Study Protocol MCRF-S-001-2015

JET-PCB Trial

JETStream Atherectomy with Adjunctive Paclitaxel-Coated Balloon Angioplasty vs Plain Old Balloon Angioplasty followed by Paclitaxel-Coated Balloon in Treating Complex Denovo Femoropopliteal Arterial Disease

Version 2
30 JUL 2016

Sponsor
Midwest Cardiovascular Research Foundation

Principal Investigator and Study Chairman
Nicolas W Shammas, MD, MS, FACC, FSCAI

Supported by
Boston Scientific

Study Protocol Acceptance

I have read this Study Protocol and agree to adhere to the requirements. I will provide copies of this Study Protocol and all pertinent information to the study personnel. I will discuss this material with them and ensure they are fully informed regarding the study devices and the conduct of the study according to the International Conference on Harmonization of Good Clinical Practices (ICH GCP) Guidelines, the Declaration of Helsinki, and the pertinent individual country laws/regulations.

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Principal Investigator Signature DD MMM YYYY

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Principal Investigator Printed Name

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Study Site

Study Protocol Synopsis

JET-PCB trial	
Protocol Number	MCRF-S-001-2015
Devices	JetStream Navitus XC 2.1 and 2.4, Ranger Paclitaxel-Coated Balloon (PCB)
Primary Purpose	The purpose of this study is to test the hypothesis that Jetstream atherectomy followed by Ranger Paclitaxel Drug Coated Balloon (DCB) improves target lesion revascularization at 1 year follow-up when compared to balloon angioplasty followed by DCB in the treatment of femoropopliteal arterial denovo disease.
Study Design	A prospective, multicenter, randomized study evaluating the use of Jetstream Atherectomy (JS) followed by DCB in comparison to the use of plain old balloon angioplasty (POBA) followed by DCB alone in the treatment of *complex* lesions in femoropopliteal arteries in subjects with claudication (Rutherford Clinical Category (RCC) of 2-4) (complex lesions are defined as long (≥ 10 cm) lesions, or moderately or highly calcified lesions, or chronic total occlusions irrespective of length)
Follow-Up Schedule	Follow-up assessments will occur at pre-discharge, 30 days, 6 months and 1 year following the study procedure.
Number of Subjects/analysis	250 subjects are planned for enrollment (with a block 2:1 randomization; 167 DCB+JS) **primary analysis**: ITT TLR (bail out stent is considered TLR) at 1 year It is assumed that TLR in the DCB alone will be 45% (including bailout stenting in the lab) and in the JS + DCB will be 25%. We will need to study 144 experimental subjects and 72 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate this null hypothesis. Accounting for 15% loss of patients on follow up, the total number that will be enrolled will be 250 patients.
Number of Sites	Up to 25 sites in the USA
Primary Outcomes	**Effectiveness: Target Lesion Revascularization at 1 Year**: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 1 year. For the primary endpoint, intra-procedural bail out stenting of the index lesion is considered meeting a TLR endpoint. (ITT analysis) **Safety**: **Major Adverse Events (MAE) at 30 days**: unplanned amputation, total mortality or TLR at 30 days (TLR includes bail out stenting)

DSMB	The study will be evaluated for safety after the first 100 patients enrolled. It is expected that stopping rules will be designed and based on a freedom from MAE at 30 days that is > 55% (Intraprocedural bail out stenting is considered a TLR and count as a MAE)
Secondary Outcomes	**1. Device Outcome:** Categorized by < 50% residual stenosis following the protocol-defined treatment (POBA + DCB or JS + DCB) and prior to bail out stenting at the target lesion as determined by the Angiographic Core Laboratory. **2. Procedural outcome:** Categorized by < 30% residual stenosis following the protocol-defined treatment and followed by bail out stenting if needed at the target lesion as determined by the Angiographic Core Laboratory. **3. Target Lesion Patency at 6 months and 1 year:** Defined as PSVR ≤ 2.4 at the treated site or < 50% stenosis by angiography as determined by the Angiographic Core Laboratory **4. Target Lesion Revascularization at 6 months**: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 6 months. For the primary endpoint, intra-procedural bail out stenting of the index lesion is considered meeting a TLR endpoint. (ITT analysis) **5. Clinically Driven target lesion Revascularization at 6 months and 1 year with the following analysis:** Defined as any re-intervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis and at least two of the following: worsening RCC by one category, worsening WIQ score by ≥20 points, or an ABI drop > 0.15 from baseline. ITT (bail out stent considered as TLR) (6 months and 1 year) ITT (bail out stent is not considered as TLR) (6 months and 1 year) Actual treatment groups (DCB alone vs DCB with bail out stent vs DCB with JS atherectomy vs DCB with JS atherectomy and bail out stenting) (6 months and 1 year) Actual treatment groups (DCB alone with or without bailout stenting vs JS atherectomy with DCB with or without bailout stenting) (6 months and 1 year) **6. Target Vessel Failure:** Defined as major unplanned amputation related to the treated limb, vascular mortality related to treated limb and target vessel revascularization at 30 days and 1 year (stenting in the lab is not considered a TLR/TVR) **7. Target Lesion failure:** Defined as major unplanned amputation related to the treated limb, vascular mortality related to treated limb and target

	lesion revascularization at 30 days and 1 year (stenting in the lab is not considered a TLR) **8.** **In-hospital Major Adverse Event Rate**: all-cause mortality, perforation requiring additional treatment, distal embolization requiring additional mechanical or pharmacological treatment, major bleeding as defined by the Thrombolysis in Myocardial Infarction criteria, vascular access site complications requiring transfusion and/or surgical repair, acute stent thrombosis as defined by the Academic Research Consortium, unplanned major or minor amputation **9.** **Major Adverse Event Rate at 30 Days:** Defined as major or minor unplanned amputation of the treated limb, vascular access site complications requiring transfusion and/or surgical repair, all-cause mortality, acute thrombosis, or clinically-driven target vessel revascularization. **10.** **Major Adverse Events at 1 year:** Defined as major or minor unplanned amputation of the treated limb, all-cause mortality or target lesion revascularization (TLR). **11.** **Change in WIQ Score at 6 Months and 1 Year:** Defined as the change in Walking Impairment Questionnaire (WIQ) score at 6 months and 1 year compared to baseline. **12.** **Change in Rutherford Clinical Category at 6 Months and 1 Year:** Defined as the change in clinical status indicated by the change in RC at 6 monthsand 1 year compared to baseline, that is attributable to the treated limb (in cases of bilateral disease): Primary sustained clinical improvement: An improvement shift in the Rutherford classification of at least one class in amputation- and TVR-free surviving subjects at 6, and 12 months post procedure Secondary sustained clinical improvement: An improvement shift in the Rutherford classification of at least one class including the need for clinically-driven TVR in amputation-free surviving subjects at 6, and 12 months post index procedure **13.** **Change in Ankle-Brachial Index at 6 Months and 1 Year:** Defined as the change in the ankle-brachial index (ABI) at 6 months and 1 year compared to baseline in subjects with compressible arteries **14.** **Assisted Primary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR $\leq$ 2.4 at 1 year, maintained by repeat percutaneous intervention of a non-occluded but restenotic index vessel **15.** **Secondary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR $\leq$ 2.4 at 1 year, maintained by repeat percutaneous intervention

	of the index vessel (whether occluded or restenotic) **16.** **Clinical Patency at 6 months and 1 year:** Defined as duplex ultrasound patency (PSVR ≤ 2.4) of target lesion and freedom from clinically driven target lesion revascularization **17.** The association of moderate and severe calcification as defined by the Peripheral Arterial Calcium Scoring System (PACSS) and the change in %DS and procedure related complications (residual stenosis ≥50%, vessel recoil and/or high-grade dissections requiring use of adjunct technologies, distal embolization requiring pharmacologic or mechanical treatment)

ABBREVIATIONS

ABI	Ankle Brachial Index
ACT	Activated Coagulation Time
AE	Adverse Event
ASA	Acetylsalicylic Acid (aspirin)
AT	Anterior Tibial
atm	atmospheres (mm/Hg)
AV	Arteriovenous
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CFA	Common Femoral Artery
CFR	Code of Federal Regulations
CSA	Cross-Sectional Area
CTO	Chronic Total Occlusion
CVA	Cerebrovascular Accident
DES	Drug Eluting Stent
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EOB	Explanation of Benefits
FDA	United States Food and Drug Administration
GCP	Good Clinical Practices
GpIIb/IIIa	Glycoprotein IIb/IIIa
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IRB	Institutional Review Board
IVUS	Intravascular Ultrasound
MAE	Major Adverse Events
MI	Myocardial Infarction
PAD	Peripheral Arterial Disease
POBA	Plain Old Balloon Angioplasty
PSV	Peak Systolic Velocity
PSVR	Peak Systolic Velocity Ratio
PT	Posterior Tibial
QVA	Quantitative Vascular Analysis
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
TIA	Transient Ischemic Attack
TLR	Target Lesion Revascularization
TPT	Tibial Peroneal Trunk
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
US	United States
VF/VT	Ventricular Fibrillation/Ventricular Tachycardia
JS	JetStream Navitus

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1.0 INTRODUCTION

1.1 Purpose

The purpose of this randomized, multicenter study is to test the hypothesis that JetStream atherectomy (JS) with adjunctive low pressure paclitaxel coated balloon (DCB) angioplasty is superior to plain old balloon angioplasty (POBA) and adjunctive DCB in reducing the primary outcome of target lesion revascularization (TLR) at 1 year follow-up.

1.2 Device Names

The JetStream XC rotational and aspiration atherectomy device (JS device) and the Ranger™ Paclitaxel-Coated Balloon (DCB) Catheters will be used.

1.3 Intended Use

The JS device catheter is intended for use in peripheral arterial intervention to treat denovo and non-stent restenotic infrainguinal lesions. JS is not intended for use in the coronary, carotid, iliac or renal vasculature. The Ranger balloon catheter is designed for dilating denovo stenotic lesions and applying and transferring paclitaxel to the vessel wall. It is approved in Europe (CE mark) but will be tested in the Jet-PCB under an IDE in the USA.

1.4 Duration of the Study

The estimated duration of the study is approximately two to three years from the time of first subject enrollment to the last Study Protocol required follow-up visit. Subjects will be followed for one year.

1.5 Number of Sites and Subjects

Two hundred and fifty (250) subjects are planned for enrollment into this randomized portion of the study at up to 25 study sites in the United States. Fifty (50) patients will be undergoing intravascular ultrasound testing (IVUS) with 25 patients randomly included in each arm.

1.6 Participating Investigators

The study Chairman and National Principal Investigator is Dr. Nicolas W. Shammas, MD, MS, FACC. Proposal for Co-national Principal Investigator is Dr Lawrence Garcia, MD, FACC.

1.7 Sponsor Contact Information

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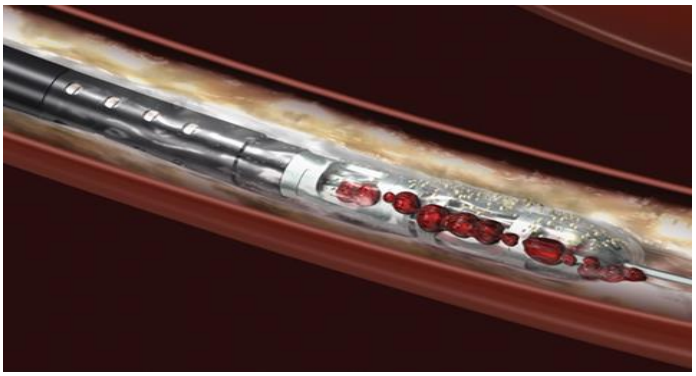
2.0 DEVICE DESCRIPTIONS

2.1 JetStream XC atherectomy Device

The Boston Scientific Jetstream XC catheter is a rotating, aspirating, expandable catheter for active removal of atherosclerotic disease and thrombus in peripheral vasculature. The JS XC System has been cleared by the FDA for use in the peripheral vasculature to treat denovo and non-stent infrainguinal lesions

JETSTREAM XC™ device has 2 sets of blades: one set is at the tip of the catheter and the other (5 blades) is mounted proximal to the tip. Counterclockwise rotation expands the proximal blades and allows wider tissue cutting. The JetStream Navitus has been improved compared to its predecessor, the Pathway device, with the aspiration port placed proximal to the blades instead of distally, allowing a more robust aspiration capacity. The recommended use of this device with tips and tricks on how to operate it can be found in prior publications.[1,2]

There are 2 cutter designs with the JETSTREAM device. The JETSTREAM® XC (or eXpandable Cutter Catheters) and the JETSTREAM® SC (or Single Cutter Catheters). The Expandable Cutter, as the name implies, can be used blades down (BD) and blades up (BU) with single insertion and are for femoropopliteal vessels. The XC or Expandable Cutters Catheters come in 2 sizes: 2.1mm/3.0mm (135 cm length) is best suited for vessel size larger than 3.0 BD and 4.0-5.0 mm BU; and the 2.4mm/3.4mm (120 cm length) is typically used for vessels 4.0-4.9mm BD and 5.0 mm or larger BU. Also, the SC or Single Cutter Catheters come in two sizes: 1.6 mm (145 cm length) best suited for vessel size 2.0-2.5 mm; and the 1.85 mm (145 cm shaft length) typically used for vessel sizes 2.6-3.0 mm. The single cutters have only have a front end cutter with no BU feature and typically are used for proximal and mid tibial and peroneal vessels. The device is retracted through the treatment area by "rexing" it until wire loop is back to its initial size.



http://www.bostonscientific.com/content/dam/bostonscientific/pi/portfolio-group/Catheters%20Atherectomy/JetStream/Resources/4137-001%20JETSTREAM%20Brochure.pdf/

2.2 Ranger™ Paclitaxel-Coated Balloon Angioplasty Catheter

The Ranger PCB catheters are designed for dilating stenotic lesions and applying and delivering a drug to the vessel wall. The catheter's dilating element is the balloon near the distal tip.

The Ranger PCB uses the 0.014" or 0.018" guidewire platform that is inserted into the wire lumen. The other lumen, with the port marked "BALLOON," is the balloon inflation lumen. The balloon is inflated by injecting a diluted contrast medium solution through this port on the hub.

Radiopaque marker bands in the proximal and distal ends are placed under the balloon segment of the catheter to provide visual reference points for balloon positioning within the vessel.

The catheter has a semi-compliant balloon mounted on the distal tip which can be inflated to exert radial force to dilate narrow vessel segments. The working pressure range for the balloon is between the nominal pressure and the rated burst pressure. All balloons distend to sizes above the nominal size at pressures greater than the nominal pressure.

The balloon component of the catheter is coated with a drug formulation of paclitaxel (active ingredient) and uses citrate ester as excipient, with a paclitaxel coating concentration of $2\mu g/mm^2$. Paclitaxel is a white powder, isolated from a spectrum of Taxus species and hybrids. It is highly lipophilic, insoluble in water, but freely soluble in methanol, ethanol, chloroform, ethyl acetate and dimethyl sulfoxide. Paclitaxel promotes the assembly of microtubules from tubulin dimmers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

The Ranger PCB catheters are intended for single patient use only and come in a variety of balloon diameters and lengths with a common shaft length of 80 or 135 cm. Balloons with diameters of 4mm, 5mm, 6mm, 7mm and 8 mm and lengths of 30mm to100mm will be provided in this study.

Ranger is an investigational product in the US and this study utilizing the Ranger will be under an IDE for treatment of denovo disease in femoropopliteal interventions. The Ranger catheter is currently approved for use in Europe under a CE mark. Ranger will be provided to the investigational sites.

For specific information on device components and steps on how to operate the Ranger catheter, refer to the most current attached Instructions for Use (IFU)(Attachment 1)

3.0 BACKGROUND AND SIGNIFICANCE

3.1 Disease Overview

Peripheral Arterial Disease (PAD) is a highly prevalent disease affecting over 12 million people in the United States. PAD is a significant marker of heightened cardiovascular events including myocardial infarction and stroke and significantly affect a person's quality of life. PAD can progress to limb ischemia and may lead to limb amputation. Claudicants progress to limb ischemia at a rate of 2-4% per year. Physical function, pain, and general health perception is similar or worse than in patients with congestive heart failure or recent myocardial infarction[3,4,5]

3.2 Plaque Excision with JetStream

Plaque excision removes atherosclerotic or restenotic plaque from within the artery lumen and increases luminal size with no dottering effect. In contrast POBA results in plaque fracture and intimal-medial dissection leading to deep vascular injury[6]. Plaque excision with JetStream is a safe and effective option for the treatment of peripheral vascular disease, with high early patency rates and acceptable complication rates[7,8,9,11]

Early data using the Pathway system, a predecessor of the JetStream, showed high procedural success (less than 30% residual narrowing) with the use of the Pathway device. Stand alone atherectomy was performed in 40% of patients, adjunctive balloon angioplasty in 47%, and stenting/endografting in 13%. Primary patency rates measured by duplex ultrasound at 1 and 6 months were 100% and 73%, respectively; the TLR rate was 0% after 6 months. The ankle-brachial index increased significantly from 0.54+/-0.3 at baseline to 0.81+/-0.20 ($p<0.05$) at 6 months[9]. This data was followed by the multicenter Pathway PVD trial (9 study sites, n=172) that showed nearly similar results. In this registry, device success was 99% (208/210 lesions) and major adverse events at 30 days was 1% (2 preplanned amputations). Clinically driven target lesion revascularization rates at 6 and 12 months were 15% (25/172) and 26% (42/162), respectively. The 1-year restenosis rate was 38.2% based on duplex imaging. The ankle-brachial index increased significantly from 0.59+/-0.21 at baseline to 0.82+/-0.27 ($p<0.05$) at 12 months. Mean Rutherford class improved from 3.0+/-0.9 at baseline to 1.5+/-1.3 at 1 year ($p<0.05$)[11].

Shammas et al.[7] recently reported on 68 patients treated with the JetStream device, the current generation of the device on the market. Patients' average age was 68.5 years, 66.2% were male, and 89.7% Caucasian. Average ankle-brachial index was 0.74±0.25, average Rutherford category was 3.15±0.78, and 17.7% presented with critical limb ischemia. Lesions were long (133.9±106.8 mm), and located mostly in the superficial femoral artery (85.3%), followed by the popliteal (13.2%), and posterior tibial artery (1.5%). In-stent restenotic (ISR) lesions comprised 47.1%, chronic total occlusions 22.1%, and lesions with heavy calcification 27.9%. Procedural success was 94.1%. Additional stenting was performed in 25% lesions and 42.6% used embolic protection with the Nav-6 (Abbott Vascular, Santa Clara, CA) filter. There were 3 (4.4%) distal embolizations, all in unprotected cases that were successfully treated with aspiration-thrombectomy. At 12-months post-procedure, target limb revascularization rate was 20.6%, stent thrombosis 1.5%, and amputation-free survival 98.5%.

The JET registry[8], the largest series reported so far, enrolled patients with Rutherford category 1-3 denovo or non stent restenotic FP lesions, ≥ 4 cm in length and ≥ 70% in severity. Lesions with in-stent restenosis, or crossed via a subintimal approach or treated within 1 month prior to index procedure were excluded. There were no prespecified criteria for stenting post JS which was left to operator's discretion. Procedural success was defined as ≤ 30% residual diameter stenosis following atherectomy ± adjunctive therapy. In-hospital major adverse events (MAE) included amputation, death, and distal embolization (DE) requiring separate intervention or hospitalization. Calcium was graded from 0 to 4 by the operator (0=none, 1= < 25% of treated segment length (TSL), 2= 25-50% of TSL, 3=>50% of TSL and 4=dense calcium of entire TSL). Preliminary results from the first 155 patients enrolled in the JET registry are as follows: mean age 66 ± 11 yrs., males 68.0%, diabetics 42%, smoking history 51.0%, hypertension 80.0%, de novo lesions 90.0%, lesion length 220 ± 290 mm, reference diameter 6.0 ± 4 mm, pretreatment stenosis 91 ± 10%, post JS residual stenosis 47 ± 21% and post JS + adjunctive treatment 9 ± 8%. Adjunctive stenting was 33.0%. Distal embolic protection was used in 19% of patients. Distal embolization requiring treatment was 2%. There were no other in-hospital device-related complications reported. Calcium scoring (0 to 4 respectively) were as follows: Preprocedure: 7, 15, 25, 31 and 22%; post procedure: 15, 28, 26, 22 and 8%. Intermediate and long term data are not available at the time of writing of this report.

Finally, the JETSTREAM Calcium Study[12], a prospective, single-arm, multicenter study to evaluate the JETSTREAM Atherectomy System for severely calcified femoral-popliteal artery lesions, i.e., patients with claudication and lesions with superficial calcium >90° and >5 mm in length as determined by intravascular ultrasound (IVUS) enrolled 55 patients that underwent angiographic screening: 26 (45%) met IVUS inclusion criteria. Angiographic calcium was moderate in eight cases and severe in 14, with no available data for four cases. Visual diameter stenosis was 86±9% pre-treatment, 37±13% post atherectomy, and 10±6% post adjunctive treatment (adjunctive PTA+stenting in eight and adjunct PTA alone in 16). IVUS showed lumen area increased from 6.6±3.7 mm2 to 10.0±3.6 mm2 (p=0.001): calcium reduction was responsible for 86±23% of the lumen increase. Although the superficial calcium arc did not change (151±70° to 146±71°, p=0.83), the arc of reverberation increased (23±20° to 65±40°, p=0.006), indicating device-related modification of calcium. Adjunctive balloon angioplasty was performed in 62% of the lesions, and stent implantation in 31%. In 11 cases with adjunctive balloon dilation, the MLA increased from 7.1 (6.4, 7.8) mm2 post atherectomy to 11.9 (10.3, 13.5) mm2 post balloon (p<0.001) without flow-limiting dissection. No major adverse events occurred up to 30 days post procedure in either the study group or the patients who were excluded from the analysis.

3.3 Paclitaxel-Coated Angioplasty Balloons

Smooth muscle cell hyperplasia remains a problem with POBA or atherectomy of the femoropopliteal arteries. Paclitaxel, an anti-proliferative drug, has been demonstrated to inhibit smooth muscle cell proliferation in pre-clinical studies.[13,14] Multiple studies

investigated the effectiveness of local administration of paclitaxel using drug coated balloons on restenosis after angioplasty of lesions located in the femoropopliteal artery.[15-18]

The THUNDER trial [15] was a multi-center study that randomized 154 patients with femoropopliteal disease with treatment with standard balloon catheters coated with paclitaxel, uncoated balloons with paclitaxel dissolved in the contrast medium, or uncoated balloons without paclitaxel (control). Twenty-seven percent of the lesions were total occlusions, and 36% were restenotic lesions. The mean lesion length was 7.4+/-6.5 cm. There were no significant differences in baseline characteristics between the groups. There were no adverse events attributable to the paclitaxel-coated balloons. At 6 months, the mean late lumen loss was 1.7+/-1.8 mm in the control group, as compared with 0.4+/-1.2 mm (P<0.001) in the group treated with paclitaxel-coated balloons and 2.2+/-1.6 mm (P=0.11) in the group treated with paclitaxel in the contrast medium. The rate of revascularization of target lesions at 6 months was 20 of 54 (37%) in the control group, 2 of 48 (4%) in the group treated with paclitaxel-coated balloons (P<0.001 vs. control), and 15 of 52 (29%) in the group treated with paclitaxel in the contrast medium (P=0.41 vs. control); at 24 months, the rates increased to 28 of 54 (52%), 7 of 48 (15%), and 21 of 52 (40%), respectively.

Werk et al[18] reported on 87 patients in Rutherford class 1 to 4 with occlusion or hemodynamically relevant stenosis, restenosis, or in-stent restenosis of femoropopliteal arteries. Treatment was performed by either conventional uncoated or paclitaxel-coated balloon catheters. The primary end point was late lumen loss at 6 months. Secondary end points included restenosis rate, ankle brachial index, Rutherford class, target lesion revascularization, and tolerance up to >18 months. Before intervention, there were no significant differences in lesion characteristics such as reference diameter (5.3+/-1.1 versus 5.2+/-1.0 mm), degree of stenosis (84+/-11% versus 84+/-16%), proportion of restenotic lesions (36% versus 33%), and mean lesion length (5.7 cm [0.8 to 22.6 cm] versus 6.1 cm [0.9 to 19.3 cm]) between treatment groups. The 6-month follow-up angiography performed in 31 of 45 and 34 of 42 patients showed less late lumen loss in the coated balloon group (0.5+/-1.1 versus 1.0+/-1.1 mm; P=0.031). The number of target lesion revascularizations was lower in the paclitaxel-coated balloon group than in control subjects (3 of 45 versus 14 of 42 patients; P=0.002). Improvement in Rutherford class was greater in the coated balloon group (P=0.045), whereas the improvement in ankle brachial index was not different. The difference in target lesion revascularizations between treatment groups was maintained up to >18 months. No adverse events were assessed as related to balloon coating.

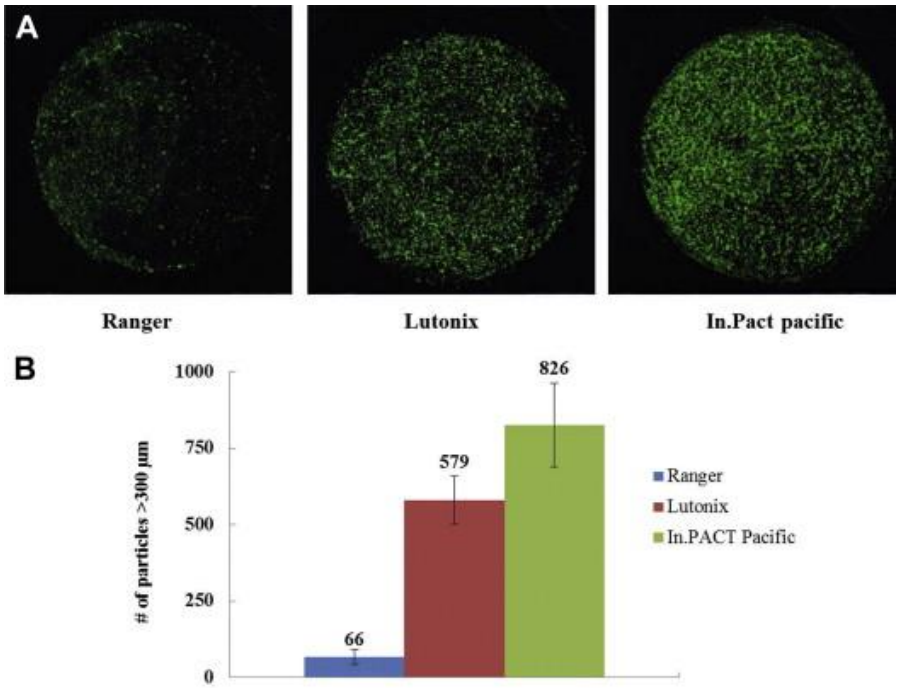
Werk et al.[17] also reported on 91 patients randomized to paclitaxel-coated IN.PACT Pacific or uncoated Pacific balloons. The primary end point was late lumen loss at 6 months assessed by blinded angiographic core lab quantitative analyses. Secondary end points were binary restenosis and Rutherford class change at 6 months, and target lesion revascularization plus major adverse clinical events (major adverse events=death, target limb amputation, or target lesion revascularization) at 6 and 12 months. Average lesion length was 7.0 ± 5.3 and 6.6 ± 5.5 cm for DEB and control arm, respectively. Procedural success was obtained in all cases. Six-month quantitative angiography showed that DEB were associated with significantly lower late lumen loss (-0.01 mm [95% CI, -0.29; 0.26] versus 0.65 mm [0.37; 0.93], P=0.001) and fewer binary restenoses (3 [8.6%] versus 11 [32.4%], P=0.01). This translated into a clinically relevant benefit with significantly fewer major adverse events for

DEB versus uncoated balloons up to 12 months (3 [7.1%] versus 15 [34.9%], P<0.01) as well as target lesion revascularizations (3 [7.1%] versus 12 [27.9%], P=0.02).

In addition, Liistro et al (19) randomized 104 patients (110 FPA lesions in 110 limbs) to either DCB + BMS or PTA + BMS. The primary endpoint was 12-month binary restenosis. Secondary endpoints were freedom from target lesion revascularization and major amputation. Post hoc subanalyses were performed for the comparison of long (≥100 mm) versus short lesions and true lumen versus subintimal approach. Mean lesion length was 94 ± 60 versus 96 ± 69 mm in the DCB + BMS and PTA + BMS groups (p = 0.8), respectively. The primary endpoint occurred in 9 (17%) versus 26 (47.3%) of lesions in the DCB + BMS and PTA + BMS groups (p = 0.008), respectively. A near-significant (p = 0.07) 1-year freedom from target lesion revascularization advantage was observed in the DCB + BMS group. No major amputation occurred. No significant difference was observed according to lesion characteristics or technical approach.

Furthermore, in the LEVANT I trial[15], patients were randomized to the Lutonix DCB (n = 49) versus uncoated balloons (control group [n = 52]), stratified by whether balloon-only treatment (n = 75) or stenting (n = 26) was intended. The primary endpoint was angiographic late lumen loss at 6 months. Secondary outcomes included adjudicated major adverse events (death, amputation, target lesion thrombosis, reintervention), functional outcomes, and pharmacokinetics. Demographic, peripheral vascular disease, and lesion characteristics were matched, with mean lesion length of 8.1 3.8 cm and 42% total occlusions. At 6 months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 ± 1.13 mm) than for the control group (1.09 ± 1.07 mm; p = 0.016). Composite 24-month major adverse events were 39% for the DCB group, including 15 target lesion revascularizations, 1 amputation, and 4 deaths versus 46% for uncoated balloon group, with 20 target lesion revascularizations, 1 thrombosis, and 5 deaths. For successful DCB deployment excluding 8 malfunctions, 6-month late lumen loss was 0.39 mm and the 24-month target lesion revascularization rate was 24%.

Finally, Gongora et al (30) tested the Ranger balloon in familial hypercholesterolemic SFA in-stent restenosis swine model. The Ranger DCB had similar neointimal inhibition but with more homogeneous healing when compared to In.Pact. In this study, the Ranger PCB had fewer observable particles than either Lutonix or In.Pact Pacific (Figure A below). Also, large particles (<300 μm) were approximately 6× to 8× lower than for both Lutonix and In.Pact Pacific (Figure B below).



Also, The Ranger SFA study is a prospective, randomized, multicenter, controlled trial (2:1 Ranger Drug Coated Balloon vs. uncoated balloon) currently ongoing in Europe (ClinicalTrials.gov NCT02013193). A total of 105 patients with femoropopliteal arterial disease will be enrolled at 11 sites. The primary endpoint is to show the superior performance of the Ranger™ paclitaxel-coated PTA balloon catheter for angioplasty for femoropopliteal artery lesions when compared to non-coated balloons at six months post-procedure when comparing Late Lumen Loss (LLL). Interim safety data was presented at CIRCE, Spain in 2015 and showed no SADE, deaths or major amputations (Albrecht, T. CIRSE 2015).

These early results appear to be promising but data on applying DCB in complex lesions (moderate to severe calcified disease, long lesions exceeding 10 cm and total occlusions) is not clear[20-22]. Although DCB appear to yield better outcome in these lesions, they remain a predictor of higher loss of patency, target lesion revascularization and complications. In a retrospective analysis of 228 patients treated for more than 10 cm femoropopliteal lesions with DCB or drug coated stents (DCS), the binary restenosis rates remained high at 23.9% (26/109) and 30.4% (24/79, p=0.319) in the DCB and DES cohorts, respectively, and clinically driven TLR rates were 15.6% (17/109) vs. 19.0% (15/79, p=0.543), respectively.[20] In addition, loss of patency following DCB has been associated with severe calcifications[22]. In sixty patients treated for novo lesions of the superficial femoral artery with DCB, patients were classified into eight groups according to circumferential distribution of calcium on CT-angiography axial images (from 0° to 360°) and to its length (length < or > 3 cm) evaluated with digital-subtraction-angiography. Ankle-brachial index (ABI), late lumen loss (LLL), target lesion revascularization (TLR), primary (PP) and secondary (SP) patency, major adverse events (MAE), and Rutherford shift were evaluated at 1-year follow-up and correlated with the amount of calcium. Revascularization was successful in all cases. Flow-limiting dissection occurred in five cases (8.3 %) with a higher circumferential degree of calcium and solved in three cases with postdilatation and in

the other two with provisional stenting. DCB effect was lower in patients with higher degree of calcium (>270° vs. <90°): ABI 0.71 ± 0.07 versus 0.92 ± 0.07; LLL 0.75 ± 0.21 versus 0.45 ± 0.1; PP 50 versus 100 %; SP 50 versus 100 %; TLR 25 versus 0 %; MAE 25 versus 0 %. The authors concluded that calcium represents a barrier to optimal drug absorption. Circumferential distribution seems to be the most influencing factor with the worst effect noticed in 360° calcium presence.

It is unclear at this time whether combining tissue debulking with a DCB will allow a more effective drug penetration and retention in the deeper layer of the femoropopliteal arteries or more likely higher concentration of drug per remaining tissue mass resulting in better outcomes with DCB. This is likely to be more important in complex disease where there is a high level of plaque burden such as CTO and long lesions or in the case of severe calcifications. Data from directional atherectomy (DA) and DCB for the treatment of heavy calcified femoro-popliteal arteries led to bail-out stenting in only 6.5% of cases. In addition, target lesion restenosis requiring reintervention was 10% and total one-year secondary patency rate 100%. The authors concluded that combined use of DA and DCB may represent a potential alternative strategy for the treatment of femoro-popliteal severely calcified lesions.[23] Furthermore, DCB use with rotational atherothrombectomy with Straub Rotarex(®) was applied in 29 patients with acute/subacute and chronic occlusions of the superficial femoral artery (SFA) and/or popliteal arteries. At 6 months follow up, the ABI shows a significant increase from 0.52 ± 0.17 to 0.91 ± 0.25 and restenosis was only 6.9% by duplex ultrasound. There was one dissection during the intervention (3.5%).[24] Finally, the 12-month results of the DEFINITIVE AR study was recently presented at Vascular Interventional Advances (VIVA) 2014 conference in Las Vegas, Nevada (25). Definitive AR randomized patients with femoropopliteal disease to directional atherectomy with DCB (DAART) versus DCB alone. DEFINITIVE AR results demonstrated higher technical success and lower incidence of flow-limiting dissections. Duplex Ultrasound primary patency rates for the long (≥10 cm) lesion subset at 12 months were 96.8 percent in patients treated with DAART compared to 85.9 percent in patients treated with DCB alone. Primary patency rates at 12 months in severely calcified lesions, per core lab assessment, were 70.4 percent in DAART patients compared to 62.5 percent in DCB alone patients.

As of now, the combination of JS with DCB versus DCB has not been tested. JS has been shown to be effective in treating complex femoropopliteal lesions including calcified lesions, long lesions and total occlusions. In this study we hypothesize that JS + Ranger DCB versus Ranger DCB will result in a higher acute procedural success and improved clinically driven target lesion revascularization (primary endpoint) and patency (secondary endpoint) at 1 year follow up.

4.0 METHODOLOGY

4.1 Study Design

This is a prospective, multicenter, randomized pilot study. One cohort will be treated with Ranger paclitaxel-coated balloon angioplasty (DCB arm). The other cohort will be treated with plaque excision using JetStream XC (JS) followed by Ranger paclitaxel-coated balloon angioplasty (JS+DCB arm). Subjects meeting the definition of RCC 2, 3 or 4 with an

atherosclerotic lesion 10 cm or longer, chronic total occlusion of any length, or moderately or severely calcified disease located in the superficial femoral artery (SFA) and/or popliteal artery are eligible for enrollment. For subjects with moderate or severely calcified lesions undergoing debulking, intravascular ultrasound imaging will be obtained to assess debulking effectiveness of the JetStream.

Study Purpose
The purpose of this study is to assess and estimate the effect of treating a vessel with plaque excision using JS in combination with Ranger paclitaxel-coated balloon angioplasty (JS+DCB) compared to treatment with Ranger DCB (DCB) alone.

4.2 Primary Outcome

Effectiveness: Target Lesion Revascularization at 1 Year: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 1 year. For the primary endpoint, intra-procedural bail out stenting of the index lesion is considered meeting a TLR endpoint. (ITT analysis)

Safety: **Major Adverse Events (MAE) at 30 days**: unplanned amputation, total mortality or TLR at 30 days (TLR includes bail out stenting).

4.3 Secondary Outcomes

The following secondary outcomes will be summarized in this study.

1. **Device Outcome:** Categorized by < 50% residual stenosis following the protocol-defined treatment (POBA + DCB or JS + DCB) and prior to bail out stenting at the target lesion as determined by the Angiographic Core Laboratory.
2. **Procedural outcome:** Categorized by ≤ 30% residual stenosis following the protocol-defined treatment and followed by bail out stenting if needed at the target lesion as determined by the Angiographic Core Laboratory.
3. **Target Lesion Patency at 6 months and 1 year:** Defined as PSVR ≤ 2.4 at the treated site or < 50% stenosis by angiography as determined by the Angiographic Core Laboratory
4. **Target Lesion Revascularization at 6 months**: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 6 months. For the primary endpoint, intra-procedural bail out stenting of the index lesion is considered meeting a TLR endpoint. (ITT analysis)
5. **Clinically Driven target lesion Revascularization at 6 months and 1 year with the following analysis:**

   Defined as any re-intervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis and at least two of the following: worsening RCC by one category, worsening WIQ score by ≥20 points, or an ABI drop > 0.15 from baseline.

ITT (bail out stent considered as TLR) (6 months and 1 year)

ITT (bail out stent is not considered as TLR) (6 months and 1 year)

Actual treatment groups (DCB alone vs DCB with bail out stent vs DCB with JS atherectomy vs DCB with JS atherectomy and bail out stenting) (6 months and 1 year)

Actual treatment groups (DCB alone with or without bailout stenting vs JS atherectomy with DCB with or without bailout stenting) (6 months and 1 year)

6. **Target Vessel Failure at 30 days and 1 year:** Defined as major unplanned amputation related to the treated limb, vascular mortality related to treated limb and target vessel revascularization at 30 days and 1 year (stenting in the lab is not considered a TLR/TVR)
7. **Target Lesion failure at 30 days and 1 year:** Defined as major unplanned amputation related to the treated limb, vascular mortality related to treated limb and target lesion revascularization at 30 days and 1 year (stenting in the lab is not considered a TLR)
8. **In-hospital Major Adverse Event Rate**: all-cause mortality, perforation requiring additional treatment, distal embolization requiring additional mechanical or pharmacological treatment, major bleeding as defined by the Thrombolysis in Myocardial Infarction criteria, vascular access site complications requiring transfusion and/or surgical repair, acute stent thrombosis as defined by the Academic Research Consortium, unplanned major or minor amputation
9. **Major Adverse Event Rate at 30 Days:** Defined as major or minor unplanned amputation of the treated limb, vascular access site complications requiring transfusion and/or surgical repair, all-cause mortality, acute thrombosis, or clinically-driven target vessel revascularization.
10. **Major Adverse Events at 1 year:** Defined as major or minor unplanned amputation of the treated limb, all-cause mortality or target lesion revascularization (TLR).
11. **Change in WIQ Score at 6 Months and 1 Year:** Defined as the change in Walking Impairment Questionnaire (WIQ) score at 6 months and 1 year compared to pretreatment baseline.
12. **Change in Rutherford Clinical Category at 6 Months and 1 Year:** Defined as the change in clinical status indicated by the change in RCC at 6 months and 1 year compared to baseline, that is attributable to the treated limb (in cases of bilateral disease).

    Primary sustained clinical improvement: An improvement shift in the Rutherford classification of at least one class in amputation- and TVR-free surviving subjects at 6, and 12 months post procedure

Secondary sustained clinical improvement: An improvement shift in the Rutherford classification of at least one class including the need for clinically-driven TVR in amputation-free surviving subjects at 6, and 12 months post index procedure

13. **Change in Ankle-Brachial Index at 6 Months and 1 Year:** Defined as the change in the ankle-brachial index (ABI) at 6 months and 1 year compared to baseline in subjects with compressible arteries.
14. **Assisted Primary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR ≤ 2.4 at 1 year, maintained by repeat percutaneous intervention of a non-occluded but restenotic index vessel
15. **Secondary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR ≤ 2.4 at 1 year, maintained by repeat percutaneous intervention of the index vessel whether occluded or restentotic
16. Clinical Patency at 6 months and 1 year: Defined as duplex ultrasound patency (PSVR ≤ 2.4) of target lesion and freedom from clinically driven target lesion revascularization
17. The association of moderate and severe calcification as defined by the Peripheral Arterial Calcium Scoring System (PACSS) and the change in %DS, procedure related complications (residual stenosis ≥50%, vessel recoil and/or high-grade dissections requiring use of adjunct technologies, distal embolization requiring pharmacologic or mechanical treatment)

4.4 Subject Selection Criteria

Assessment of eligibility is based on data available to the Investigator at the time of subject enrollment.

4.4.1 General Inclusion Criteria

Subject must meet all of the following general inclusion criteria.

1. Has a Rutherford Clinical Category of 2 - 4.
2. Is willing and capable of complying with all follow-up evaluations at the specified times (including an angiogram at the 1-year follow-up visit).
3. Is ≥ 18 years old.
4. Is able and willing to provide written informed consent prior to study specific procedures.

4.4.2 Angiographic Inclusion Criteria

Subject must meet all of the following angiographic inclusion criteria. Unless otherwise specified, the Investigator performing the procedure bases all angiographic inclusion criteria on visual determination at the time of the procedure.

1. Has evidence at the target lesion of ≥ 70% *de novo* stenosis of a. ≥ 10 cm length, or b. any chronic total occlusion (> 1 month by history or known by conventional or CT angiography or arterial duplex ultrasound) in the SFA (at least 1 cm from the bifurcation of the profunda) and/or popliteal artery, or 3. at least grade 2 or higher calcification as defined by the peripheral arterial calcium scoring system (PACCS)[26]
2. Has evidence of at least one runoff vessel to the ankle/foot of the limb to be treated that does not have significant (< 70%) stenosis during the index procedure.
3. Has a reference vessel diameter of 4 - 7 mm.
4. Has a target lesion an exchangeable guidewire can cross via the true lumen (without using a re-entry device or a subintimal approach).

4.4.3 General Exclusion Criteria

The subject must not meet any of the following general exclusion criteria.

1. Has one or more of the contraindications listed in the JetStream or Ranger IFUs.
2. Has a contraindication or known untreated allergy to antiplatelet therapy, anticoagulants, thrombolytic drugs or any other drug anticipated to be used (that cannot be reasonably substituted).
3. Is expected to require cilostazol (Pletal) during the one-year follow-up period.
4. Has a hypersensitivity to contrast material that cannot be adequately pretreated.
5. Has known hypersensitivity to treatment device materials including paclitaxel or nitinol.
6. Has known uncontrollable hypercoagulable condition, or refuses blood transfusion.
7. Has life expectancy of less than 24 months.
8. Is pregnant, of childbearing potential not taking adequate contraceptive measures, or nursing.
9. Has surgical or endovascular procedure of the target vessel within 30 days prior to the index procedure.
10. Has any planned surgical intervention (requiring hospitalization) or endovascular procedure within 30 days after the index procedure.
11. Is currently participating in an investigational drug or another device study that may clinically interfere with the study outcomes.
12. Has any co-morbid condition that in the judgment of the physician precludes safe percutaneous intervention.
13. Has had a previous peripheral bypass affecting the target vessel (allowable for physician to pass through bypass graft in aorta-iliac region to get to the target lesion).
14. Has chronic renal insufficiency (eGFR < 30 ml/min or creatinine ≥ 2.5 including dialysis patients).
15. Has planned laser, cryo, TurboHawk or any other treatment except study treatment within 30 days after the index procedure.

16. Has had superficial thrombophlebitis or deep venous thrombus within 30 days prior to index procedure.
17. Has had a stroke within 3 months prior to index procedure.
18. Has had a myocardial infarction within 1 month prior to index hospitalization
19. Has history of significant gastrointestinal bleeding in the past 2 months prior to index procedure, or any history of hemorrhagic diathesis.
20. Has a known or suspected systemic infection at the time of the index procedure.
21. Patients with ipsilateral Iliac and CFA disease are allowed in the study but these lesions have to be treated successfully first (<30% residual) before patient can be enrolled. Treatment as per investigator's preference.
22. Aneurysm located in the target vessel or aneurysmal vessel

4.4.4 Angiographic Exclusion Criteria

The subject must not meet any of the following angiographic exclusion criteria. The Investigator performing the procedure bases all angiographic exclusion criteria on visual determination at the time of the procedure.

1. Has < 70% stenosis prior to treatment of the target lesion.
2. Has in-stent restenosis of the target lesion.
3. Has an acute intraluminal thrombus within the target lesion.
4. Has an aneurysmal target vessel
5. Patient has already been enrolled in the study or any other study that by the investigator judgment may interfere with the outcome of this trial
6. Has two or more lesions that require treatment in the target vessel. Lesions have to be separated by > 5 cm in order to be considered different lesions. Only one lesion per target vessel can be enrolled during the index procedure
7. Has disease that precludes safe advancement of the JS device to the target lesion.
8. P3 segments of the popliteal vessel (figure 1)

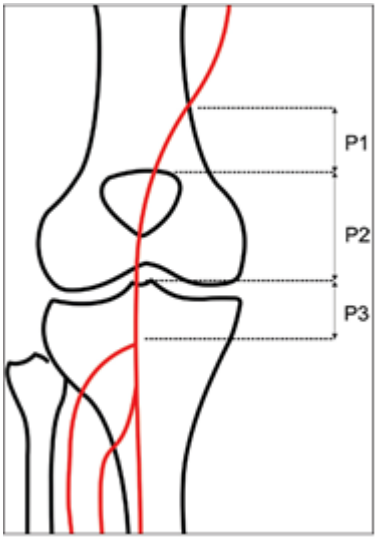


Fig 1. Popliteal segments P1, P2 and P3

4.5 Patient Screening

It is recommended that all eligible patients be approached for enrollment in the study and be screened at the study site. Study personnel will explain to the patient that even if the patient agrees to participate in the study and signs the written informed consent, angiography may demonstrate that the patient is not a suitable candidate for the study.

4.6 Subject Enrollment

The subject is enrolled in the study after he/she has signed the subject informed consent and it has been determined that he/she meets all of the inclusion criteria and none of the exclusion criteria. The point of enrollment is defined as the moment an exchangeable guidewire and treatment catheter cross the target lesion in the true lumen.

4.7 Randomization

Randomization occurs after the subject is enrolled into the study. The eligible subjects will be randomized to either the JS + DCB arm or the DCB arm, at a ratio of 2:1 respectively. Crossover to the other treatment arm is not allowed. Randomization will be carried on by CRO and as outlined by the Procedure Manual.

4.8 IVUS substudy

Fifty (50) subjects will undergo IVUS per core laboratory instructions (25 in each arm). The IVUS data will be used for the following analysis which has been previously described (31)

1. Minimal Luminal area (MLA) in each arm will be determined and compared.
2. Severity of calcium will be determined by Core Laboratory (Arc of calcium 90, 180, 270 and 360 degrees, depth and length)
3. Analyze how much tissue/calcium excision accounted for MLA gain by comparing preintervention to postintervention MLA (preintervention, post atherectomy and post adjunctive balloon angioplasty)

4. Analyze pre intervention maximum calcium site and corresponding site at post intervention. Analysis will be done at three slices having the max calcium among the lesions. The change at the worst slice is the most clear to show the removal.
5. Evaluate severity of dissection (by arc, length, depth) in the final IVUS image
6. Correlate the degree of plaque removal and calcium severity in all cohort and each arm on overall patency and clinical patency at 6 months and 1 year

4.9 Blinding

Every effort should be made to follow the blinding practices as described below. When it is not possible to follow these practices, document the reason why.

Study Subjects: Subjects will be informed of the 2:1 randomization between the JS + DCB versus DCB arms but will remain blinded as to which treatment they actually receive until after their 1-year follow-up visit.

Investigators: It is not possible to blind the Investigators due to the substantial treatment differences between the two treatment arms. Investigators and site personnel should make every effort to keep the randomized subjects blinded to the treatment assignments.

Angiographic Core Laboratory: It is not possible to blind the Angiographic Core Laboratory due to the substantial treatment differences between the two treatment arms which will be evident from the procedure angiogram.

Duplex Ultrasound Core Laboratory: The Duplex Ultrasound Core Laboratory will be blinded to subject treatment assignment while reviewing the duplex scans.

Clinical Events Committee (CEC): All adverse event information provided to the CEC will be unblinded to treatment assignment in order for the committee to determine the relationship of events to the study devices. If an event does not require establishing a relationship to study device, medical records, source documentation and event information will be blinded to treatment assignment.

Data Safety Monitoring Board (DSMB): Information provided to the DSMB will be unblinded to the treatment assignment in order to render their opinion on the safety of the study design and conduct.

4.10 Overview of Study Conduct

The Table 1 provides an overview of the assessment requirements for the study. All testing and assessments should be conducted at the study site.

Table 1: Study Assessment Requirements

				Follow-Up Visits		
	Baseline	**Procedure**	**Pre-Discharge**	**30-Day**	**6-Month**	**1-Year**
	Within 45 days prior to enrollment		**Prior to discharge (or within 5 days after index procedure)**	**30-45 days after index procedure**	**150-210 days after index procedure**	**320-410 days after index procedure**
Informed Consent	X					
Medical History and Physical Exam	X			X	X	X
Medication Use	X			X	X	X
Creatinine (non-standardized)	X					X
Hemoglobin A1C	X†					X
Rutherford Clinical Category Assessment	X			X	X	X
Walking Impairment Questionnaire (WIQ)	X			X	X	X
Ankle Brachial Index (ABI)	X			X	X	X
Angiogram		X				
Intravascular Ultrasound (IVUS)		X				
Duplex Ultrasound			X*		X	X
Adverse Event Evaluation		X	X	X	X	X

† Blood draw for hemoglobin A1C assessment can occur at the baseline evaluation or during the procedure.

* The first duplex ultrasound can occur any time within 45 days of the index procedure.

4.11 Required Assessments and Tests

The following section details the study-required assessments and tests.

4.11.1 Medical History and Physical Examination

The subject's clinical history and pre-existing conditions will be assessed and documented at baseline and at every visit at 30 days, 6 months and 1 year.

4.11.2 Medication Use

The subject's medication use will be documented at baseline, at 30 days, 6 months and 1 year. Medication use will include anticoagulants and antiplatelet medications. Cilostazol (Pletal) use is not allowed during the study.

4.11.3 Creatinine

Creatinine (non-standardized) will be obtained and documented at baseline and at the 1-year follow-up visit.

4.11.4 Hemoglobin A1C (Hb A1C)

Glycosylated hemoglobin (Hb A1C) will be obtained and documented at either baseline or on the day of the procedure, and at the 1-year follow-up visit.

4.11.5 Rutherford Clinical Category Assessment

The subject's clinical status as indicated by RCC per clinical description will be assessed and documented at baseline and all follow-up visits.

4.11.6 Ankle-Brachial Index (ABI)

The subject's ABI will be measured and documented at baseline and all follow-up visits. An ABI is the ratio of the highest ankle systolic pressure to the highest brachial systolic pressure.

4.11.7 Walking Impairment Questionnaire (WIQ)

Each subject will undergo a WIQ assessment and the results will be documented at baseline and all follow-up visits. The WIQ is an interviewer-administered subject-reported functional assessment focused on difficulty in walking.

4.11.8 Angiogram

For procedural angiogram requirements see Section 4.13.1. Angiograms will be obtained per the Angiographic Protocol determined by the Angiographic Core.

4.11.9 Duplex Ultrasound (DUS)

It is required that the subject undergo a DUS, the results be documented and copies of the scan be sent to the core laboratory. DUS is required within 45 days of the index procedure (at either the pre-discharge or 30-day visit), at 6 months, and at 1 year post-procedure. DUS will be obtained as per Core lab protocol.

4.11.10 Adverse Event (AE) Evaluation

Adverse event evaluations will be performed during the procedure, prior to discharge, and at all follow-up visits. Refer to Section 4.4 for AE definitions.

4.12 Baseline Requirements

Informed consent must be obtained from each subject prior to enrollment into the study in accordance with the ICH/GCP guidelines, Declaration of Helsinki, and pertinent individual country laws/regulations.

Table 2 summarizes the list of all assessments and tests that are required at baseline. The blood sample for the assessment of creatinine will be taken at baseline. The blood sample for the hemoglobin A1C test may be taken at baseline or during the procedure.

Table 2: Baseline Requirements

Baseline Requirements	Timeframe Window

Informed consent	Within 45 days prior to enrollment
Medical history and physical exam	
Creatinine	
Hemoglobin A1C†	
Concomitant medication use	
Rutherford Clinical Category assessment	
Walking Impairment Questionnaire (WIQ)	
Ankle Brachial Index (ABI)	

† Blood draw for hemoglobin A1C assessment can occur at the baseline evaluation or during the procedure.

4.13 Procedure Requirements

The subject will undergo percutaneous revascularization of the superficial femoral and/or popliteal arteries. The target lesion must be at least 1 cm distal to the ostium of the profunda. The DCB group will be treated with POBA followed by PCB alone to cover all the treated segment. The JS + DCB group will be treated with the JS device followed by treatment with DCB to cover all the treated segment.

The following describes the required assessments and activities during the procedure.

4.13.1 Angiogram

A sheath will be inserted and after insertion the subject should receive anticoagulation medications as indicated by the Investigator to maintain appropriate clotting time. Selective angiography of the limb to be treated including the distal aorta, bilateral iliac, ipsilateral femoral, popliteal and tibial-peroneal vessels (to the pedal level) will be performed to identify the anatomical characteristics of the vasculature and to best isolate and define the lesion. If a pre-procedure assessment has been completed with CTA/MRA, the angiography can be limited to the target vessel, with a baseline assessment of run-off. Angiography must be conducted according the Angiographic Protocol (refer to Core Lab requirement). Gadolinium and CO2 are not allowed for use as contract material.

During angiography the Investigator performing the procedure will assess the subject for the angiographic inclusion and exclusion criteria. It is required that a radiopaque ruler be used to define lesion length and define anatomical measurement references. If the subject meets all the angiographic inclusion criteria and does not meet any of the angiographic exclusion criteria, the subject is enrolled when an exchangeable guidewire crosses the target lesion. Upon enrollment, subjects will be randomly assigned to DCB (pretreatment with a POBA is required before DCB in the DCB alone arm) or JS + DCB treatment (Pretreatment with POBA after JS and before DCB is not allowed).

Angiographic films, including run-off, will be obtained immediately prior to and after treatment (after POBA+DCB and after bail out stenting if needed; or after JS+DCB and after bail out stenting if needed) according to the Angiographic Core Lab Protocol. Capture images that demonstrate the stenosis in two views that minimize the degree of vessel overlap and demonstrate the stenosis in its most severe view. A final angiogram of the target lesion and run-off will be done following adjunctive procedures (if required). Angiographic results must be sent to the Angiographic Core Laboratory.

The Angiographic Core Laboratory assessments will supersede the measurements by the Investigator performing the procedure for data analysis purposes; however, the measurements by the Investigator performing the procedure will be used to determine subject eligibility at the time of enrollment.

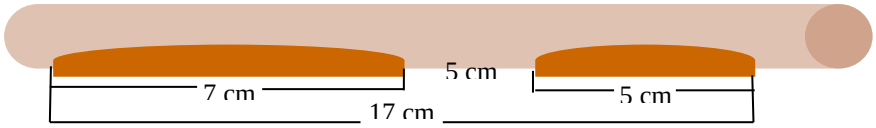
4.14 Treatment of the Target Vessel

4.14.1 Target Lesion

The lesion intended for treatment at the time of the index procedure that meets the inclusion criteria and none of the exclusion criteria will be considered the "target lesion." Each subject can have only one target lesion. The point of enrollment is defined as the moment an exchangeable guidewire and treatment catheter cross the target lesion in the true lumen.

If there are 5 cm or less between diseased segments needing treatment in the SFA and/or popliteal artery, then it can be considered one lesion (see example below). If there are more than 5 cm between diseased segments, they will be considered separate lesions and count as two or more lesions. If multiple lesions in the target vessel require treatment, pretreatment of the non-target lesions is required or the subject is not eligible for enrollment (see Section 4.10.2).

Single lesion: 17 cm lesion since separation is **≤ 5.0 cm**



4.14.2 Non-Target Lesions

In the case of more than one lesion in the target vessel requiring treatment, it is acceptable to treat the other non-target lesion(s) at least 30 days prior to the index procedure. Otherwise, if pre-treatment is not possible, the patient is not eligible for enrollment.

4.15 Treatment of Non-Target Vessels

Lesions in the ipsilateral or contralateral iliac arteries or ipsilateral common femoral arteries to the target limb that require treatment may be revascularized during the index procedure. These lesions must be successfully treated prior to the point of enrollment. Stent placement in the common femoral arteries will exclude patient from enrolment.

If a patient has an infrapopliteal lesion that requires treatment for significant (> 70% stenosis or occlusion) stenosis, patient cannot be enrolled.

Lesions in the non-target limb may be treated up to one day prior to the index procedure, but not within 30 days following the index procedure.

4.16 JS + DCB Group Procedures

The selection of the JS XC device will be at the discretion of the treating physician. In general however, the 2.4 XC is for vessel diameter > 5 mm and 2.1 XC for 4-5 mm. The plaque excision procedure will follow the steps previously described.[2] The Spartacore

(Abbott) or Thruway Wire (Boston Scientific) are recommended with the use of the JetStream device. The Grand Slam wire and hydrophilic wires are not recommended. Filters are encouraged but left to investigator's discretion. If a filter is used, the off label use of the Nav-6 (Abbott) filter is recommended. The long BareWire will need to be used. JetStream IFU has no recommendations on filter use.

Residual stenosis following the plaque excision treatment must be documented by angiography per the Angiographic Protocol. It is recommended that residual stenosis be < 50% prior to treatment with DCB.

Following JS atherectomy, predilation of the lesion will be done with a 1:1 regular non DCB balloon (semi-compliant or non-compliant balloon) inflated only to a pressure that leads to full balloon expansion. This will be followed by dilation of the lesion by DCB with a 1:1 balloon size. The diameter of the study balloon will be selected based on the vessel reference diameter distal to the target lesion. The length of the DCB balloon will be selected in lengths approximately 2 cm longer than the target treated segment with the non DCB balloon to allow the balloon to extend approximately 1 cm beyond the proximal and distal edges of the target lesion treated segment (per Investigator's visual estimate). If more than one study balloon is required to cover the entire length of a longer lesion, the second study balloon will be placed such that there is approximately 1 cm of overlap between the coverage areas (per Investigator's visual estimate).

The inflation pressure of the DCB must be at least at nominal inflation pressure or to achieve the full expansion of the balloon, If the full expansion of the balloon is not achieved at nominal pressure, the inflation pressure should be increased by increments of 1 atm every 5 seconds, until full balloon expansion is achieved, but must not exceed the rated burst pressure (see the Ranger IFU). If there is a complication during JS, treatment with the DCB is at the operator's discretion. If a perforation occurs in the area of plaque excision, it must be sealed and distal outflow must be established prior to delivery of the DCB. If a perforation occurs and it is not successfully sealed or requires reversal of anticoagulation, or distal outflow is not established, delivery of the DCB is not allowed.

4.17 DCB Group Procedures

Predilation of the lesion will be done with a 1:1 regular non DCB balloon (semi-compliant or non-compliant balloon) inflated only to a pressure that leads to full balloon expansion. This will be followed by dilation of the lesion by DCB with a 1:1 balloon size. The diameter of the study balloon will be selected based on the vessel reference diameter distal to the target lesion. The length of the DCB balloon will be selected in lengths approximately 2 cm longer than the target treated segment with the non DCB balloon to allow the balloon to extend approximately 1 cm beyond the proximal and distal edges of the target lesion treated segment (per Investigator's visual estimate). If more than one study balloon is required to cover the entire length of a longer lesion, the second study balloon will be placed such that there is approximately 1 cm of overlap between the coverage areas (per Investigator's visual estimate). The inflation pressure of the DCB must be at least at nominal inflation pressure or to achieve the full expansion of the balloon, If the full expansion of the balloon is not achieved at nominal pressure, the inflation pressure should be increased by increments of 1

atm every 5 seconds, until full balloon expansion is achieved, but must not exceed the rated burst pressure (see the Ranger IFU).

Adjunctive Procedures

Adjunctive procedures should be avoided if possible. In the event of a major flow limiting dissection (type D and higher), perforation, or occlusive complication (e.g., recoil), prolonged balloon inflation (5 minutes) with a non-drug coated balloon must be attempted first. All efforts should be made to eliminate the need for bail-out stent placement. In cases where the results after prolonged balloon inflation are suboptimal, bail-out stenting is allowed. A cine following the prolonged balloon inflation must be captured; all bail-out stenting procedures will be reviewed by the Angiographic Core Laboratory. Adjunctive treatment with cutting balloons or scoring balloons is not allowed. Covered stents are not allowed except to seal a perforation.

4.18 Procedure Completion

An angiogram of the treated segment(s) must be recorded for subsequent Angiographic Core Laboratory analysis of the post-treatment residual stenosis.

The end of the procedure is defined as the time after a complete angiogram, including runoff, has been performed **AND** the last guidewire and catheter have been removed. If the subject returns to the procedure room and a guiding catheter is reinserted and dilation is performed, this is considered a re-intervention and should be documented accordingly. The sheath(s) may be removed at the physician's discretion.

4.19 Adverse Event Evaluation

An AE evaluation will be performed during and at the end of the procedure. See Section 4.4 for the AE definitions. Adverse event evaluations will also occur prior to discharge and at all follow-up visits.

4.20 Medical Anticoagulant/Antiplatelet Therapy

Pre-Procedure

The subject should be optimally medically-managed for peripheral arterial disease per the standard institutional regimen.

Peri-Procedure

The subject should receive anticoagulation as indicated by the Investigator to maintain appropriate clotting time (300 seconds using Hemochron or 250 seconds using iStat if heparin administered). ACT not required if bivalirudin is used. If not loaded with clopidogrel, patient will receive clopidogrel 600 mg po loading dose. Maintenance dose of Clpidogrel is 75 mg po daily.

Post-Procedure

The subject should be optimally medically-managed for peripheral arterial disease per the standard institutional regimen. ADP receptor antagonist (clopidogrel) and asa are to be used for 3 months post procedure and asa indefinitely. ASA can be 81 to 325 mg dose.

The use of cilostazol (Pletal) is not allowed during the study.

4.21 Follow-Up requirements

All enrolled (randomized and non-randomized) subjects are required to complete all follow-up visits as shown in Figure 2.

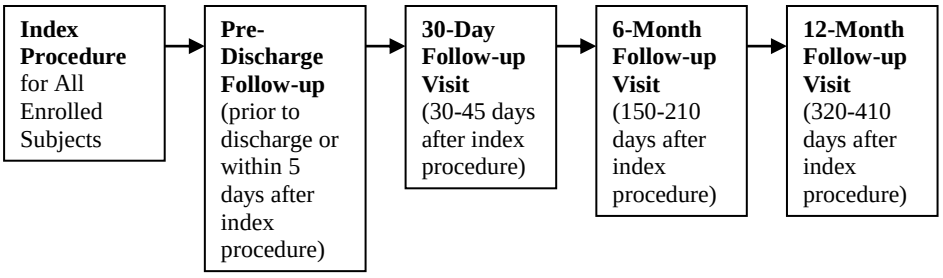


Figure 2: Study Diagram of Follow-up Requirements

4.22 Pre-discharge Follow-up Requirements

All subjects are required to have a pre-discharge assessment. Pre-discharge assessment requirements are listed in Table 3.

Table 3: Pre-Discharge Assessment Requirements

Pre-Discharge Requirements	Timeframe
Adverse event evaluation	Prior to discharge (or within 5 days after index procedure)
Duplex Ultrasound*	
**** First duplex ultrasound can occur any time within 45 days of the procedure.*** *Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.*	

4.23 Follow-up Visit Requirements

All subjects are required to have a follow-up visit at 30 days, 6 months, and 1 year post-procedure. Tables 4-6 below list the follow-up assessment requirements and visit windows, according to number days following the index procedure.

Table 4: 30-Day Follow-Up Visit Requirements

Follow-up Requirements	Target	Window
Rutherford Clinical Category assessment	30 Days	30-45 Days
Ankle-brachial index		
WIQ		

Duplex Ultrasound*		
Adverse event evaluation		
**** First duplex ultrasound can occur any time within 45 days of the procedure.*** *Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Ultrasound Core Laboratory for review.*		

Table 5: 6-Month Follow-Up Visit Requirements

Follow-up Requirements	Target	Window
Rutherford Clinical Category assessment	180 Days	150-210 Days
Ankle-brachial index		
WIQ		
Duplex Ultrasound*		
Adverse event evaluation		
**Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.*		

Table 6: 1-Year Follow-up Visit Requirements

Follow-up Requirements	Target	Window
Hemoglobin A1C	365 Days	320-410 Days
Creatinine		
Rutherford Clinical Category assessment		
Ankle-brachial index		
WIQ		
Duplex Ultrasound*		
Adverse event evaluation		
**Must be conducted per the Core Laboratory Protocols. Copies must be sent to the Core Laboratories for review.*		

4.24 Unscheduled and Re-intervention Visits During Follow-up

Completion of study assessments at unscheduled follow-up visits prior to the 1-year visit should be done as clinically indicated and corresponding data should be documented and submitted to the Sponsor.

If a subject is clinically indicated for a re-intervention of the target lesion prior to the 1-year follow-up visit and the subject does not want to proceed with an invasive angiogram or re-intervention, it will not be considered a deviation from the Study Protocol. If possible, all non-invasive assessments should be captured for the study, including ABI, RCC, WIQ, and duplex ultrasound, even if the re-intervention and angiogram are declined. Copies of any angiographic or duplex ultrasound results must be sent to the appropriate core laboratory. These data will be collected and used for adjudication by the Clinical Event Committee for "clinically-driven" reintervention.

4.25 Termination of Participation

All subjects have the right to withdraw from participation at any point during the study. In addition, Principal Investigators also have the ability to terminate subject participation in the

study. A description of the reason for a subject's termination will be documented. Reasons for termination include: subject withdrawal, physician-directed subject withdrawal, and lost-to-follow-up.

4.26 Lost to Follow-Up

Every attempt must be made to have all subjects complete the required follow-up visits according to the visit schedule. A subject will not be considered lost-to-follow-up unless efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three attempts to make contact via telephone. Telephone contact efforts to obtain follow-up must be documented in both the subject's medical records and on the study electronic case report forms (eCRFs).

4.27 Subject Withdrawal

Whenever possible, the site staff should obtain written documentation from the subject that wishes to withdraw his/her consent for future follow-up visits and contact. If the site staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate eCRFs must be completed for the subject and clear documentation of the subject's withdrawal must be provided to the Sponsor.

Withdrawal of a subject from the study can occur at the discretion of the Principal Investigator or the Sponsor. Reasons for physician and/or Sponsor-directed subject withdrawal include, but are not limited to: the subject is not adhering to the Study Protocol requirements, the subject has enrolled in another study that conflicts with this Study Protocol outcomes, or if it is in the best interest for the safety or welfare of the subject to withdraw.

4.28 Deviations to the Study

Principal Investigators and site staffs should avoid Study Protocol deviations. Any deviations from clinical protocol requirements will be considered protocol deviations and need to be reported to the Sponsor. Any emergency deviations (deviations from the Study Protocol to protect the life or physical well being of a subject, such as, surgical repair of the target vessel) that occur must be reported to the Sponsor and the site Ethics Committee (EC) per their local guidelines.

4.29 Adverse Events

4.29.1 Adverse Event Definitions

Serious Adverse Event (SAE) is defined as any untoward and unintended clinical sign, symptom, or disease in a subject, regardless of the relationship between the adverse event and the device under investigation, that:

- Led to a death,
- Led to a serious deterioration in the health of the subject that:
    1. Resulted in a life-threatening illness or injury,

2. Resulted in a permanent impairment of a body structure or a body function,
3. Required inpatient hospitalization or prolongation of existing hospitalization, or
4. Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or body function.

- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

A written report must be provided to the Sponsor or representative within 24 hours of the Investigator learning of an SAE and must be provided to the EC according to reporting guidelines.

4.29.2 Adverse Event Classifications

In addition to the definitions above, adverse events will be classified as follows:

Major Adverse Events

1. **In-hospital Major Adverse Event Rate**: all-cause mortality, perforation requiring additional treatment, distal embolization requiring additional mechanical or pharmacological treatment, major bleeding as defined by the Thrombolysis in Myocardial Infarction criteria, vascular access site complications requiring transfusion and/or surgical repair, acute stent thrombosis as defined by the Academic Research Consortium, unplanned major or minor amputation
2. **Major Adverse Event Rate at 30 Days:** Defined as major or minor unplanned amputation of the treated limb, vascular access site complications requiring transfusion and/or surgical repair, all-cause mortality, acute thrombosis, or clinically-driven target vessel revascularization.
3. **Major Adverse Events at 1 year:** Defined as major or minor unplanned amputation of the treated limb, all-cause mortality or target lesion revascularization (TLR).

Unanticipated or Unexpected Adverse Device Effects: 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 protocol 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.

4.29.3 Adverse Event Relationships

The Investigators will evaluate whether or not the adverse events were related to the procedure, study requirements, and/or investigational products (e.g., JS device, angioplasty balloon, drug coating) according to the following categories:

Related: AE that has a strong temporal relationship to the study procedure, a study requirement, or the presence or performance of the investigational device/system or drug and an alternative etiology is highly unlikely.

Possibly Related: AE that has a temporal relationship to the study procedure, a study requirement, or the presence or performance of the investigational device/system or drug and an alternative etiology is unlikely.

Not Related: AE is due to the underlying disease state or concomitant medication or therapy, and was not caused by the study procedure, a study requirement, or the investigational device/system or drug.

Not Assessable: It is not possible to assess whether or not the adverse event is related to the study procedure, a study requirement, or the investigational device/system or drug.

4.30 Deaths

Each subject death must be reported to the Sponsor. A death must be reported to the Sponsor or representative as soon as possible (within 24 hours) after the site's knowledge of the event. A written report will be provided to the Sponsor within 10 business days after the Investigator learns of a death and will be provided to the EC according to reporting guidelines. It is requested that a copy of the death certificate, autopsy report, and any other source documents related to the death be sent to the Sponsor or representative when available. In the event that no source documents are available, the PI will be required to submit a letter to the Sponsor describing the circumstances of the subject's death.

4.31 Core Laboratory Requirements

4.31.1 Angiographic Core Laboratory

An independent Angiographic Core Laboratory will review all scheduled and unscheduled angiographic procedure data. See Core Lab Angiographic Protocol.

4.31.2 Ultrasound Core Laboratory

An independent Ultrasound Core Laboratory will review all scheduled and unscheduled duplex scans and intravascular ultrasounds. See Core Lab Duplex Ultrasound Protocol.

4.31.3 IVUS Core Laboratory

An independent IVUS Core Laboratory will review all scheduled and unscheduled duplex scans and intravascular ultrasounds. See Core Lab IVUS Protocol.

4.32 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be established. The CEC will consist of physicians who are not Investigators in the study and who do not have any significant investment in Boston Scientific, Bard or any of their entities. The committee may include, but not be limited to, the specialties of interventional cardiology, vascular surgery, and interventional radiology.

The CEC is responsible for reviewing all reported adverse events. The CEC will classify the pertinent outcome events as defined in the Study Protocol.

4.33 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established. The DSMB will consist of a biostatistician and physicians from a variety of relevant medical specialties, including interventional cardiology, vascular surgery, and interventional radiology, who are not Investigators in the study. Members will not have any significant investment in Boston Scientific or Bard, or any of their entities.

The role of the DSMB will be to monitor and make recommendations regarding the protocol and the overall conduct of the study, to ensure the rights, safety, and welfare of the study participants, and to evaluate interim data to determine if there are any specific safety concerns.

The DSMB will convene when 30-day safety data are available for 100 randomized subjects. Subsequently, the DSMB will review the data at time intervals per their discretion.

4.34 Case Report Forms

Electronic case report forms (eCRFs) will be used to collect study data. The eCRFs will be reviewed and electronically signed by the Principal Investigator. All appropriate sections of the eCRFs must be completed.

The Sponsor will use the study data for statistical and tracking purposes and will treat the information as confidential.

5. STATISTICAL METHODS

5.24 Sample Size

250 subjects are planned for enrollment (with a block 2:1 randomization; 167 JS + DCB). Sample size is based on the primary analysis of ITT TLR (bail out stent in the cath lab is considered TLR) at 1 year.

It is assumed that TLR in the PCB alone will be 45% (including bailout stenting in the lab) and in the JS + PCB will be 25%. We will need to study 144 experimental subjects and 72 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate this null hypothesis. Accounting for 15% loss of patients on follow up, the total number that will be enrolled will be 250 patients.

5.25 Data Analysis Plan

5.25.1 General Principles

All statistical analyses will be performed using a widely accepted statistical or graphical software. An intention to treat analysis will be carried on with bailout stenting as TLR and without bail out stenting as TLR. Also analysis will be done by actual treatment.

Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.

For AE reporting, the primary analysis will be based on subject counts. A subject with more than one event will be counted only once toward the event rate based on the total number of subjects with AEs. An event rate based on event counts will also be presented. For example, if a subject experiences one major unplanned amputation of the treated limb and two clinically-driven TLRs within 30 days, the subject will be counted once in the rate of total subjects with a 30-day MAE; the same subject will be counted once in the individual event category of "Major Unplanned Amputation of the Treated Limb" and twice in the "Clinically-Driven TLR" category.

5.25.2 Analysis of Baseline Demographics and Procedural Characteristics

All clinically relevant baseline demographics and procedure characteristics will be tabulated for the randomized and non-randomized treatment arms. For categorical variables, differences between the randomized arms will be tested using appropriate contingency table analyses (Exact or Chi-square approximations). For continuous variables, the differences will be tested using unpaired Student's t-test or a nonparametric test, depending on variable distribution.

5.25.3 Analysis of Outcomes

Study outcomes including the primary outcome will be provided by treatment group for both the randomized and non-randomized treatment arms and will be compared using standard statistical methods when appropriate. It is acknowledged that these analyses are for exploratory purposes only, because the study is not designed to have adequate power for such analyses.

5.25.4 Analysis of Ability to Pool Data across Investigational Sites

This is a multi-center clinical study with standardization of subject enrollment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, and common data collection procedures and forms. To present the data from this clinical study in a summary form, a comparison across all sites will be completed to determine if the generated data can be pooled.

Potential site effects on the primary outcome will be explored. In addition, a comparison of variables will be completed to assess the appropriateness of pooling data from across all sites.

6. RISK/BENEFIT ANALYSIS

The study is designed to minimize risk through observance of strict site and Investigator selection criteria, careful subject selection and management, and rigorous adherence to a standardized schedule of post-procedure evaluations.

6.24 Potential Benefits

There are no guaranteed benefits from participation in this study; however, it has been shown that treatment with plaque excision or DCB improves blood flow through the treated artery in some patients. Information gained from the conduct of this study may be of benefit to other persons with the same medical condition.

6.25 Potential Risks

6.25.1 Risks Associated with Plaque Excision

The risks associated with JS atherectomy of the SFA and/or popliteal artery may include, but are not limited to, the following:

- Access site complications
- Amputation
- Arterial dissection
- Arterial perforation
- Arterial rupture
- Arterial spasm
- Arterial thrombosis
- Arterio-venous (AV) fistula
- Bleeding complications
- Death
- Embolism
- Emergency or non-emergency arterial bypass surgery
- Hypotension
- Infection
- Ischemia
- Restenosis of the treated segment
- Total occlusion of the peripheral artery
- Vascular complications which may require surgical repair

As with any device requiring mechanical deployment and retraction, there exists a risk of mechanical failure of the device resulting in potential surgical intervention.

All of the above could cause prolonged illness, permanent impairment of daily function or, in rare cases, death. Possible treatments could include, but are not limited to, vascular surgery.

Extensive reliability engineering testing has been performed on the study device to mitigate risks to the subject due to product failure. Additionally, studies using the JS device have been conducted to ensure that the systems perform as intended without introducing more risks during the index procedure or during follow-up. Risks of atherectomy may be further limited by providing medications such as aspirin or clopidogrel and continuing to monitor subjects following treatment.

While some of the potential risks identified have occurred in prior atherectomy trials, and while Boston Scientific believes that the risk for significant injury or death due to the JS XC device is quite low, these risks have yet to be adequately and fully quantified. .

6.25.2 Risks Associated with Ranger DCB

Subjects undergoing percutaneous intervention with Ranger DCB may be at risk for bleeding and vascular complications that require surgical repair or additional treatments. The severity of the event may be mild to requiring emergent action or even result in death.

The risks associated with the use of the DCB, the procedure, and/or the concomitant medications may included, but are not limited to, the following anticipated adverse events:

- Amputation (minor or major)
- Access site complications (bleeding, pain, tenderness)
- Abrupt occlusion of the treated artery
- Allergic reaction to the dye used during the procedure
- Allergic reaction to the balloon material, the contrast medium used, or other procedural medications used
- Arterio-venous (AV) fistula
- Cardiac complications (angina, myocardial infarction, irregular heart beat)
- Compromised renal function
- Death
- Embolism (including air or plaque)
- Emergency surgery to repair a damaged artery
- Hematoma, hemorrhage, transfusion
- Hyperperfusion injury to the treated limb
- Hypotension or hypertension
- Infection
- Medication side effects (GI upset, diarrhea, rash, bleeding disorders)
- Neurologic complications (transient or permanent)
- Pseudoaneurysm formation
- Pyrogenic reaction (fever)
- Restenosis of the dilated artery
- Surgical bypass for lower extremity
- Thromboembolic events with transient or permanent ischemia or infarction
- Vascular dissection or perforation with stenosis or occlusion
- Vascular spasm
- Vessel thrombosis

Potential adverse events not captured above, that may be unique to the paclitaxel drug coating, include the following:

- Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds)
- 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
- Potential drug interactions which may occur with any drug that affects CYP2C8 and CYP3A4 isoenzymes.

7. SITE REQUIREMENTS

7.24 Site Selection

The Sponsor or a representative of the Sponsor will evaluate each potential site to ensure the Principal Investigator and his/her staff has the facilities and expertise required for the study.

Principal Investigators, Sub-Investigators and sites will be selected based upon the following factors, including, but not limited to:

- Previous experience with clinical research and percutaneous procedures, including experience treating lower extremity arteries with the JS device
- Currently treating patients who meet the inclusion/exclusion criteria
- Ability to enroll an adequate number of subjects in the study
- Ability to perform required clinical testing, including angiography, IVUS and duplex ultrasound
- Ability and willingness to provide the Sponsor's representatives access to the hospital records, study files, and subject files as they pertain to the study
- Willingness to participate, including adherence to all study requirements
- Adequate staff to conduct the study.

7.25 Training/Initiation Visit

The Sponsor or a representative of the Sponsor will conduct a training session with each Investigator and his/her staff to review the Study Protocol, IFU of the study devices, eCRFs, the informed consent process, Ethics Committee (EC) involvement and guidelines, responsibilities and obligations, reporting requirements, and general guidelines for good clinical practices.

Prior to enrolling subjects at a study site, the following documentation must be provided to the Sponsor:

- EC approval for the Study Protocol
- EC approval for the Principal Investigator to conduct the study
- EC and Sponsor approved Informed Consent Form for the study
- Investigator(s') curriculum vitae (CV)
- Signed Investigator Agreement and if applicable, Sub-Investigator Agreement(s)
- Completed training documentation form (provided by Sponsor or representative) to verify the appropriate study staff has been trained accordingly.

8. MONITORING PROCEDURES

8.24 Monitoring Procedures

MCRF as the Sponsor will be responsible for ensuring that adequate monitoring at each site is completed to ensure protection of the rights and safety of subjects, and the quality and integrity of the data collected and submitted. Appropriately trained personnel appointed or subcontracted by MCRF will conduct monitoring at each site. Monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, compliance with applicable laws

and regulations, compliance with the Study Protocol, compliance with the signed investigator agreement, and compliance with EC conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the Principal Investigator/site staff is cause for the Sponsor to put the Investigator/site staff on probation or withdraw the Investigator/site staff from the study. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

8.25 Monitoring Reports

After each monitoring visit, the monitor will send to the Principal Investigator a letter summarizing the monitoring visit. A monitoring report will be kept on file. The Principal Investigator will be responsible for ensuring that follow-up actions needed to resolve issues at the site are completed in an accurate and timely manner.

8.26 Final Monitoring Visit

Final monitoring visits at the sites will be conducted at the close of the study. The purpose of the final visit is to collect all outstanding study data documents, ensure that the Principal Investigator's files are accurate and complete, review record retention requirements with the Principal Investigator, make a final accounting of all investigational devices shipped to the Principal Investigator/site, provide for appropriate disposition of any remaining supplies, and ensure that all applicable study requirements are met.

9. RESPONSIBILITIES, RECORDS and REPORTS

9.24 Responsibilities and Record Retention

The Principal Investigator/site must maintain adequate records on all aspects of the study, including the following:

- Ethics Committee approvals
- Informed Consent Forms
- Case Report Forms
- Serious Adverse Events (and source documents)
- Subject termination information
- Study Protocol Deviations
- Correspondence file regarding study

The Principal Investigator/site must maintain the study records for at least two years after cessation of the study and must contact the Sponsor prior to disposal of study records.

9.25 Reports

Reports that are the Principal Investigator's responsibility to generate are listed in Table 7. The table also displays information regarding to whom this information is to be sent, and the frequency and time constraints around report submission. If applicable laws, regulations, or EC requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 7: Principal Investigator Reporting Responsibilities

Type of Report	Principal Investigator Reporting Responsibilities

	Report Prepared For	Reporting Time Frame
Serious Adverse Events or Serious Adverse Device Effects	Sponsor and EC	ASAP, but to Sponsor or representative within 24 hours of when Investigator is first aware of the event. To EC according to local guidelines.
Withdrawal of EC approval (or other action on the part of the EC that affects the study)	Sponsor	Within 5 working days of EC decision.
Progress reports	Sponsor and EC	At intervals dictated by the EC, but no less than yearly.
Emergency protocol deviations	Sponsor and EC	ASAP, but to Sponsor no later than 5 working days after the deviation occurs. To EC according to local guidelines.
Use of inappropriate Informed Consent Form	Sponsor and EC	To Sponsor within 5 working days after the deviation occurs. To EC according to local guidelines.
Final report	Sponsor and EC	To Sponsor within 3 months after termination or completion of study or Investigator's participation. To EC according to local guidelines.
Other	As Required	Upon request by the EC to provide accurate, complete, and current information about any aspect of the study.

9.26 Records Custody

An Investigator may withdraw from the study. If the Principal Investigator withdraws from the study, responsibility for follow-up and maintaining the records must be transferred to a responsible party (such as another study Investigator). Notice of transfer must be provided in writing by the Principal Investigator to the Sponsor and the EC no later than 10 working days after transfer occurs.

10.DATA and QUALITY MANAGEMENT

A full-featured relational database will be on a secure central server that is backed up regularly. The server will be accessible by password for all approved users via the internet, and data analytical workstations will be used for data processing and management. Conventional data verification sub-routines will be extensively programmed to test entry and logical errors, while all individual (subject-based) eCRFs will be linked for cross-reference. Periodic analysis of each data field (across subjects) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. Corrections to data mistakes will be requested via queries. Each completed query response must be verified by the Investigator (or designee) and submitted.

All information and data concerning subjects or their participation in this study will be considered confidential. Only authorized personnel will have access to these confidential files. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject.

11.PUBLICATION STRATEGY

At the conclusion of all 1-year follow-up visits, a multi-site abstract reporting the results will be prepared and presented at one or more major national or international endovascular meetings by the national Principal Investigator Dr Nicolas W Shammas. Other presentations following the

presentation of the main findings of the study may be presented by other investigators based on interest and number of patients enrolled in the study. In all presentations the Sponsor needs to be clearly identified as the Midwest Cardiovascular Research Foundation and the Grantor as Boston Scientific. All presentations and publications from this study has to be approved by the Sponsor 30 days prior to presentation or submission for publication. A multi-site publication may also be prepared for print in a peer-reviewed scientific journal at the conclusion of the study. The study Principal Investigator and chairman Dr Nicolas W Shammas will be the leading author on the main multicenter manuscript. Up to 9 additional co-authors, including the Co-Principal Investigator, site and core lab main investigators will be added to the main and IVUS substudy manuscripts by order of number of patients enrolled in the study or degree of involvement in the project. Investigators deemed to have significant protocol deviations may not be considered as authors.

The publication of results from any single-site experience within the study must not be submitted for publication until approval from the Sponsor is granted and only after presentation of the main study data and submission of the main manuscript for publication

A proposal for a publication will be sent to the Sponsor for review and approval. MCRF will review and approve all publications for presentation at any meeting or for publications in journals or magazines. A significant contribution by each author is expected for authorship. The national PI Dr Nicolas Shammas will review, approve and co-author proposed secondary publications.

12.DEFINITIONS

Abrupt Closure: Vessel occlusion at the site of treatment within 24 hours after successful index procedure.

Access Site Complications: Adverse sequelae at the access site as a result from cathether-based interventions, including arterio-venous fistula, bleeding, hematoma, infection and pseudoaneurysm.

Adjunctive Treatment: A procedure performed after treatment with the protocol-defined treatment (JS + DCB or DCB) to treat major flow limiting dissection (grade D or greater), perforations, occlusive complications (i.e. recoil) or residual stenosis greater than 30% in the target lesion.

Adverse Event: Any untoward and unintended clinical sign, symptom, or disease in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Adverse Event Definitions: Reportable Events

Serious Adverse Event (SAE)	An adverse event that led to a death or led to a serious deterioration in the health of the subject that 1) resulted in a life-threatening illness or injury, 2) resulted in a permanent impairment of a body structure or a body function, 3) required inpatient hospitalization or prolongation of existing hospitalization, or 4) resulted in medical or surgical intervention to prevent permanent impairment to a body structure or body function. This definition also includes any adverse event that led to fetal distress, fetal death or a congenital abnormality or birth defect.
Major Adverse Events	1. **In-hospital Major Adverse Event Rate**: all-cause mortality, perforation requiring additional treatment, distal embolization requiring additional mechanical or pharmacological treatment, major bleeding as defined by the Thrombolysis in Myocardial Infarction criteria, vascular access site complications requiring transfusion and/or surgical repair, acute stent thrombosis as defined by the Academic Research Consortium, unplanned major or minor amputation 2. **Major Adverse Event Rate at 30 Days:** Defined as major or minor unplanned amputation of the treated limb, vascular access site complications requiring transfusion and/or surgical repair, all-cause mortality, acute thrombosis, or clinically-driven target vessel revascularization. 3. **Major Adverse Events at 1 year:** Defined as major or minor unplanned amputation of the treated limb, all-cause mortality or target lesion revascularization (TLR).

UADE	**Unanticipated or Unexpected Adverse Device Effects:** 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 protocol 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.

Adverse Event Relationship Categories:

Related: AE that has a strong temporal relationship to the study procedure, a study requirement, or the presence or performance of the investigational device/system or drug and an alternative etiology is highly unlikely.

Possibly Related: AE that has a temporal relationship to the study procedure, a study requirement, or the presence or performance of the investigational device/system or drug and an alternative etiology is unlikely.

Not Related: AE is due to the underlying disease state or concomitant medication or therapy, and was not caused by the study procedure, a study requirement, or the investigational device/system or drug.

Not Assessable: It is not possible to assess whether or not the adverse event is related to the study procedure, a study requirement, or the investigational device/system or drug.

Amputation:

Major Unplanned Amputation: Surgical removal of a limb or a part of a limb above the metatarsal line where prosthesis is required for standing or walking, that was unanticipated prior to the index procedure.

Minor Amputation: Surgical removal of toes at or below metatarsus preserving functionality of foot.

Aneurysm: A localized, pathological, blood-filled dilatation of a blood vessel caused by a weakening of the vessel wall.

Ankle-Brachial Index (ABI): The ratio of the highest ankle systolic pressure to the highest brachial systolic pressure.

Artery Dissection: Intimal disruption of the vessel wall with or without medial or adventitial contrast staining. See also **National Heart, Lung and Blood Institute (NHLBI) Classification of Dissection.**

Artery Perforation: Identifiable by extravasation of contrast media outside the arterial adventitial space.

Artery Rupture: Large transmural disruption of a vessel with gross extravasation and hemorrhage.

Arterio-venous (AV) Fistula: A communication between an artery and a vein in which the arterial blood flows directly into a neighboring vein.

Bleeding: Blood loss resulting from the percutaneous interventional procedure or adjunctive drug therapy that may require transfusion of blood products.

Chronic Renal Insufficiency: Dialysis dependent, or eGFR < 30 ml/min or creatinine >2.5.

Clinically Significant Distal Embolism: A clinically relevant obstruction of a blood vessel by a foreign substance (plaque or debris) or a blood clot that requires further mechanical or pharmacologic treatment besides vasodilators. Clinical relevance is determined either by a surgical or medical intervention and/or the presence of symptoms (i.e. decreased ABI, symptomatic claudication, etc).

Compressible Artery: An artery without significant calcification that can be evaluated by duplex ultrasound or an artery that results in an ABI value < 1.3.

Death: The termination of life.

Device Outcome: Categorized by < 50% residual stenosis following the protocol-defined treatment (POBA + PCB or JS + PCB) and prior to bail out stenting at the target lesion as determined by the Angiographic Core Laboratory.

Diabetes (History of): Defined as patients who have been diagnosed with either Type I or Type II diabetes and are currently taking oral hypoglycemics or insulin or have a hemoglobin A1C > 7%.

Discharge: The time point when the subject is released from the admitting hospital, transferred to another facility, or has expired.

Distal Embolization: Migration of air, plaque, thrombus, or debris that occludes the distal target vessel or one of its branches.

Embolism: Obstruction of a blood vessel by a foreign substance (air, plaque, debris) or a blood clot.

Emergent Surgical Revascularization: Surgery performed on an urgent or emergent basis as a result of the PTA procedure and/or use of a study device.

Enrollment: The subject is enrolled in the study after he/she has signed the patient informed consent and has been determined to meet all inclusion and none of the exclusion criteria. The point of enrollment is defined as the moment an exchangeable guidewire and treatment catheter cross the target lesion in the true lumen.

Fever: An increase in internal body temperature to levels that are above normal (37°C, 98.6°F).

Gastrointestinal (GI) bleeding: any bleeding that starts in the gastrointestinal tract, which may extend from the mouth to the anus.

Hematoma: Localized mass of extravasated blood ≥ 5 cm that prolongs hospitalization.

Hemorrhage: Bleeding requiring hospitalization, repeat procedure, operation or transfusion.

Hypertension: Increase in systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg.

Hypotension: Fall in systolic blood pressure that requires intravenous treatment with vasopressors or inotropic agents.

Index Procedure: The procedure in which the subject has the study procedure performed or attempted.

Infection: Inflammation caused by bacterial or viral sources, such as, urinary tract infection, puncture site infection, sepsis, endocarditis, and bacteremia from IV site.

Inflammation: An immunologic response to infection or trauma that can result in localized redness, swelling, heat, pain and dysfunction of the organs involved.

Inflow Tract: Vascular access point to the area of the target lesion.

Intraluminal thrombus: A blood clot within a vessel.

Intimal Flap: Superficial dissection of the vessel that does not result in medial or adventitial contrast staining (NHLBI Type A dissection).

Invasive Assessment/Procedure: Any assessment, intervention or therapy that penetrates the skin, excluding administration of parenteral fluids or drugs.

Ischemia: a restriction in arterial blood flow by stenosis, restenosis or occlusion that, if prolonged, can lead to tissue damage.

Major bleed by TIMI criteria: Loss of more than 5 gm/dl of Hemoglobin or the need to transfuse 5 Units of blood or intracranial bleed

Minor Bleed by TIMI criteria: a bleed other than non TIMI major bleed

Myocardial Infarction (Non-Q wave): Post-treatment elevation of CK-MB more than 3 times the upper limit of lab normal value without evidence of pathologic Q-waves present on EKG. Elevated serum troponin levels are not sufficiently validated to be considered sole evidence of an MI in the absence of CK-MB elevations.

Myocardial Infarction (Q wave): Development/appearance of new pathological Q-waves in more than 2 contiguous leads per 12-lead electrocardiogram (EKG/ECG).

National Heart, Lung and Blood Institute (NHLBI) Classification of Dissection:[27]

Dissection	Description
Type A	Small radiolucent area within the lumen of the vessel disappearing with the passage of 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 delayed runoff of the contrast material in the distal vessel
Type E	Persistent luminal filling defect with delayed runoff of the contrast material in the distal vessel
Type F	Filling defect accompanied by total coronary occlusion

Net Lumen: The difference between the target lesion minimum lumen diameter at baseline and at follow-up per angiographic assessment.

Occlusion: An obstruction within an artery.

Patency Classifications:

- **Patency via Duplex (Peak Systolic Velocity ≤ 2.4):** Defined by duplex ultrasound measurement of peak systolic velocity (PSV) ratio ≤ 2.4 at the target lesion.
- **Patency via angiography:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory.
- **Assisted Patency via angiography:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, maintained by repeat percutaneous intervention

Percent Stenosis: Native vessel diameter as measured at the most narrow point of the lesion divided by the estimated native vessel diameter (the mean of the vessel diameters proximal and distal to the lesion) at that location.

$$\% \text{ Stenosis} = \frac{Diameter\ at\ most\ narrow\ segment\ of\ lesion\ (mm)}{\left[\left(proximal\ vessel\ diameter + distal\ vessel\ diameter\right)/2\right]}$$

Physician-Directed Subject Withdrawal: Withdrawal of a subject from the study at the direction of the Principal Investigator. Reasons for physician-directed subject withdrawal include, but are not exclusive to: the subject is not adhering to the Study Protocol requirements, the subject has enrolled in another study that conflicts with the JET-PCB outcomes of interest, or the physician deems it in the best interest for the safety or welfare of the subject to withdraw.

Pre-Procedure: The time until the procedure begins (before arterial access is obtained).

Principal Investigator: Physician responsible for overall clinical management of subjects enrolled at his/her institution. Assumes overall responsibility and accountability for the clinical team and for data obtained from each subject participating in the study. Ensures compliance with the Study Protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs eCRF indicating documents are accurate and complete.

Protocol Deviation: Any divergence from the Study Protocol.

Pseudoaneurysm: Perforation of the vessel with arterial blood flow outside of the vessel.

Renal Failure: Failure of the kidneys to perform essential functions that requires dialysis.

Runoff Vessel: An artery distal to treated vessel, including the popliteal, peroneal tibials and the dorsalis pedis.

Rutherford Clinical Category: A classification system of clinical categories of chronic limb ischemia ranging from 0 to 6. The categories and clinical descriptions are:

Category	Clinical Description
0	Asymptomatic--no hemodynamically significant occlusive disease
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4*	Ischemic rest pain
5*	Minor tissue loss—non-healing ulcer, focal gangrene with diffuse pedal ischemia
6*	Major tissue loss--extending above TM level, functional foot no longer salvageable

*Categories 4, 5, and 6 are embraced by the term chronic *critical* ischemia.†Five minutes at 2 mph on a 12% incline.

Sepsis: Systemic inflammatory response to infection.

Serious Adverse Event: Any adverse events that led to a death or led to a serious deterioration in the health of the subject that 1) resulted in a life-threatening illness or injury, 2) resulted in a permanent impairment of a body structure or a body function, 3) required inpatient hospitalization or prolongation of existing hospitalization, or 4) resulted in medical or surgical intervention to prevent permanent impairment to a body structure or body function. This definition also includes any adverse event that led to fetal distress, fetal death or a congenital abnormality or birth defect.

Severe or Moderate Calcification: Grade 2 or higher as defined by the Peripheral Arterial Calcium Scoring System (PACSS)[26]

Proposed Fluoroscopy/DSA based Peripheral Arterial Calcification Scoring System **(PACSS)**: Intimal and medial vessel wall calcification at the target lesion site as assessed by high intensity fluoroscopy and digital subtraction angiography (DSA) assessed in the AP projection.

Grade 0: No visible calcium at the target lesion site

Grade 1: unilateral calcification < 5cm; a) intimal calcification; b) medial calcification; c) mixed type

Grade 2: unilateral calcification ≥ 5cm; a) intimal calcification; b) medial calcification; c) mixed type

Grade 3: bilateral calcification < 5cm; a) intimal calcification; b) medial calcification; c) mixed type

Grade 4: bilateral calcification ≥ 5cm; a) intimal calcification; b) medial calcification; c) mixed type

Stenosis: An abnormal narrowing of an artery.

Stroke: Neurological dysfunction caused by a brain disturbance or ischemia, with clinical symptoms lasting >24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms.

Study Coordinator: Employee at study site who assists Principal Investigator with study activities as delegated by the Principal Investigator, including tracking subjects involved in the study, scheduling testing and follow-up visits, maintaining study records, completing and providing eCRFs to the Sponsor in a timely manner.

Sub-acute Closure: Vessel occlusion at the site of treatment between 24 hours and 4 weeks after successful index procedure.

Sub-Investigator(s): Physician(s) responsible for study activities in coordination with Principal Investigator and in accordance to the Study Protocol.

Systemic Infection: the bloodstream infection that affects a number of organs and/or tissues, or affects the body as a whole.

Target Lesion: The lesion meeting all of the angiographic inclusion criteria and none of the exclusion criteria is the target lesion. Only one target lesion is allowed per subject.

Target Lesion Revascularization (TLR): Re-treatment by an invasive procedure, including atherectomy, angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter of the target lesion. TLRs will be classified as clinically-

driven or non-clinically driven through an adjudication process. Diameter stenosis will be determined per Angiographic Core Laboratory assessment.

Clinically-Driven Target Lesion Revascularization: any reintervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis (PSVR > 3.5 may substitute if a pre-intervention angiogram is not available) and at least one of the following: worsening Rutherford score, or an ABI drop > 0.15 from baseline.

Non-Clinically-Driven Target Lesion Revascularizations are those in which the subject undergoes a non-emergent revascularization within the target lesion for a diameter stenosis < 70% with or without any one of the following: worsening Rutherford score, or an ABI drop > 0.15 from baseline.

TASC: See Trans-Atlantic Inter-Society Consensus

Femoropopliteal TASC II classification**[33]	**Type A.** Single stenosis ≤10 cm in length Single occlusion ≤5 cm in length **Type B.** Multiple lesions (stenoses or occlusions), each ≤5 cm Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass Heavily calcified occlusion ≤5 cm in length Single popliteal stenosis **Type C** 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** Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery) Chronic total occlusion of popliteal artery and proximal trifurcation vessels ** Eur J Vasc Endovasc Surg 33, S1eS70 (2007) http://www.sirweb.org/clinical/cpg/TASC_guidelines.pdf

Thrombosis: The formation or development of thrombus inside a blood vessel, obstructing the flow of blood.

Thrombus: A blood clot within a vessel, which obstructs the flow of blood.

Total Occlusion: 100% stenosis within an artery.

Trans-Atlantic Inter-Society Consensus II (TASC II)[29]: A classification scheme for the assessment and management of peripheral arterial disease published in 2007.

Transient Ischemic Attack (TIA): Brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction.

Unanticipated or Unexpected Adverse Device Effect: 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 protocol 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.

Vessel Spasm: A sudden, brief tightening of a blood vessel.

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