Statistical Analysis Plan

A 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

Study Reference number (S6052)

APPROVALS (Check/Complete one below):

☐ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

_____	_____
Lead Biostatistician – [Anusha Jain, Biostatistician]	Date (dd-mon-yyyy)
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Clinical Project/Trial Manager – [Monica Zhou, Sr. Project Manager]	Date (dd-mon-yyyy)
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Medical Director – [Qing Li, Medical Affair Manager]	Date (dd-mon-yyyy)

Revision History

Version Date	Version No	Section	Change	Reason for Change
May, 05, 2020	Version 01	NA	Initial Release	NA
June, 25, 2020	Version 02	Section 1.3, 3.1.2, 3.2.2	Change sample size from 123 to 139	To align with the latest release of Protocol
		Section 3.2.2	Change attrition rate from 15% to 25%	
		Section 3.2.2, 4.3	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	
July, 23, 2020	Version 03	Section 1.3, 3.1.2, 3.2.2	Sample size was changed from 139 to 123.	To align with the latest release of Protocol
		Section 3.2, 3.2.1, 3.2.3	Replace “vessel patency” with “Lesion patency” in the notes	
		Section 5.1	Specify the time point for evaluating clinical success and hemodynamic success	
		Section 3.2	Modify the wording of primary efficacy endpoint	
		Section 5.3	The classification of the target lesion location was changed from “ATK and BTK” to “distal, mid, proximal and ostial”	
		Section 3.2.2	The attrition rate was changed from 25% to 15%.	
		Section 3.2.2	Removed Sensitivity analysis as per the confirmation from Statistician	
		Section 3.2.2	Included SAS codes for Univariate and Multivariate Analysis	
August 17, 2020	Version 04	Section 3.4	Included Sensitivity Analysis	Additional request from the Sponsor

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1 PROTOCOL SUMMARY

The clinical study is conducted in accordance to demonstrate the acceptable safety and performance of angioplasty with the Ranger Drug Coated Balloon (DCB) in native femoropopliteal artery lesions in Chinese patient cohort with lower extremity artery disease. Based on a systematic evaluation of device characteristics performed by the legal manufacturer and study Sponsor, the study device is considered safe for conducting clinical evaluations in patients.

1.1 Study design

This clinical study is a prospective, non-randomized, multicenter study.

1.2 Study objectives

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

1.3 Number of sites and patients

Subjects will be enrolled in a non-randomized process. All patients with qualifying lesions would be considered for enrollment and treated with the Ranger DCB catheter. The Ranger China trial will be conducted in up to 15 sites in Mainland China with planned enrollment of approximately 123 subjects.

1.4 Description of the study population

All the subjects who has signed the IRB/IEC-approved study ICF, has met all the clinical and angiographic inclusion criteria and none of the exclusion criteria will be considered eligible to be enrolled in the trial.

1.5 Description of device(s) including model numbers used in the study

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. They have a drug coating formulation consisting of paclitaxel (the active pharmaceutical ingredient) and an excipient (the inactive ingredient).

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:

	Diameters of Ranger & Ranger SL & Ranger LE DCB								
Length	**2.0 mm**	**2.5 mm**	**3.0 mm**	**3.5 mm**	**4.0 mm**	**5.0 mm**	**6.0 mm**	**7.0 mm**	**8.0 mm**
30 mm	-	-	-	-	X	X	X	X	X
40 mm	-	-	-	-	X	X	X	X	X
60 mm	-	-	-	-	X	X	X	X	X
80 mm	X	X	X	X	X	X	X	X	X
100 mm	X	X	X	X	X	X	X	X	-
120 mm	X	X	X	X	X	X	X	X	-
150 mm	X	X	X	X	X	X	X	X	-
200 mm	-	-	-	-	X	X	X	X	-

1.6 Study procedure

All enrolled subjects will receive PTA treatment with the Ranger DCB catheter. 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. The investigator selects the size of Ranger DCB according to the proximal and distal reference vessel diameters and lesion length.

Data will be collected from subjects upon screening (up to 14 days prior to index procedure) into the study, enrollment, index procedure. Subsequently, there will be clinic follow up at pre-discharge, 30-day, 3-month, 6-month, 12-month post-index procedure. 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.

1.7 Follow-up schedule

After index procedure the patient visit include:

a. Pre-discharge
b. 30-Day Follow up (via telephone or in-person interview)
c. 3-Month Follow-up (in-person visit)
d. 6-Month Follow-up (via telephone or in-person interview)
e. 12-Month Follow-up (in-person visit)

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

1.8 Study duration

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

1.9 Key Inclusion Criteria

- Subjects must be age 18 or older
- Subject is willing and able to provide informed consent
- Subject is available and willing to attend all required follow-up visits
- Subject has a clinically significant symptomatic leg ischemia
- Subject has a Rutherford clinical category of 2 - 4
- If the index lesion is restenotic, the prior PTA must have been > 90 days prior to treatment in the current study
- 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
- 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

1.10 Key Exclusion Criteria

- Subjects who have undergone prior vascular surgery of the SFA/PPA in the index limb to treat atherosclerotic disease
- History of major amputation in the same limb as the target lesion
- Presence of aneurysm in the target vessel(s)
- Acute ischemia and/or acute thrombosis in any artery of the lower limbs
- Acute Myocardial Infarction within 30 days before the index procedure

- History of hemorrhagic stroke within 3 months
- History of thrombolysis or unstable angina within 2 weeks of enrollment
- Persistent, intraluminal thrombus of the proposed target lesion post thrombolytic therapy
- Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated
- Known allergies against Paclitaxel or other components of the used medical devices
- Intolerance to antiplatelet, anticoagulant, or thrombolytic medications that would be administered during the trial
- Platelet count < 80,000 mm3 or > 700,000 mm^3
- Concomitant renal failure with a serum creatinine > 2.0 mg/dL(176.8 umol/L)
- Receiving dialysis or immunosuppressant therapy
- Life expectancy of less than one year
- Women of child-bearing potential cannot use a reliable method of contraception from the time of screening through 12 months after the index procedure.
- 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).
- Previously planned stenting of the index lesion (stents will be allowed for bailout situations, such as flow-limiting dissection)
- Use of adjunctive therapies (debulking, laser, cryoplasty, re-entry devices)
- Subjects who had any major procedures (cardiac, aorta, peripheral) within 30 days prior to the index procedure
- Planned or expected procedures (cardiac, aorta, peripheral) within 30 days post the index procedure
- Presence of outflow lesions requiring intervention within 30 days of the index procedure
- Heavily calcified target lesions resistant to PTA
- 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
- Current or past intervention using drug-coated/drug-eluting technologies in the index limb
- 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)

1.11 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

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

2 INTRODUCTION

This statistical analysis plan addresses the planned analyses for the RANGER CHINA-Clinical Trial based on the latest version of protocol dated Jul 01, 2020, Version AF. Specified analyses may be used for scientific presentations and/or manuscripts, and regulatory submissions.

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.

For primary endpoint evaluation, the data of each subject must be collected until the 12-month follow-up. The primary safety analysis will be based on MAEs including all device and/or procedure related mortality, clinically-driven Target Lesion Revascularization (TLR), target limb major amputation through 30 days post-procedure. The primary efficacy endpoint is based on primary lesion patency of the treated segment(s) as assessed by computed tomography angiography (CTA) at 12 months post-procedure without clinically-driven TLR. All safety parameters and additional endpoints will also be analyzed. These analyses are more elaborately detailed in the below endpoint analysis

3 ENDPOINT ANALYSIS

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.

3.1 Primary Safety Endpoint

The safety goal is designed to demonstrate the performance of Ranger DCB to be acceptable in terms of MAE-free rate through 30 days post-procedure.

The primary safety endpoint is based on the rate of major adverse events (MAE) within 30 days post-procedure.

Definition of MAE:
Major Adverse Events (MAEs) defined as all device and/or procedure-related death, target limb major amputation, and/or clinically-driven target lesion revascularization (TLR) through 30 days.

3.1.1. Primary Safety Statistical Hypothesis

The primary safety hypothesis to be tested based on 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) treated with Ranger DCB exceeds a performance goal (PG) of 88% at a one-sided significance level of 5% without adjustment.

The null hypothesis (H_0) states that the MAE-free rate has a PG $\leq$ 88% as opposed to the alternative hypothesis (H_1) which states that the PG exceeds 88% through 30 days post-procedure. The hypothesis inequalities are shown below:

H_0: Safety ≤ 0.88
H_1: Safety > 0.88

where Safety is the 30 days MAE-free rate for all subjects.

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.

3.1.2. Sample Size consideration based on Safety

The overall sample size is based on the subjects enrolled in the study. Approximately 123 subjects with femoropopliteal artery lesions are planned to be enrolled. The sample size justification is based on the following assumptions.

- Expected 30-day composite MAE-Free rate for all subjects = 99%
- Safety Performance Goal = 88%
- Test significance level $\alpha = 0.05$ (one-sided normal approximation)
- N =104 subjects are driven by the efficacy endpoint to provide at least 99%
- power to assess the primary safety endpoint at 30 days

3.1.3. Safety Statistical Methods

A normal approximation test (e.g. Chi-Square Test) for comparing observed 30-day MAE-free rate with the PG of 88% will be used to assess the safety hypotheses.

3.2 Primary Efficacy Endpoint

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

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

3.2.1. Primary Efficacy Statistical Hypothesis

The primary efficacy hypothesis to be tested is that the rate of primary lesion patency at 12 months post-procedure without clinically-driven TLR exceeds a PG of 53% at a one-sided significance level of 5% for femoropopliteal artery segments treated with the Ranger DCB.

The null hypothesis (H_0) states that the primary lesion patency rate has a PG $\leq$ 53% as opposed to the alternative hypothesis (H_1) which states that the PG exceeds 53% at 12 months post-procedure. The hypothesis inequalities are shown below:

H_0: Patency ≤ 0.53
H_1: Patency > 0.53
where Patency is the 12-month primary lesion patency for all subjects.

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.

3.2.2. Sample Size consideration based on Efficacy

The sample size justification is based on the following assumptions.

- Expected 12-Month vessel patency = 65%
- Efficacy Performance Goal = 53%
- Test significance level $\alpha = 0.05$ (one-sided normal approximation)
- N = 104 subjects (minimum) are required to provide adequate power of 80% to assess the primary efficacy endpoint at 12 months
- Expected maximum attrition for all reasons at 12 months = 15%
- Minimum enrollment to account for expected attrition = 123 subjects

3.2.3. Efficacy Statistical Methods

A normal approximation test (e.g. Chi-Square Test) for comparing observed 12-month primary lesion patency with the PG of 53% will be used to assess the efficacy hypotheses.

3.3 Missing Data, Drop-Outs, and Protocol Deviations Handling

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

- Ensure that site personnel are properly trained on the data that is required to be collected and the importance of planning for the follow-up visits.
- Tools in the site's Manual of Operations to assist with follow-up visit planning (e.g. follow-up wheels or similar tools).
- The use of trial newsletters to remind sites of upcoming visits and other project-related milestones to ensure data is being entered promptly and is complete.

3.4 Sensitivity Analysis for Missing Outcome Data

Sensitivity analyses for the primary safety endpoint and primary efficacy endpoint will be conducted to assess the impact of missing data on the result's robustness. The tipping point analysis will be performed for the Intent-to-Treat analysis set to consider all combinations of present/absent for all subjects with missing primary outcome in Ranger DCB as applicable.

3.5 Missing Event Dates Considerations

All event rates will be calculated relative to the date of procedure (i.e. post-procedure).

When calculating rates of adverse events with missing event date (i.e. mm/dd/yyyy), the ideal is to work with safety and/or data management representatives to query sites for

missing data. However missing and partial missing dates may be handled as using the worst-case scenario as follows:

Partial Date Description	Action Taken
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

4 GENERAL STATISTICAL CONSIDERATION

4.1 Analysis Sets

All the primary and additional endpoints related to safety and efficacy will be analyzed by both Intent-to-Treat (ITT) and Per-Protocol (PP) populations.

4.1.1. Intent-to-treat (ITT) group

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. The Intent-to-Treat group be will be analyzed for both safety and efficacy data.

4.1.2. Per-Protocol (PP) group

Per-Protocol population is the subset of ITT subjects who are treated with the Ranger DCB. 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. The Per-Protocol group be will be analyzed for both safety and efficacy data.

4.2 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.

4.3 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.

5 ADDITIONAL DATA ANALYSES

5.1 Secondary Endpoints Assessments

The following secondary endpoints are subject of the investigation:

- 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 TLR, target limb major amputation or thrombosis at target lesion) within 24 hours of the index procedure
- 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 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 (including all-cause death, clinically-driven TLR, target limb major amputation or thrombosis at target lesion)

Note that 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.

No formal tests of hypotheses are proposed for secondary endpoints. Statistical comparisons may be performed for exploratory purposes. No formal inferences are planned on the additional assessments.

5.2 Interim Analyses

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

5.3 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

5.4 Multivariable Analyses

Univariate and multivariable analyses will be performed to assess the effect of potential predictors on the primary safety and efficacy endpoint by using logistic regression.

Clinically and/or statistical meaningful baseline covariates will be selected in the regression model. The predictors will be listed in ascending order of p-value. Univariate analyses will be performed overall as well. For the multivariable analyses, only coefficients in the final model, i.e., with p-values less than 0.1 will be considered.

No formal conclusion will be made by this secondary post-hoc analysis. The sample code detailed in Section 7.4.

5.5 General considerations

All continuous measurements will be summarized descriptively at each visit by treatment using observed data. Endpoints that are analyzed untransformed and endpoints that are not formally analyzed are summarized by the arithmetic mean, standard deviation (SD), minimum and maximum value with counts (N). Mean and SDs rounded to one decimal, minimum, maximum is presented exact as per the data values.

5.6 Other Analyses

5.6.1. Baseline Data Analyses

Subject demographics, clinical/medical history, risk factors, pre-procedure lesion characteristics and laboratory reported measurements will be summarized using descriptive statistics. For continuous variables, the descriptive statistics will include mean, standard deviation, number evaluated, minimum and maximum. For discrete variables, frequency tables will be displayed. No formal statistical testing will be done since this is a single-arm trial.

5.6.2. Post-procedure Analyses

Post-procedure information will be collected at 30-day, 3-month, 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 and frequency tables or proportions for discrete variables. No formal statistical testing will be done in this single-arm trial.

5.6.3. Other Endpoint Analyses

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.

5.6.4. Patient disposition/status

Number of subjects enrolled by investigator and site will be summarized with counts and percent based on Intent-to-Treat population.

A table based on Subject Disposition of Follow-up Compliance will be provided at Pre-discharge, 30-days, 3-month, 6-month, 12-month visits after the index procedure. A listing based on deaths will be provided with related to study device and study procedure, with date of death and duration of days from index procedure date.

5.6.5. Analysis of Adverse and Serious Adverse Events

Subject-level event rates will be calculated at various time points (e.g. exact days) based on all events reported by the site regardless of whether they are ultimately adjudicated to be (or lead to) a MAE. These safety parameters will be summarized using descriptive statistics.

Frequency of site reported Serious adverse events and Non-serious adverse events associated with the Ranger DCB with total available subjects based on ITT population. The events are summarized by MedDRA system organ class and MedDRA preferred terms with events and rates.

A listing based on Non-MedDRA coded site reported adverse events with seriousness and duration days are listed out and a listing for all un-anticipated adverse device events with seriousness and duration from onset date is listed.

For calculating events and rates, need to consider ‘Events numbers’ are total episodes of each type of event among all subjects. ‘Rate of Subjects with Event’ numbers are percent of subjects who experienced one or more episodes of the event. ‘Events’ numbers for “TOTAL” are the sum of the individual event category totals. ‘Rate of Subjects with Event’ numbers for “TOTAL” is the percent of subjects who experienced an adverse event.

5.6.6. Protocol Deviations

A summary table for Deviations from Investigational Protocol collated during procedure and post procedure for all the planned events as specified in protocol.

- Screening
- Baseline
- Index Procedure
- < 1day Post-Procedure
- Discharge
- 30-day Visit
- 3-Month Visit
- 6-Month Visit
- 12-Month Visit
- End of Study

A summary table by protocol deviation are summarized with counts and percent and another summary table presented based on deviations reasons. A connected listing will be provided by subject with deviation, reason, visit and assessment/procedure requirement during the study.

5.6.7. Device Deficiencies

A table exhibited based on device deficiencies with count and percent for the available parameters. Also presenting the counts and percent of serious AEs in connect to the device deficiencies. A supported listing also provided by subject, deficiency type, and if its leading to any event and preventive action taken for that.

5.6.8. Time-To-Event Kaplan-Meier Analysis

The Kaplan-Meier product-limit method will be used to estimate event or event-free rates for time-to-event outcomes as post-hoc analyses.

<u>Kaplan-Meier for MAE-Free</u>

The Kaplan-Meier analysis will capture the first event for MAE-free composite endpoint and/or for selected individual components.

MAE includes all-cause death, clinically-driven TLR, target limb major amputation or thrombosis at target lesion through 12-months.

<u>Kaplan-Meier for Primary Patency</u>

The Kaplan-Meier analysis is aimed to capture the first event for each subject. To determine the first event of

- Clinically-driven TLR date by CEC

- Ultrasound data or CTA data to identify a subject not patent (i.e. PSVR>2.4 or grade of stenosis >50%)

5.6.9. Time to CEC Adjudicated Events and Time to Adequate Follow-Up

The MAE binary rates (overall and individual components), as opposed to Kaplan-Meier rates, will be calculated based on the subjects who have adequate follow-up and/or have experienced any components of MAE.

The protocol-defined MAEs include:

- all causes of device and/or procedure-related death
- target limb major amputation
- clinically-driven TLR

Note: CEC Adjudicated Events includes Target limb major amputation, Death, Clinically-driven Target Vessel Revascularization (TVR) and Thrombosis at target lesion through 12-months.

5.7 Analyses Software

All statistical analyses will be performed and validated by the independent CRO (e.g. IQVIA in Bangalore) using the Statistical Analysis Software (SAS), version 9.2 or later (Copyright © 2002-2010 by SAS Institute Inc., Cary, North Carolina 27513, USA. All rights reserved). BSC will review statistical reports.

5.8 Changes to Planned Analyses

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

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. Statistical analyses and validation will be done by an independent CRO.

7 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by the independent CRO.

7.1. Statistical Software

All statistical analyses will be done using The SAS System Version 9.2 software or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2. Format of Output

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3. Rules and Definitions

For baseline categorical variables, missing values will not be counted in rate denominators. Number of patients completing the visit will be considered in denominators.

7.4. SAS Codes for Chi-Square Test, Univariate/Multivariate Analysis

For the PG hypotheses testing, the confidence interval and the Chi-Square test p-value can be produced by the following SAS codes.

```
proc freq data=;
tables xx/binomial(p=) alpha=;
run;
```

For Univariate and Multivariable analysis, p-value can be produced by the following SAS codes.

```
 proc logistic data=dataset descending outest=uni;
 class trt/ param=ref;
 model endpoint = factor;
 run;
proc logistic data= dataset descending outest=multi ;
class trt/param=ref;
model endpoint=trt factors /include=1 selection=stepwise slentry=0.1 slstay=0.1;
run;
```