment cap to give more flexibility for site which has potential to enroll more patients.
AE	December 7，2018	90702637 Rev./Ver. AJ	P52，Delegation of responsibility	Insert “Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site.”	To be consistent with the latest version of BSC global protocol template.
AE	December 7，2018	90702637 Rev./Ver. AJ	P53, Investigator responsibilities	Edited and added some appropriate wordings in the section of “Investigator Responsibilities” according to the new protocol template	To be consistent with the latest version of BSC global protocol template.
AE	December 7，2018	90702637 Rev./Ver. AJ	P53, Institutional Review Board/ Ethics Committee	Edited and added some appropriate wordings in the section of “Institutional Review Board/ Ethics Committee” according to the new protocol template	To be consistent with the latest version of BSC global protocol template.
AE	December 7，2018	90702637 Rev./Ver. AJ	P53, Role of Boston scientific representatives	Delete “without the approval and presence of the HCP” according to the new protocol template	To be consistent with the latest version of BSC global protocol template.
AE	December 7，2018	90702637 Rev./Ver. AJ	P55, Insurance	Edited the section of “Insurance” according to the new protocol template	To be consistent with the latest version of BSC global protocol template.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	Home Page; Header	The protocol version was updated from AE to AF. The protocol template version was updated from AJ to AL.	Update the protocol and to be consistent with the latest version of BSC global protocol template.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P2, Contact Information	Project manager was changed from Wen Jian to Zhou Jing.	PM changed.

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AF	Apr 30, 2020	90702637 Rev./Ver. AL	P13, Indications for Use	Added indications of the study device in the synopsis.	To be consistent with the latest version of BSC global protocol template.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P16, Participant Duration	Added participant duration in the synopsis.	To be consistent with the latest version of BSC global protocol template.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P14, Planned number of subjects; P21, Sample size parameters; P32, Scale and Duration; P35, Study population and eligibility; P38, Enrollment controls; P45, Sample size	Sample size was changed from 139 to 123.	The new added 16 subjects can't get the approval by HGRAC, so the original sample size was used.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P14, Primary Endpoint; P15, Additional Endpoints	Replace "vessel patency" with "Lesion patency" in the notes.	To be consistent with the description of primary efficacy endpoint
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P15/P31, Additional Endpoints	Specify the time point for evaluating clinical success and hemodynamic success	To be consistent with Table 11.1-1: Data Collection Schedule
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P20/P45, Primary Statistical Hypothesis; P20/P46, Statistical Test Method; P31/P45, The primary efficacy endpoint	Modify the wording of primary efficacy endpoint	To be consistent with the description of primary efficacy endpoint in synopsis

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AF	Apr 30, 2020	90702637 Rev./Ver. AL	P47, Subgroup Analyses	The classification of the target lesion location was changed from " ATK and BTK" to "distal, mid, proximal and ostial"	Per protocol, all the target lesions are in the SFA and/or PPA, not involved BTK artery.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P20, Sample size parameters; P38, Enrollment controls; P45, Sample size	The attrition rate was changed from 25% to 15%.	Considering that the 12-month follow-up is now nearing completion, and the last 9 subjects have entered the follow-up window to be followed, the attrition rate was adjusted according to the actual follow-up rate.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P38, Definitions of End-of-study	Added the definition for end-of-study.	To be consistent with the latest version of BSC global protocol template.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P47, Number of subjects per investigator site	The maximum number of subjects per site was changed from 42 to 37.	Updated according to the final sample size.
AF	Apr 30, 2020	90702637 Rev./Ver. AL	P64, Reporting to Regulatory Authorities/ IRBs/ECs/ Investigators	Added the following contents in this section:" Investigator and investigational site is responsible for reporting all SAEs and device deficiencies that could lead to SAEs to IRBs/ECs, local Food and Drug Administration and the same level Commission of Health within 24 hours of investigator becoming aware of the event."	To be consistent with the latest version of BSC global protocol template.

2. Protocol Synopsis

<table>
<tr><th colspan="2">Prospective, non-randomized, multicenter clinical study of the Boston Scientific Paclitaxel-Coated PTA Balloon Catheter (Ranger™ and Ranger™ SL (OTW) DCB) in China
RANGER CHINA</th></tr>
<tr><td>Study Objective(s)</td><td>The primary objective of this study is to demonstrate acceptable safety and performance of the Ranger™（Ranger & Ranger LE） and Ranger™ SL (OTW) paclitaxel-coated PTA balloon catheter used for angioplasty of femoropopliteal artery lesions.</td></tr>
<tr><td>Indications for Use</td><td>The Ranger（Ranger & Ranger LE） and Ranger SL balloon catheters are indicated for PTA in the peripheral vasculature, including iliac and infrainguinal arteries.</td></tr>
<tr><td>Test Device</td><td>Boston Scientific Ranger™（Ranger & Ranger LE） and Ranger™ SL Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB)</td></tr>
<tr><td>Control Device</td><td>N/A</td></tr>
<tr><td>Device Sizes</td><td>The working length is 80cm and 135cm for Ranger DCB catheter and 90 cm and 150cm for Ranger SL and Ranger LE DCB catheter. Balloons with the following dimensions will be used in this trial:
<table>
<tr><th></th><th colspan="8">Diameters of Ranger & Ranger SL & Ranger LE DCB</th></tr>
<tr><th>Length</th><th>2.0 mm</th><th>2.5 mm</th><th>3.0 mm</th><th>3.5 mm</th><th>4.0 mm</th><th>5.0 mm</th><th>6.0 mm</th><th>7.0 mm</th><th>8.0 mm</th></tr>
<tr><td>30 mm</td><td>-</td><td>-</td><td>-</td><td>-</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>40 mm</td><td>-</td><td>-</td><td>-</td><td>-</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>60 mm</td><td>-</td><td>-</td><td>-</td><td>-</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>80 mm</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>100 mm</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>-</td></tr>
<tr><td>120 mm</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>-</td></tr>
<tr><td>150 mm</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>-</td></tr>
<tr><td>200 mm</td><td>-</td><td>-</td><td>-</td><td>-</td><td>X</td><td>X</td><td>X</td><td>X</td><td>-</td></tr>
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</td></tr>
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Study Design	This clinical study is a prospective, non-randomized, multicenter study to demonstrate the acceptable safety and performance of angioplasty with the Ranger DCB in native femoropopliteal artery lesions. It is intended that all patients with qualifying lesions would be considered for enrollment and treated with the Ranger DCB catheter.
Planned Number of Subjects	Approximately 123 patients with femoropopliteal artery lesions will be enrolled. All lesions will be treated with the Ranger DCB.
Planned Number of Sites / Countries	Up to 15 clinical sites located in China are expected to participate.
Primary Endpoint	The primary safety endpoint is the rate of following major adverse events through 30 days post-procedure: • all device and/or procedure related mortality • target limb major amputation at • Clinically-driven Target Lesion Revascularization (TLR) The primary efficacy endpoint is primary lesion patency of the treated segment(s) as assessed by computed tomography angiography (CTA) at 12 months post-procedure without clinically-driven TLR. **Notes** • Lesion patency is defined as freedom from more than 50% diameter stenosis • All CTA readings will be assessed by an independent core laboratory
Additional Endpoints	• Technical success (defined as ability to cross and dilate the lesion to achieve residual angiographic stenosis no greater than 30%) • Procedural success (defined as technical success with no Major Adverse Events (MAEs, including all-cause death, clinically-driven

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	TLR, target limb major amputation or thrombosis at target lesion) within 24 hours of the index procedure • Target lesion patency assessed by duplex ultrasound sonography (DUS) at 3 month post index procedure • All-cause death at 30 days, 3, 6 and 12 months • Clinically-driven TLR at 3, 6 and 12 months • Time to first clinically-driven TLR through 12 months post-procedure • Clinical success (defined as improved Rutherford classification by at least +1 class) at pre-discharge, 3 and 12 months, as compared to baseline • Hemodynamic success (defined as positive change in Ankle-Brachial Index(ABI)) at pre-discharge, 3 and 12 months, as compared to baseline • MAEs through 12 months **Notes** • Lesion patency is defined as freedom from more than 50% stenosis based on DUS peak systolic velocity ratio comparing data within the treated segment to the proximal normal arterial segment. • A systolic velocity ratio > 2.4 suggests > 50% stenosis.
Safety Parameters	The following will be collected and reported at each follow-up interval • MAEs including all-cause death, clinically-driven TLR, target limb major amputation or thrombosis at target lesion • All adverse Events (including but not limited to unanticipated, major, serious, device/procedure-related)
Method of Assigning Patients to Treatment	Once a patient signs the Ethics Committee-approved Informed Consent Form, and has met all inclusion criteria and has no exclusion criteria, they are eligible to be enrolled in the clinical study. All eligible subjects will receive treatment with the Ranger DCB. Enrollment occurs at the time of advancement of the Ranger DCB into the body.

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Follow-up Schedule	Follow-up time points include: pre-discharge; 30 days, 3, 6 and 12 months. Tests planned to occur during follow-up visits include the following: • CTA assessment before procedure • Angiography during the procedure • DUS at 3-month follow-up visit • CTA at 12-month follow-up visit (evaluated by an independent core lab)
Study Duration	Approximately 1 year of enrollment and 1 year of follow-up
Participant Duration	The study duration for each subject is expected to be 12 months
Required Medication Therapy	• If patients do not already take acetylsalicylic acid (ASA) (minimum 75 mg per day) and/or Clopidogrel (75 mg/day) ≥ 72 hours at the time of index procedure, they will receive recommended peri-procedural loading doses of 300 mg ASA and/or 300 mg Clopidogrel before the balloon angioplasty procedure or no later than 2 hours after the index procedure. • At the time of the procedure, patients receive an intra-arterial bolus of heparin (usually 3000-5000 IU), or alternate anticoagulants as substitutes for heparin if justified by individual subject conditions. • After the procedure, all patients will be treated with ASA (minimum 75 mg per day) indefinitely, and with Clopidogrel (minimum 75 mg per day) for 3 months.
Key Inclusion Criteria	1. Subjects must be age 18 or older 2. Subject is willing and able to provide informed consent 3. Subject is available and willing to attend all required follow-up visits 4. Subject has a clinically significant symptomatic leg ischemia 5. Subject has a Rutherford clinical category of 2 - 4 6. If the index lesion is restenotic, the prior PTA must have been > 90 days prior to treatment in the current study 7. Only one lesion per limb can be treated under this protocol, which means that one index lesion, on one index limb will be “in treatment”. However, both limbs may be treated during either the index procedure and/or subsequent procedures

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	8. Successful intraluminal wire crossing of the target lesion ***Angiographic Inclusion Criteria:*** AI1. The index lesion is a clinically and hemodynamically *de novo* stenotic or restenotic lesion located in the native nonstented superficial femoral artery or proximal popliteal artery between the Hunter's Canal and the popliteal fossa (i.e. within the P1 segment), with the following characteristics by visual assessment: • Degree of stenosis ≥ 70% • Target vessel diameter ≥ 2.0 mm and ≤ 8.0 mm • Lesion length ≥ 20 mm and ≤ 200 mm, to be covered by one or two balloon(s) (must be overlapped to cover targeted lesion(s)) • The lesion length of total occluded lesion ≤ 100 mm • For diffuse lesion or multiple tandem lesions (may including a total occluded lesion) in the same target vessel, the total lesion length, including the distance between lesions, must be ≤ 200 mm, with the separation of ≤ 30 mm (3 cm) between two adjacent lesions AI2. The subject has at least one patent infrapopliteal artery (< 50% stenosis) to the foot prior to index procedure
Key Exclusion Criteria	1. Subjects who have undergone prior vascular surgery of the SFA/PPA in the index limb to treat atherosclerotic disease 2. History of major amputation in the same limb as the target lesion 3. Presence of aneurysm in the target vessel(s) 4. Acute ischemia and/or acute thrombosis in any artery of the lower limbs 5. Acute Myocardial Infarction within 30 days before the index procedure *6.* History of hemorrhagic stroke within 3 months 7. History of thrombolysis or unstable angina within 2 weeks of enrollment 8. Persistent, intraluminal thrombus of the proposed target lesion post thrombolytic therapy 9. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated 10. Known allergies against Paclitaxel or other components of the used medical devices 11. Intolerance to antiplatelet, anticoagulant, or thrombolytic medications that would be administered during the trial

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	12. Platelet count < 80,000 mm^3 or > 700,000 mm^3 13. Concomitant renal failure with a serum creatinine > 2.0 mg/dL(176.8 umol/L) 14. Receiving dialysis or immunosuppressant therapy 15. Life expectancy of less than one year 16. Women of child-bearing potential cannot use a reliable method of contraception from the time of screening through 12 months after the index procedure. 17. Woman who is pregnant or nursing. (Pregnancy test must be performed within 72 hours prior to the index procedure, except for women who definitely do not have child-bearing potential). 18. Previously planned stenting of the index lesion (stents will be allowed for bailout situations, such as flow-limiting dissection) 19. Use of adjunctive therapies (debulking, laser, cryoplasty, re-entry devices) 20. Subjects who had any major procedures (cardiac, aorta, peripheral) within 30 days prior to the index procedure 21. Planned or expected procedures (cardiac, aorta, peripheral) within 30 days post the index procedure 22. Presence of outflow lesions requiring intervention within 30 days of the index procedure 23. Heavily calcified target lesions resistant to PTA 24. Current participation in another drug or device trial that has not completed the primary endpoint, including any clinical study using drug-coated or drug-eluting technology, that may potentially confound the results of this trial, or that would limit the subject's compliance with the follow-up requirements 25. Current or past intervention using drug-coated/drug-eluting technologies in the index limb *26.* Target lesion with in-stent restenosis (any stent or stent-graft) ***Angiographic Exclusion Criteria:*** AE1. Subjects with ipsilateral iliac inflow lesions, and unsuccessful treatment prior to the index procedure (i.e., residual stenosis ≥ 30% post treatment AE2. Subjects with no patent infrapopliteal artery (i.e., ≥ 50% stenosis) to the foot prior to index procedure (even with successfully treatment during the procedure, these subjects should be excluded from enrollment)

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	AE3. Failure to successfully antegrade cross the target lesion with a guidewire (successful crossing is defined as the tip of crossing device is distal to the target lesion in the true lumen without flow-limiting dissection or perforation as evidenced by extravasation of contrast media)
Multiple Interventions	**Prior to or during Index Procedure:** • Prior to treatment of the index limb, successful (< 30% residual stenosis) treatment of ipsilateral iliac inflow lesions may be performed • Prior to treatment of the index limb, successful treatment of the arteries of the non-index limb may be performed • Prior to treatment of the index limb, absence of clinical complications such as embolism, thrombosis, severe dissection, vessel rupture must be confirmed **IMPORTANT NOTE: Use of drug coated devices** **Additional Index Limb Treatment** • No other Drug Coated Balloon (DCB) or Drug Eluting Stent (DES) treatment in the **index lesion** is allowed throughout the study duration • DCB or DES treatment in **non-index lesions** of the index limb is allowed after 12 months post procedure **Non-index Limb Treatment** • The non-index limb may be treated with DCB or DES before and after the index procedure
Statistical Methods	
Primary Statistical Hypothesis	Primary Safety Endpoint: The rate of freedom from device and/or procedure-related death, target limb major amputation and/or clinically-driven target lesion revascularization through 30 days post procedure (i.e. the rate of composite MAE-free) exceeds a PG of 88%. H_0: *Safety* ≤ 0.88 H_1: *Safety* > 0.88 Primary Efficacy Endpoint:

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	The rate of primary lesion patency at 12 months post-procedure without clinically-driven TLR exceeds a PG of 53% for femoropopliteal artery segments treated with the Ranger DCB. H_0: *Patency* ≤ 0.53 H_1: *Patency* > 0.53
Statistical Test Method	The primary hypotheses will be tested in a sequential manner to allow testing of each of primary safety and efficacy endpoints at the specified significance level of 5% without adjustment. The hierarchical testing procedure for multiple comparisons with the testing order starting with the primary safety endpoint followed by the primary efficacy endpoint. That is, the primary efficacy hypothesis will be tested only if the primary safety hypothesis is rejected. For safety, if the one-sample normal approximation one-sided 95% lower confidence bound of the observed 30-day composite MAE-Free rate is greater than 0.88, then the Ranger DCB will be considered to have acceptable safety performance, and 12-month efficacy performance testing will be allowed. For efficacy, if the one-sample normal approximation one-sided 95% lower confidence bound of the observed 12-month lesion patency is greater than 0.53, then the Ranger DCB will be considered to have acceptable performance.

Sample Size Parameters	**Safety**
	• Expected 30-day composite MAE-Free rate for all subjects = 99%
	  o Safety Performance Goal = 88%
	• Test significance level α = 0.05 (one-sided normal approximation)
	• A minimum of 104 evaluable subjects are driven by the efficacy endpoint to provide at least 99% power to assess the primary safety endpoint at 30 days
	
	Efficacy
	• Expected 12-Month vessel patency = 65%
	  o Efficacy Performance Goal = 53%
	• Test significance level α = 0.05 (one-sided normal approximation)

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	• A minimum of 104 evaluable subjects are required to provide adequate power of 80% to assess the primary efficacy endpoint at 12 months • Expected attrition for all reasons at 12 months ≤ 15% • Approximately 123 subjects will be enrolled to account for expected attrition
Core Lab	Computed tomography angiography (CTA) readings will be assessed by a blinded core lab.

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

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

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

The femoropopliteal artery is the most commonly involved site in patients with PAD.[7] Endovascular therapy, percutaneous transluminal angioplasty (PTA) with optional bailout stenting is currently recommended for the majority of symptomatic patients by ACCF/AHA and TASC II.[5, 8] Although the primary success rate of PTA is high (above 90%), the long femoropopliteal lesions have a high rate of restenosis after endovascular treatment, [9, 10] because of the unique anatomy and biomechanics of femoropopliteal arteries. Both bare and drug-eluting stents were developed to improve the acute and long-term clinical outcomes of PTA. However, the high restenosis rate and stent-based complications (such as stent fracture) remain a challenge in the patients with femoropopliteal lesions. Hence, drug-coated balloons (DCB) have been developed to further reduce the restenosis rate and address the limitations of stents.

Currently marketed DCBs are coated with Paclitaxel which inhibits the proliferation of neointimal vascular smooth muscle cells. This effect has been shown first in a number of multicenter randomized clinical trials in the prevention of restenosis following coronary angioplasty,[11, 12] and in studies in peripheral arteries (e.g. THUNDER trial, Tepe et al.).[13] Restenosis in treated peripheral arteries is caused by an interaction of a variety of mechanical and biological processes. These processes involve early vessel recoil causing residual stenosis, negative vascular remodeling, and excessive neointimal proliferation.[14 - 16] The DCB technology adds the benefits of local drug delivery to the mechanical procedure of PTA resulting in more effective inhibition of neointimal proliferation and restenosis. In addition, DCB also provides more homogenous drug transfer, rapid release of the drug with little impact on long-term healing, absence of a polymer carrier which could decrease chronic inflammation, the anatomy of the vessel stays intact, and no overdependence on antiplatelet therapy. [11]

The safety and performance of DCB in the treatment of peripheral occulusive artery disease of the lower extremities has been demonstrated in randomized clinical trials and a series of clinical studies. Werk et al. [17] randomly assigned 87 patients with femoropopliteal peripheral artery disease to uncoated or paclitaxel-coated balloons (Paclitaxel dose density of 3 µg/ mm^2 balloon surface area). Eligible patients had an occlusion or > 70% diameter stenosis of the superficial femoral artery and/or popliteal artery, with clinical Rutherford

stage 1 to 5. The primary endpoint of angiographic late lumen loss (LLL) at 6 months was significantly reduced in patients treated with DCB when compared to bare PTA control, as well as the endpoint of binary restenosis (DCB group, n=6 of 31, 19%; control group, n=16 of 34, 47%; p=0.035), and the clinical endpoint of improvement in Rutherford class at 6 months compared to pretreatment (p=0.045). The advantage of paclitaxel-coated balloon treatment over PTA with regard to Target Lesion Revascularization (TLR) was maintained out to 18 to 24 months after intervention.

Similar results were observed in the THUNDER trial[13] which was a prospective, randomized, multicentre trial to evaluate the safety and efficacy of a paclitaxel-coated PTA balloon (Paccocath; coated with paclitaxel at a dose density of 3 µg/ mm_2 balloon surface area) vs. an uncoated PTA balloon for the treatment of symptomatic peripheral artery disease (Rutherford stages 1 to 5). All patients had one or more obstructive lesion, either de novo or restenotic lesions in the superficial femoral artery, the popliteal artery, or both. The angiographic restenosis rate was significantly lower for patients treated with paclitaxel coated balloons than for patients in the control group (17% vs. 44%, p=0.01). The rate of target lesion revascularization remains significantly lower for the paclitaxel-coated balloon group through 24 months.

The Ranger™ and Ranger™ SL (OTW) Paclitaxel-Coated PTA Balloon Catheters (Ranger DCB) are intended to be used in PTA in the peripheral vasculature including iliac and infrainguinal arteries. This intended use includes PTA of stenotic and occlusive lesions in the femoropopliteal segment (SFA/PPA).

It has been demonstrated that various currently marketed drug-coated balloons are safe and effective for the treatment of peripheral artery disease. The core of Ranger DCB technology is a proprietary drug and excipient formulation applied to the balloon component of an approved, state-of-the-art conventional PTA balloon catheter, with a highly effective drug/excipient coating formulation allowing for a reduced drug dose density of 2µg/mm^2. This coating composition has been shown to be comparably effective to 3µg/mm^2 formulations of other DCB platforms while reducing systemic drug exposure.

Based on a systematic evaluation of device characteristics (risk assessment, design verification and validation, biocompatibility, stability, sterility, evaluations of pharmacokinetic characteristics and histopathology in a representative preclinical animal model) performed by the legal manufacturer and study Sponsor, the study device is considered safe for starting clinical evaluations in patients.

The primary objective of this study is to demonstrate acceptable safety and performance of the Ranger™ （Ranger & Ranger LE）and Ranger™ SL (OTW) DCBs for angioplasty for femoropopliteal artery lesions in Chinese LEAD patient cohort.

5. Device Description

5.1. Ranger™ DCB Description

The Ranger™（Ranger & Ranger LE） and Ranger™ SL Paclitaxel-Coated PTA Balloon Catheters (Ranger (Ranger & Ranger LE)and Ranger SL balloon catheters) are Over-the-Wire (OTW) Percutaneous Transluminal Angioplasty (PTA) balloon catheters with a semi-compliant balloon coated with a formulation of paclitaxel (drug) and an excipient. The Ranger （Ranger & Ranger LE）and Ranger SL balloon catheters are designed to inhibit restenosis by delivering drug to diseased arterial tissue.

The Ranger（Ranger & Ranger LE） and Ranger SL balloon catheters have a coaxial shaft design. The outer lumen is used for inflation of the balloon, and the wire lumen permits the use of guidewires 0.014 in or 0.018 in (0.36 mm or 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 catheter includes a tapered tip to facilitate advancement of the catheter to and through the stenosis.

The Ranger（Ranger & Ranger LE） and Ranger SL balloon catheters have two radiopaque marker bands (one proximal and one distal) which, in conjunction with fluoroscopy, aid in the placement of the balloon. The proximal shaft marks define the length to the distal end of the catheter.

The working lengths of the Ranger balloon catheters are 80 cm and 135 cm. The 80 cm working length catheter has one mark at 50 cm and two marks at 60 cm. The 135 cm working length catheter has one mark at 90 cm and two marks at 100 cm.

The working lengths of the Ranger SL and Ranger LE balloon catheters are 90 cm and 150 cm. The 90 cm working length catheter has one mark at 50 cm and two marks at 60 cm. The 150 cm working length catheter has one mark at 90 cm and two marks at 100 cm.

The proximal portion of the Ranger （Ranger & Ranger LE）and Ranger SL balloon catheters includes one female
Luer-lock port connected to the inflation lumen, and one female Luer-lock port for the guidewire lumen. In addition, the Ranger（Ranger & Ranger LE） and Ranger SL balloon catheters are equipped with a loading tool to help protect the drug coating as it enters the hemostatic valve.

5.1.1. Drug Component Description

The Ranger（Ranger & Ranger LE） and Ranger SL balloon catheters have a drug coating formulation consisting of paclitaxel (the active pharmaceutical ingredient) and an excipient (the inactive ingredient).

5.1.1.1. Paclitaxel

The active pharmaceutical ingredient in the balloon coating is paclitaxel. It is a white powder, isolated from a spectrum of Taxus species and hybrids. The dose of Paclitaxel is 2.0 µg per mm2 of the balloon surface. The Chemical name of paclitaxel is: Benzenepropanoic acid, β -(benzoylamino) α - hydroxy -,6,12b – bis (acetyloxy) - 12- (benzoyloxy) - 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11- dihydroxy-4a,8,13,13- tetramethyl-5 oxo-7,11 methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR- [2aα,4β,4aβ,6β,9α (αR*,βS*), 11α,12α,12aα,12bα]].
Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol and a molecular formula of C47H51NO14. It is highly lipophilic, insoluble in water, but freely soluble in methanol, ethanol, chloroform, ethyl acetate and dimethyl sulfoxide.

5.2. Intended Use

The Ranger（Ranger & Ranger LE） and Ranger SL balloon catheters are indicated for PTA in the peripheral vasculature, including iliac and infrainguinal arteries.

5.3. Device Labeling

A copy of the Directions for Use (DFU) for Ranger（Ranger & Ranger LE） and Ranger SL DCBs is included in the Ranger China Manual of Operations. The labeling will include at least the following information:

- Product Name
- Project Name, Storage & Shipment condition

The following statements appear on the Ranger China product labeling for clinical distribution:

Caution: For Clinical Trial Use Only

Device labeling will be provided in Chinese per China regulations.

6. Study Objectives

The primary objective of this study is to demonstrate acceptable safety and performance of the Ranger™（Ranger & Ranger LE） and Ranger™ SL (OTW) paclitaxel-coated PTA balloon catheter used for angioplasty of femoropopliteal artery lesions.

7. Study Endpoints

7.1. Primary Endpoints:

7.1.1. The primary safety endpoint:

The primary safety endpoint is the rate of following major adverse events:

- All device and/or procedure related mortality through 30 days
- Target limb major amputation at 30 days
- Clinically-driven Target Lesion Revascularization (TLR) at 30 days post-procedure

7.1.2. The primary efficacy endpoint:

The primary efficacy endpoint is primary lesion patency of the treated segment as assessed by computed tomography angiography (CTA) at 12 months post-procedure without clinically-driven TLR.

Notes

- Lesion patency is defined as freedom from more than 50% diameter stenosis .
- All CTA readings will be assessed by an independent core laboratory.

7.2. Additional Endpoints

- Technical success, defined as the ability to cross and dilate the target lesion to achieve residual angiographic stenosis no greater than 30%
- Procedural success, defined as technical success without any Major Adverse Events （MAEs，including all-cause death, clinically-driven TLR, target limb major amputation or thrombosis at target lesion）within 24 hours of the index procedure
- Target lesion patency assessed by duplex ultrasound sonography (DUS) at 3month post index procedure
- All-cause death at 30 days, 3, 6 and 12 months
- Clinically-driven TLR at 3, 6 and 12 months
- Time to first clinically-driven TLR through 12 months post-procedure
- Clinical success (defined as improved Rutherford Classification by at least +1 class) at pre-discharge, 3 and 12 months, as compared to baseline
- Hemodynamic success (defined as positive change in Ankle-Brachial Index (ABI)) at pre-discharge, 3 and 12 months, as compared to baseline
- MAEs through 12 months

Notes

- Lesion patency is defined as freedom from more than 50% stenosis based on DUS peak systolic velocity ratio comparing data within the treated segment to the proximal normal arterial segment.
- A systolic velocity ratio > 2.4 suggests > 50% stenosis.[18, 19]

8. Study Design

The Ranger China is a prospective, non-randomized, multicenter clinical study to demonstrate the acceptable safety and performance of angioplasty with the Ranger DCB catheter in native femoropopliteal artery lesions. It is intended that all patients with qualifying lesions would be considered for enrollment and treated with the Ranger DCB catheter.

8.1. *Scale and Duration*

The Ranger China trial will be conducted in up to 15 sites in Mainland China with planned enrollment of approximately 123 subjects.

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

All subjects will be screened according to the protocol inclusion and exclusion criteria. Subjects will be enrolled in a non-randomized process. Clinical follow-up will be required at the following time points: pre-discharge and 30 days, 3, 6 and 12 months post-index procedure.

A schematic of the Ranger China trial design is shown below in Figure 8.1-1.

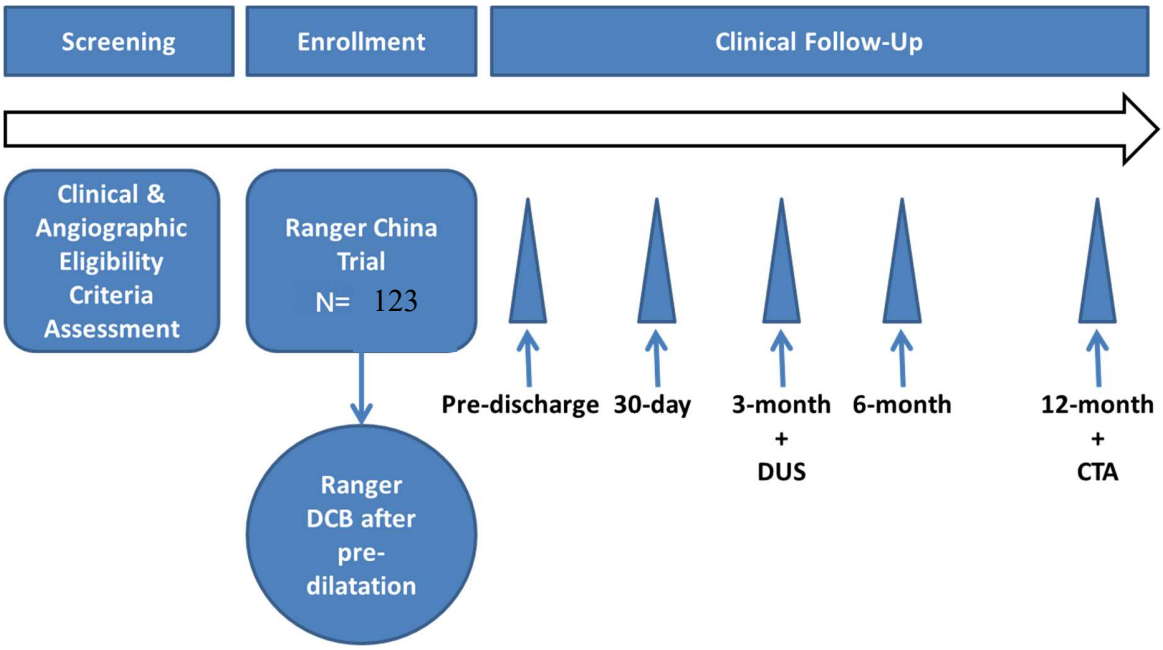

Figure 8.1-1: Ranger China Study Design

The study will be considered complete after all subjects have completed the 12-month follow-up visit, are withdrawn from the trial (due to death or having been lost to follow-up) or their follow-up window (i.e., 30 days after a scheduled follow-up visit) has closed.

8.2. *Treatment Assignment*

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

8.2.1. Treatment and Control

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

8.2.2. Target and Non-target Lesions

A target lesion is a lesion selected by the Investigator for treatment with a study DCB catheter. Target lesions must meet all the angiographic selection criteria. A diffuse lesion or multiple lesions within the same target vessel segment can be considered as one target lesion if the total lesion length (including the distance between lesions) is ≤ 200 mm.

Only one target lesion is allowed to be treated per limb (Index Limb) under this protocol, i.e., one target lesion on one index limb will be "in treatment". However, both limbs may be treated during either the index procedure and/or subsequent procedures with the investigational device (see "Multiple Interventions" in Section11.6.1.

No other DCB or drug-eluting stent (DES) treatment in the index lesion is allowed throughout the study duration. DCB or DES treatment in non-index lesions of the index limb is allowed after 12 months. DCB or DES treatment in the non-index limb is allowed before and after the index procedure.

For non-target lesion procedures, see "Multiple Interventions" in Section 11.6.1.

8.3. *Justification for the Study Design*

The Ranger China trial is designed to evaluate the safety and efficacy of the Ranger DCBs for the treatment of subjects in China with atherosclerotic lesion(s) in native femoropopliteal arteries.

During the trial, clopidogrel will be administered for 3 months post index procedure and aspirin use will be required indefinitely post index procedure. Ongoing dynamic data safety monitoring will be performed throughout the trial to minimize subject risk. All enrolled subjects receiving the Ranger DCB treatment will be followed for 12 month post index procedure.

8.4. *Treatment*

All enrolled subjects will receive PTA treatment with the Ranger DCB catheter approved for this indication. Before Ranger DCB treatment, the target lesion must be pre-dilated with an

uncoated PTA balloon. All Ranger DCB balloons may be inflated only once. A second Ranger DCB catheter will be used for lesions exceeding the length of the first balloon.

Note: Balloon catheter pre-dilatation is **required** for all target lesions**.** It is recommended to always use a smaller diameter balloon dilatation catheter to pre-dilate the target lesion with residual stenosis < 50% to facilitate passage of the DCB catheter. Incremental pre-dilatation technique is recommended, and the diameter of last pre-dilation balloon catheter should not exceed the diameter of DCB catheter.

8.4.1. Device sizing selection

The investigator selects the size of Ranger DCB according to the proximal and distal reference vessel diameters and lesion length. The diameter ratio of DCB to the reference vessel should be 1:1 and not less; and the recommended length of DCB should include the segment of vessel treated with the study device and the 5 mm proximal and 5 mm distal to the treated segment.

To facilitate passage of the Ranger DCB, it is mandatory to use a smaller diameter balloon (< the diameter of reference vessel) dilatation catheter to pre-dilate the target lesion.

The investigators shall follow the instructions in the DFU.

8.4.2. Number of device per lesion

Whenever possible, the lesion should be treated with a single balloon that fully covers the stenosed or occluded vessel segment. If the lesion requires the use of more than one balloon, the Ranger DCB must be overlapped to cover targeted lesion(s), and a 1 cm overlap is recommended. Typically, a longest properly sized balloon should be used first and followed by a second balloon of appropriate dimensions to complete the procedure.

8.4.3. Number of inflation

All study devices (Ranger DCB) may be inflated only once, as transfer of therapeutic drug levels occurs only during the first inflation. Repeat inflation of a Ranger DCB at the treatment site should be limited to emergency / bail-out situations, e.g. to treat vessel perforations or flow-limiting dissections when exchange for an uncoated balloon is deemed inappropriate due to safety considerations. A Ranger DCB may not be re-inflated in a segment adjacent to or outside the primarily treated target lesion.

8.4.4. Treatment of dissection

Dissections shall be treated at the discretion of the investigator with non-drug-coated technology. If balloon treatment alone is not sufficient to treat a flow-limiting dissection, consider the use of a stent.

8.4.5. Role of stenting

Limit stenting to bail-out situations such as flow-limiting dissections that cannot be repaired using prolonged balloon inflation alone; or greater than 50% residual stenosis post DCB treatment. In such situations, use bare metal stents of appropriate dimensions, but try to use the shortest stent suitable to achieve good flow. Whenever possible, avoid the use of long stents, overlapping stents and stent grafts. Do not use drug-eluting stents or bio-absorbable stents in combination with the Ranger DCB.

Handling Instructions of Study Devices
It is important for investigators to follow the corresponding DFU for Ranger DCB treatment and for the study device product matrix.
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9. Subject Selection

9.1. *Study Population and Eligibility*

A total of 123 patients with symptomatic PAD of the femoropopliteal artery (Rutherford clinical category of 2 to 4) receiving percutaneous transluminal balloon angioplasty will be enrolled into this study. Clinical and angiographic inclusion and exclusion criteria for the Ranger China trial are included in Section 9.2 and Section 9.3 respectively. Prior to enrollment in the trial, a subject should meet all of the clinical and angiographic inclusion criteria and none of the exclusion criteria.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 9.3) is met.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	CI1. Subjects must be age 18 or older CI2. Subject is willing and able to provide informed consent CI3. Subject is available and willing to attend all required follow-up visits CI4. Subject has a clinically significant symptomatic leg ischemia CI5. Subject has a Rutherford clinical category of 2 - 4 CI6. If the index lesion is restenotic, the prior PTA must have been > 90 days prior to treatment in the current study CI7. Only one lesion per limb can be treated under this protocol, i.e., one index lesion on one index limb will be "in treatment". However, both limbs may be treated during either the index procedure and/or subsequent procedures CI8. Successful intraluminal wire crossing of the target lesion
Angiographic Inclusion Criteria	AI1. The index lesion is a clinically and hemodynamically *de novo* stenotic or restenotic lesion located in the native non-stented superficial femoral artery and proximal popliteal artery between the Hunter's Canal and the popliteal

(visual estimate)	fossa (i.e. within the P1 segment), with the following characteristics by visual assessment: • Degree of stenosis ≥ 70% • Target vessel diameter ≥ 2.0 mm and ≤ 8.0 mm • Lesion length ≥ 20 mm and ≤ 200 mm, to be covered by one or two balloon(s) (must be overlapped to cover targeted lesion(s)) • The lesion length of total occluded lesion ≤ 100 mm For diffuse lesion or multiple tandem lesions (may including a total occluded lesion) in the same target vessel, the total lesion length, including the distance between lesions, must be ≤ 200 mm, with the separation of ≤ 30 mm (3 cm) between two adjacent lesionsAI2. The subject has at least one patent infrapopliteal artery (< 50% stenosis) to the index foot prior to index procedure

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	CE1. Subjects who have undergone prior vascular surgery of the SFA/PPA in the index limb to treat atherosclerotic disease CE2. History of major amputation in the same limb as the target lesion CE3. Presence of aneurysm in the target vessel(s) CE4. Acute ischemia and/or acute thrombosis in any artery of the lower limbs CE5. Acute Myocardial Infarction within 30 days before the index procedure CE6. History of hemorrhagic stroke within 3 months CE7. History of thrombolysis or unstable angina within 2 weeks of enrollment CE8. Persistent, intraluminal thrombus of the proposed target lesion post thrombolytic therapy CE9. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated CE10. Known allergies against Paclitaxel or other components of the used medical devices CE11. Intolerance to antiplatelet, anticoagulant, or thrombolytic medications that would be administered during the trial CE12. Platelet count < 80,000 mm^3 or > 700,000 mm^3 CE13. Concomitant renal failure with a serum creatinine > 2.0 mg/dL(176.8 umol/L) CE14. Receiving dialysis or immunosuppressant therapy CE15. Life expectancy of less than one year

	CE16. Women of child-bearing potential cannot use a reliable method of contraception from the time of screening through 12 months after the index procedure. CE17. Woman who is pregnant or nursing. (Pregnancy test must be performed within 72 hours prior to the index procedure, except for women who definitely do not have child-bearing potential). CE18. Previously planned stenting of the index lesion (stents will be allowed for bailout situations, such as flow-limiting dissection) CE19. Use of adjunctive therapies (debulking, laser, cryoplasty, re-entry devices) CE20. Subjects who had any major procedures (cardiac, aorta, peripheral) within 30 days prior to the index procedure CE21. Planned or expected procedures (cardiac, aorta, peripheral) within 30 ays post the index procedure CE22. Presence of outflow lesions requiring intervention within 30 days of the index procedure CE23. Heavily calcified target lesions resistant to PTA CE24. Current participation in another drug or device trial that has not completed the primary endpoint, including any clinical study of drug-coated or drug-eluting technology, that may potentially confound the results of this trial, or that would limit the subject's compliance with the follow-up requirements CE25. Current or past intervention using drug-coated/drug-eluting technologies in the index limb CE26. Target lesion with in-stent restenosis (any stent or stent-graft) ***Angiographic Exclusion Criteria:*** AE1. Subjects with ipsilateral iliac inflow lesions , and unsuccessful treatment prior to the index procedure (i.e., residual stenosis ≥ 30% post treatment) AE2. Subjects with no patent infrapopliteal artery (i.e., ≥ 50% stenosis) to the foot prior to index procedure (even with successfully treatment during the procedure, these subjects should be excluded from enrollment) AE3. Failure to successfully antegrade cross the target lesion with a guidewire (successful crossing is defined as the tip of crossing device is distal to the target lesion in the true lumen without flow-limiting dissection or perforation as evidenced by extravasation of contrast media

10. Subject Accountability

10.1. *Point of Enrollment*

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

10.2. *Withdrawal*

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

10.3. *Enrollment Controls*

A minimum of 104 enrolled subjects are needed to adequately assess the primary endpoint at 12 months. To account for attrition, the total enrolment shall be about 123 subjects, assuming a maximum attrition of 15% for all reasons at 12 months. The enrollment cap for each study site is 30% of total enrolled subjects.

10.4. *Definitions of End-of-study*

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the data collection schedule.

11. Study Methods

11.1. *Data Collection*

The data collection schedule is shown in Table 11.1-1. Please note that the time window for 30-day follow-up is +/- 7 days, for 3, 6 or 12 months follow-up is +/- 30 days.

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

Table 11.1-1: Data Collection Schedule

Procedure/Assessment	Screening (≤ 14 days prior to index procedure)	Enrollment	Index Procedure	Post-procedure/ Pre-hospital Discharge	Follow-up Visit [f]			
					30-day [f] (± 7 Days)	3-month (± 30 Days)	6-month [f] (± 30 Days)	12-month (± 30 Days)
In-person Visit	X	X	X	X	O	X	O	X
Informed Consent process, including informed consent signature date	X							
Demographics (including date of birth, gender, and race and ethnicity)	X							
Physical Assessment	X							
Medical History (including, concomitant diseases, concomitant medication and medical treatments)	X							
Routine Laboratory (including serum creatinine, platelet count and pregnancy tests)[a]	X							
CTA[b]	X							X
DUS[b]	O					X		
ABI	X			X		X		X
Rutherford Categories Assessment	X[c]			X		X		X
Angiographic assessment		X[d]	X[e]					
PTA			X[e]					
Adverse Events and Device Deficiency Assessment			X	X	X	X	X	X

X = required; O = optional but recommended

CTA = computed tomography angiography; DUS = Duplex Ultrasound; ABI = Ankle Brachial Index; PTA = Percutaneous Transluminal Angioplasty

a: Excluded from the study if serum creatinine > 2mg/dL, or platelet count < 80.000/mm^3, or positive pregnancy test (pregnancy test is required within 72 hours prior to index procedure)

b: CTA and DUS (test results within 30 days prior to the index procedure are acceptable): primary patency, binary restenosis (> 50%) of the target lesion.

c: Inclusion criterion: Rutherford category 2 - 4

d: Adhere to Angiographic Inclusion criteria. Note: calcifications are categorized as mild, moderate, severe; severe calcification of the target lesion is an exclusion criterion.

e: Procedural, target lesion, pre-dilatation, and post DCB dilatation information are collected；angiographic data will be used to localize the target lesion(s)

f: Follow-up dates will be calculated from the date of the index procedure. The 30-day, and 6-month follow-ups may be via telephone interview (in-person clinic visit is recommended if subjects have worsen symptoms). but 3-month and 12-month follow-ups are in-person clinic visits. The time window for 30-day follow-up is +/- 7 days; for 3, 6 or 12-month follow-up is +/- 30 days.

11.2. *Study Candidate Screening*

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

11.3. *Informed Consent*

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

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

Refer to Section 10.1 for definition of point of enrollment.

11.4. *Screening (Up to 14 Days Prior to Index procedure)*

After a subject has signed the IRB/IEC-approved study ICF, the screening process may begin. The screening process will be used to determine the inclusion or exclusion of a subject in the study. This process includes the investigator's assessment of subject's medical records and diagnosis, and following pre-procedure data must be collected within 14 days prior to the index procedure (unless otherwise specified), for all subjects:

- Confirmation of clinical eligibility criteria
- Demographics including age, gender, and races others than Han (unless restricted by local laws)
- Physical assessment, including weight and height
- Medical history (including concomitant diseases, concomitant medication and medical treatments)
- Physical assessment
- Routine laboratory tests (including pregnancy test)
  - Serum creatinine
  - Complete blood count (CBC) with platelets
  - Pregnancy test for females of childbearing potential with analysis per local practice (serum and/or urine) is required within 72 hours prior to the index procedure
- Computed tomography angiography (CTA)* – baseline CTA readings will be assessed by core laboratory to facilitate the localization of target lesion(s)
- Duplex ultrasound (DUS)* – optional (at the discretion of the investigator)
- Ankle brachial Index (ABI)
- Rutherford category assessment
- Current antiplatelet medications

* CTA and DUS test results within 30 days prior to the index procedure are acceptable.

11.5. *Required Concomitant Medications*

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

Antiplatelet medications such as P2Y12 inhibitor (Clopidogrel) and acetylsalicylic acid (ASA) are administered before the procedure, to minimize thrombotic complications and the development of restenosis. Clopidogrel is recommended, unless it is not tolerated by the subject, Ticlopidine can be used.

11.5.1. Prior to the index procedure

- For subjects who have been taking dual antiplatelet therapy (DAPT) for ≥ 72 hours at the time of the index procedure, a loading dose is not required.
- For subjects who do not already take DAPT drugs for ≥ 72 hours at the time of index procedure should receive appropriate peri-procedural loading doses before the index procedure, or no later than 2 hours after the index procedure. Recommended minimum loading doses are 300 mg for ASA and/or 300 mg for clopidogrel.

11.5.2. In the Catheterization Laboratory

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

11.5.3. Post-procedure

- Subjects shall receive DAPT during a period of at least 3 months post the index procedure, if tolerated. The typical recommended DAPT regimen consists of ASA (min. 75mg/d) and a P2Y12 inhibitor, e.g. clopidogrel (min. 75mg/d).
- Alternate DAPT regimens may be followed if justified by individual subject conditions, e.g. if there is documented intolerance to any of these drugs, or the patient is already in a different antiplatelet therapy (with at least 2 approved drugs) due to comorbid conditions. The investigator shall be guided by the drug manufacturer´s instructions, available scientific evidence and medical guidelines applicable to patients with peripheral arterial disease.
- After 3 months of DAPT post procedure, all subjects will be treated with ASA (minimum 75 mg/d) indefinitely.

  Note: The risk of bleeding may be increased in the subjects who need anticoagulation in addition to DAPT.. If needed, oral warfarin can be used, but no new generation of oral anticoagulants, such as rivaroxaban, apixaban or dabigatran is allowed. Patients

receiving anticoagulant therapy **should not** receive additional antiplatelet therapy if, in the opinion of the investigator, this could present an intolerable bleeding risk.

11.6. *Enrollment & Index Procedure*

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

- Perform vascular angiography
- Confirm angiographic eligibility criteria of lesion(s).
- Use of radiopaque rulers to document the exact distance of the lesion from a same anatomical landmark (such as the patella or the iliac or femoral bifurcation) at baseline and during follow-up visits is required.
- Pre-dilate/pretreat the target lesion(s): before Ranger DCB treatment, pre-dilatation with an uncoated PTA balloon (smaller in diameter than the Ranger DCB) is required.
- Deliver the Ranger DCB treatment to the target lesion(s): all Ranger DCB balloons may be inflated only once. A second Ranger DCB catheter will be used for lesions exceeding the length of the first balloon (must be overlapped to cover targeted lesion(s)).

The start of the index procedure is defined as the time of guide catheter insertion. The balloon dilatation procedure, including deployment to the target lesion and balloon inflation, deflation and retrieval, is performed under fluoroscopic observation. Refer to Section 8.4. for detailed instructions for index lesion treatment.

After dilation of the entire index lesion, the balloon catheter is withdrawn through the guide sheath/introducer sheath, and a post-PTA angiogram is performed to evaluate the technical result and possible procedural complications.

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

11.6.1. Multiple Interventions

11.6.1.1. Prior to or during Index Procedure:

- Prior to treatment of the index limb, successful (< 30% residual stenosis) treatment of ipsilateral iliac inflow lesions may be performed before or during the index procedure.
- Prior to treatment of the index limb, successful treatment of the arteries of the non-index limb may be performed before or after the index procedure.
- Prior to treatment of the index limb, absence of clinical complications such as embolism, thrombosis, severe dissection, vessel rupture must be confirmed.

IMPORTANT NOTE: Use of drug coated devices
Additional Index Limb Treatment

- No other drug-coated balloon (DCB) or drug-eluting stent (DES) treatment in the **index lesion** is allowed throughout the study duration
- DCB or DES treatment in **non-index lesions** of the index limb is allowed after 12 months post procedure

Non-index Limb Treatment

- The non-index limb may be treated with DCB or DES before and after the index procedure

11.6.2. End of the Index Procedure

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

- Document procedural, target lesion, pre-dilatation, and study device information on the appropriate eCRFs.
- Record medications
- Record antithrombotic medications
- Complete AE assessment and collect source documents as described in Section 20.
- Finalize angiographic and related required documentation to submit to the Core Laboratories per instructions in the Manual of Operations

11.7. *Post-Procedure / Pre-Discharge*

The post-procedure/pre-discharge follow-up is an in-person visit and the following data will be collected:

- ABI
- Rutherford category assessment
- Adverse events

11.8. *30-Day Follow-up (+/- 7 days)*

30-day follow-up may be via telephone or in-person interview. The following data will be collected:

- Adverse events

11.9. *3-Month Follow-up (+/- 30 days)*

The 3-month follow-up is an in-person visit and the following data will be collected:

- DUS
- ABI
- Rutherford category assessment
- Adverse events

11.10. *6-Month Follow-up (+/- 30 days)*

The 6-month follow-up may be via telephone or in-person interview; and the following data will be collected:

- Adverse events

11.11. *12-Month Follow-up (+/- 30 days)*

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

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

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

11.12. *Study Completion*

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

11.13. *Source Documents*

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

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Safety Endpoint

The primary safety endpoint is an acceptably low rate of major adverse events defined as:

- All device and/or procedure related mortality through 30 days post-procedure
- Target limb major amputation at 30 days post-procedure
- Clinically-driven TLR at 30 days post-procedure

12.1.2. Primary Efficacy Endpoint

The primary efficacy endpoint is primary lesion patency of the treated segment as assessed by computed tomography angiography (CTA) at 12 months post-procedure without clinically-driven TLR.

12.2. *Hypotheses*

12.2.1. Primary Safety Endpoint:

The rate of freedom from device and/or procedure-related death, target limb major amputation and/or clinically-driven target lesion revascularization through 30 days post procedure (i.e. the rate of composite MAE-free) exceeds a PG of 88%.[9]

H_0: *Safety* ≤ 0.88
H_1: *Safety* > 0.88

12.2.2. Primary Efficacy Endpoint:

The rate of primary lesion patency at 12 months post-procedure without clinically-driven TLR exceeds a PG of 53% for femoropopliteal artery segments treated with the Ranger DCB.[20]

H_0: *Patency* ≤ 0.53
H_1: *Patency* > 0.53

12.3. *Sample Size*

The sample size has been estimated based on the following assumptions:

Safety

- Expected 30-day composite MAE-Free rate for all subjects = 99%
  - Safety Performance Goal = 88%[9]
- Test significance level α = 0.05 (one-sided normal approximation)
- A minimum of 104 evaluable subjects are driven by the efficacy endpoint to provide at least 99% power to assess the primary safety endpoint at 30 days

Efficacy

- Expected 12-Month vessel patency = 65%
  - Efficacy Performance Goal = 53%[20]
- Test significance level α = 0.05 (one-sided normal approximation)
- A minimum of 104 evaluable subjects are required to provide adequate power of 80% to assess the primary efficacy endpoint at 12 months
- Expected attrition for all reasons at 12 months ≤ 15%
- Approximately 123 subjects will be enrolled to account for expected attrition

12.4. *Statistical Test Methods*

The primary hypotheses will be tested in a sequential manner to allow testing of each of primary safety and efficacy endpoints at the specified significance level of 5% without adjustment. The hierarchical testing procedure for multiple comparisons with the testing order will start with the primary safety endpoint followed by the primary efficacy endpoint. That is, the primary efficacy hypothesis will be tested only if the primary safety hypothesis is rejected.

For safety, if the one-sample normal approximation one-sided 95% lower confidence bound of the observed 30-day composite MAE-Free rate is greater than 0.88, then the Ranger DCB will be considered to have acceptable safety performance, and 12-month efficacy performance testing will be allowed.

For efficacy, if the one-sample normal approximation one-sided 95% lower confidence bound of the observed 12-month lesion patency is greater than 0.53, then the Ranger DCB will be considered to have acceptable performance.

12.5. *Secondary Endpoints*

The following secondary endpoints are subject of the investigation:

- Technical success
- Procedural success
- Target lesion patency assessed by DUS at 3 months post index procedure
- All-cause death at 30 days, 3, 6 and 12 months
- Clinically-driven TLR at 3, 6 and 12 months
- Time to first clinically-driven TLR through 12 months post-procedure
- Clinical success (defined as improved Rutherford catergory by at least +1 class) at pre-discharge, 3 and 12 months, as compared to baseline
- Hemodynamic success (defined as positive change in ABI) at pre-discharge, 3 and 12 months, as compared to baseline
- MAEs through 12 months (including all-cause death, clinically-driven TLR, target limb major amputation or thrombosis at target lesion)

12.6. *General Statistical Methods*

12.6.1. Analysis Sets

The primary and pre-specified additional endpoints will be analyzed on an ITT basis and on a per-protocol basis. For the ITT analysis, all subjects who sign the written ICF and are enrolled in the study will be included in the analysis sample, regardless of whether the study PTA with the Ranger DCB was performed. For the per-protocol analysis, Only enrolled subjects who are treated with the study device in the target lesion will be included in the analysis sample.

12.6.2. Control of Systematic Error/Bias

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

12.6.3. Number of Subjects per Investigative Site

A maximum of 37 patients (30% of total enrolled subjects) will be recruited from any site to avoid treatment center bias and ensure homogeneous study results.

12.7. *Data Analyses*

12.7.1. Baseline Comparability

Subject demographics, clinical history, risk factors, and pre-procedure lesion characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables. No formal statistical testing will be done since this is a single-arm trial.

12.7.2. Post-procedure Endpoints

Post-procedure information will be collected at 30-day, 6-month and 12-month scheduled follow-up assessment as detailed in the clinical trial schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. No formal statistical testing will be done in this single-arm trial.

12.7.3. Other Endpoint Measurements

Clinical event rates will be presented as proportions and continuous data will be summarized by presenting sample sizes, means, standard deviations, minimums, and maximums. Point estimates and 95% confidence intervals will be provided. No statistical testing will be performed for the additional endpoints.

12.7.4. Interim Analyses

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

12.7.5. Subgroup Analyses

Primary and pre-specified additional endpoints will be summarized by the following subgroups of subjects.

- Location of the target lesions, such as distal, mid, proximal, and ostial.

12.7.6. Changes to Planned Analyses

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

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

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

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

13.2. *Data Retention*

The Principal Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for 10years after the formal discontinuation of the clinical investigation of the product. These documents will be retained by BSC until the product/device is no longer in use in compliance with local regulations. The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining

these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13.3. *Core Laboratories*

Computed tomography angiography (CTA)data from Ranger China trial will be assessed by a blinded core lab. All centers have to send the de-identified data records of baseline CTA and the CTA performed at the12-month follow-up visit for blinded assessment to the core lab.

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

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 from IRB/EC 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 of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

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

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

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

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

16. Device/Equipment Accountability

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

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

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

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

17. Compliance

17.1. *Statement of Compliance*

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

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of

Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

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

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

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. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

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

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

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF. Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

17.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations.. Only authorized BSC personnel and/ or a BSC representative including Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

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

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, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during implant or follow-up, assist with the conduct of testing

specified in the protocol, and interact with the subject to accomplish requested activities. Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed form
- Print out programming reports directly from the programmer and provide original reports to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

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

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

17.5. *Insurance*

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

18. Monitoring

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

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

19. Potential Risks and Benefits

19.1. *Risks / Adverse Events Associated with the Study Device*

The following anticipated adverse events (AE) have been identified for this study, including, but are not limited to, the following:

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

19.2. *Risks Associated with Paclitaxel*

Potential adverse events not captured above, that may be due to systemic administration of paclitaxel, include, but are not limited to, the following:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or coating or its individual components
- Alopecia
- Anemia
- Blood product transfusion

- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/Arthralgia
- Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time.

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

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

19.4. *Risk Minimization Actions*

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

19.5. *Anticipated Benefits*

Anticipated benefits include the effective treatment of atherosclerotic stenosis and occlusion in the peripheral arteries, and improvement in the symptoms of peripheral artery disease.

19.6. *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 use of the Ranger DCB catheters demonstrate that when used under the conditions intended, the benefits associated with use of the Ranger DCB catheters should outweigh the risks.

20. Safety Reporting

20.1. *Definitions and Classification*

Safety definitions are provided in **Error! Reference source not found.**. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 12/2010.

Table 20.1-1: Safety Reporting Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011*	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 (any procedure in the clinical investigation plan). 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*	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*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization of existing hospitalization, or o 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*	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*	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*	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. **NOTE 1**: All device deficiencies that could have led to a SADE if a) suitable action had not been taken or b) if intervention had not been made or c) if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national regulations, or the protocol.

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

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

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

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

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

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

Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see **Error! Reference source not found.** for AE definitions).

Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

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

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

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

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

20.2. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in**Error! Reference source not found.**

Table 20.2-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

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

Classification	Description
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious 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 serious 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 investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Investigator must assess the relationship of the AE to the antiplatelet medication using the following categories and definitions (Table 20.2-2).

Table 20.2-2: Criteria for Assessing Relationship of Antiplatelet Medication to Adverse Event

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.

20.3. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Error! Reference source not found.**.

Table 20.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event.

Event Classification	Communication Method	Communication Timeline
Adverse Device Effect (UADE/USADE)		• Terminating at the end of the study
Serious Adverse Event including Serious Adverse Device Effects(SADE)	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if: a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency eCRF with all available new and updated information.	• Within 24 hours of first becoming aware of the event. • Reporting required through the end of the study
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner but no later than10 business days after becoming aware of the information • Reporting required through the end of the study

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

20.4. *Boston Scientific Device Deficiencies*

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

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

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

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

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

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

According to China local reporting requirements, Boston Scientific Corporation will report all SAEs and device deficiencies that could lead to SAEs to the local regulatory authorities within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sites and IRBs/ECs in a timely manner.

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

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

Boston Scientific Corporation, Investigator, or Site must notify the EC of UADEs, USADEs, SADEs, SAEs, Device Deficiencies and/or other CEC events as applicable according to local reporting requirements. A copy of the Investigator's reports and other relevant reports (if applicable) to the **IRB/IEC** must be provided to BSC in accordance with local requirements.

21. Informed Consent

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

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

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

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

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

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

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

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

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, vascular angiography may demonstrate that the subject is not a suitable candidate for the trial. A Screening Log will be maintained to document select information about candidates who fail to meet the Ranger China 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, study Principal Investigator will be convened. This committee will be responsible for the overall conduct of the study which will include protocol development, study progress, subject safety, overall data quality and integrity, and timely dissemination of study results through appropriate scientific sessions and publications. As appropriate the Executive Committee may request participation of Ranger China Investigators on the Committee.

22.2. Safety Monitoring Process

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

22.3. Clinical Events Committee

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

The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, for all reported cases of clinically-driven TVR, target limb major amputation, thrombosis at target lesion, and death.

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

23. Suspension or Termination

23.1 Premature Termination of the Study

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

23.1.1 Criteria for Premature Termination of the Study

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

- Any new important information that affects the study to continue (eg. safety or properties of product),
- A decision of regulatory authorities to discontinue the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

Note: According to the section 20, even if the study is terminated, all the AEs, SAEs, SADEs and Device Deficiency should be evaluated and reported for the subjects who have received the treatment of study device.

(China Medical Device GCP requirement: The reasons and criteria based on biostatistics of study termination are: the statistics method of all the data is missing, data is missing or error (including withdraw and termination) and unreasonable data handling methods.)

23.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

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

23.3 Requirements for Documentation and Subject Follow-up

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

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

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

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

23.4 Criteria for Suspending/Terminating a Study Site

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

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

According to Section 20, all the ongoing AEs should be evaluated and reported for the subjects who have been treated by study device. And the ongoing AEs should be followed up by investigators continues, unless BSC informed the sites.

24. Publication Policy

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

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

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26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in **Error! Reference source not found.**.

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
ASA	Acetylsalicylic Acid
ABI	Ankle Brachial Index
ADE	Adverse Device Defect
AE	Adverse Event
AP	Ankle Pressure
ASADE	Anticipated Serious Adverse Device Effect
BMS	Bare Metal Stent
BRR	Binary Restenosis Rate
CA	Competent Authority
CAD	Coronary Artery Disease
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
Core lab	Core Laboratory
CRF	Case Report Form
DCB	Drug-coated Balloon
DES	Drug Eluting Stent
DFU	Directions for Use
DUS	Duplex Ultrasound Sonography
EC	Ethics Committee
EDC	Electronic Data Capturing
eCRF	Electronic Case Report Form
HCP	Health Care Personnel
ICF	Informed Consent Form
ISF	Investigator Site File
LLL	Late Lumen Loss
MAE	Major Adverse Events
MAX	Maximum
MI	Myocardial Infarction
MIN	Minimum
MLD	Minimal Lumen Diameter
OTW	Over The Wire
PAD	Peripheral Artery Disease
PPA	Proximal Popliteal Artery
PSVR	Peak Systolic Velocity Ratio

Abbreviation/Acronym	Term
PTA	Percutaneous Transluminal Angioplasty
PVR	Pulse Volume Recording
QoL	Quality of Life
QVA	Quantitative Vascular Angiography
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
StDev	Standard Deviation
TLR	Target Lesion Revascularization
TM	Transmetatarsal
TP	Toe Pressure
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect

26.2. *Definitions*

Table 26.2-1: Definitions

Term	Definition
AMPUTATION	• Major Amputation: amputation of the lower limb at the ankle level or above; and can be further specified as *below-the-knee* and *above-the-knee* amputations, as well as *planned* and *unplanned* amputations. • 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. An ABI <0.9 indicates the presence of peripheral arterial disease in symptomatic patients as well as in asymptomatic patients. In addition, an ABI <0.9 reflects the presence of generalized asymptomatic or symptomatic atherosclerotic disease, and its associated increased cardiovascular risk.
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including but not limited to, sinus arrhythmia, premature beats, heart block, ventricular or atrial fibrillation, ventricular tachycardia, or atrial flutter.

Term	Definition
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 study or autopsy showing infarction.
CLINICAL Success	Clinical success defined as improved Rutherford classification by at least +1 class compared to baseline.
COMPLETE BLOOD COUNT (CBC)	A blood test used to measure several components and features of blood, including: Red Blood Cells, White Blood Cells, Hemoglobin, Hematocrit and Platelets.
COMPLICATION	An undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the investigational product(s).

Term	Definition
DEATH	All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, an unexpected death in subjects with coexisting potentially fatal non-cardiac diseases (e.g. Cancer, infection) should be classified as cardiac. All death events will be submitted to 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. Index Limb-Related Death: In the Ranger China Trial, all death will also be adjudicated by the Clinical Event Committee (CEC) as "likely related" to a complication of the index limb. Perioperative Death is the death within 30 days of the index procedure.
DIAMETER STENOSIS	The maximal narrowing of the target lesion relative to the reference vessel diameter.
DISSECTION- NHLBI GRADE TYPES	Type A- Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material. Type B- Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles. Type C- Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material. Type D- Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow. Type E- Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen. Type F- Filling defect accompanied by total vessel occlusion.
DISTAL EMBOLIZATION	Migration of a filling defect, or thrombus, to distally occlude the target vessel or one of its branches.
HEMATOMA	A localized swelling filled with blood resulting from a break in a blood vessel.

Term	Definition
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.
HEMODYNAMIC SUCCESS	Hemodynamic success is defined as a positive change in Ankle-Brachial Index compared to baseline.
HYPOTENSION	Systolic blood pressure < 80 mmHg lasting more than 30 minutes or requiring intervention (e.g. pacing, IABP, intra venous vasopressors to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.
INTIMAL FLAP	An extension of the vessel wall into the arterial lumen.
LESION LENGTH	Measured as the distance from the proximal shoulder to the distal shoulder of the lesion, in the view that demonstrates the stenosis in its most elongated projection.
MAJOR ADVERSE EVENTS (MAEs)	In the Ranger China Trial, Major Adverse Events (MAEs) include all-cause death, clinically-driven TLR, target limb major amputation or thrombosis at target lesion.
MINIMAL LUMEN DIAMETER	The vessel diameter as measured at the most narrow point of the lesion.
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	In Ranger China, ***vessel patency*** is defined as freedom from more than 50% diameter stenosis. ***Primary patency*** is the absence of more than 50% stenosis assessed by either CTA or DUS (peak systolic velocity ratio ⩽ 2.4), without clinically-driven target lesion revascularization post the index procedure.
PRIMARY SUSTAINED CLINICAL IMPROVEMENT	Improvement in Rutherford classification of one or more categories as compared to pre-procedure without the need for repeat TLR.

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>PROCEDURAL SUCCESS</td><td>Technical success with no MAEs noted within 24 hours of the index procedure.</td></tr>
<tr><td>PSEUDO-ANEURYSM</td><td>An encapsulated hematoma in communication with an artery.</td></tr>
<tr><td>PRODUCT NON-CONFORMITY</td><td>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>REPEAT INTERVENTION (PERCUTANOUS AND/OR SURGERY)</td><td>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>Angiographic measurement of the artery proximal and/or distal to the lesion intended for treatment.</td></tr>
<tr><td>RESTENOSIS</td><td>Diameter stenosis > 50% assessed by angiography, CTA or DUS (peak systolic velocity ratio 〉 2.4)</td></tr>
<tr><td>RUTHERFORD / BECKER CLASSIFICATION</td><td>
<table>
<tr><th>Category</th><th>Clinical Description</th><th>Objective Criteria</th></tr>
<tr><td>0</td><td>Asymptomatic</td><td>Normal Treadmill /stress test</td></tr>
<tr><td>1</td><td>Mild claudication</td><td>Completes treadmill exercise; ankle pressure (AP) after exercise < 50 mm Hg, but > 25 mm Hg less than BP</td></tr>
<tr><td>2</td><td>Moderate claudication</td><td>Between categories 1 and 3</td></tr>
<tr><td>3</td><td>Severe claudication</td><td>Cannot complete treadmill exercise and AP after exercise < 50 mm Hg</td></tr>
<tr><td>4</td><td>Ischemic rest pain</td><td>Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording (PVR); toe pressure (TP) < 30 mm Hg</td></tr>
<tr><td>5</td><td>Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal edema</td><td>Resting AP < 60 mm Hg, ankle or metatarsal (MT) PVR flat or barely pulsatile; TP < 40 mm Hg</td></tr>
<tr><td>6</td><td>Major tissue loss – extending above MT level</td><td>Same as Category 5</td></tr>
</table>
</td></tr>
<tr><td>SECONDARY SUSTAINED CLINICAL IMPROVEMENT</td><td>Improvement in Rutherford classification of one or more categories as compared to pre-procedure including those subjects with repeat TLR.</td></tr>
</table>

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

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

Term	Definition
TRANSATLANTIC INTER-SOCIETAL CONSENSUS (TASC) LESION GUIDELINES	Type A lesion: • 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	Technical success is defined as the ability to cross and dilate the lesion to achieve residual angiographic stenosis no greater than 30% (by visual estimate in 2 near-orthogonal projections) without balloon rupture, or inflation/deflation abnormalities.
THROMBUS (ANGIOGRAPHIC)	Discrete, mobile intraluminal filling with defined borders with/without associated contrast straining; these are classified as either absent or present.
TOTAL OCCLUSION	Lesion with no flow; implies 100% diameter stenosis.
VASCULAR COMPLICATION	An occurrence of hematoma > 5 cm, pseudoaneurysm, arteriovenous (AV) fistula, or need for vascular surgical repair.
VESSEL PATENCY	Vessel patency is defined as freedom from more than 50% diameter stenosis assessed by angiography, CTA or DUS (with peak systolic velocity ratio ＞ 2.4).

Term	Definition

Abbreviations are defined in Table 26.1-1.

Investigator Statement (See Chinese version protocol)