Study Protocol MCRF-S-002-2015

JET-ISR Trial

JetStream Atherectomy for the Treatment of In-stent Restenosis of the Femoropopliteal Artery

Version 2

29 FEB 2016

Sponsor

Midwest Cardiovascular Research Foundation

National Principal Investigators

Nicolas W Shammas, MD, MS, FACC, FSCAI
Subhash Banerjee, MD, 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.

_____ _____/_____/_____

Principal Investigator Signature DD MMM YYYY

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Principal Investigator Printed Name

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Study Site

Study Protocol Synopsis

JET-ISR trial	
Protocol Number	MCRF-S002-2015
Devices	JetStream Navitus XC 2.1 and 2.4
Primary Purpose	The purpose of this study is to test the hypothesis that Jetstream atherectomy and adjunctive balloon angioplasty (JS +PTA) improves target lesion revascularization (TLR) at 6 months follow-up when compared to historic data from balloon angioplasty alone (PTA) in the treatment of femoropopliteal arterial In-stent restenotic (ISR) disease
Study Design	A prospective, multicenter, single arm study evaluating the investigational use of Jetstream Atherectomy (JS) *and adjunctive balloon angioplasty (JS +PTA) in the treatment of f*emoropopliteal ISR lesions in subjects with claudication or limb ischemia (Rutherford clinical category (RCC) of 2-4) (lesion length ≥ 4 cm). The comparator arm is historic data from plain old balloon angioplasty derived from a Meta-analysis of the 3 published randomized trials in the field.
Follow-Up Schedule	Follow-up assessments will occur at pre-discharge, 30 days, 6 months and 1 year following the study procedure.
Statistical assumption and analysis	Assumptions: TLR with bailout stenting from historic control from meta-analysis: 37.9% TLR with bailout stenting from Jetstream ISR feasibility study: 20.7% Power 80% Alpha 0.05 We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0.38. If the true failure rate for experimental subjects is 0.21, we will need to study 112 experimental subjects and 112 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 (meta-analysis from published randomized trials provides data on 182 controls). The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. Assumingly a loss of 20% of patients on follow-up a minimum of 134 patients will be enrolled.
Number of Sites	Up to 14 sites in the USA

Primary Outcomes	**Effectiveness: Target Lesion Revascularization (TLR) 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) **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 60 patients enrolled. Stopping rule will be based on freedom from MAE at 30 days that is > 78% (bailout stent in the PTA control arm ranged from 7 to 20% in the randomized trial. Bailout stent is included as a MAE (part of the TLR definition). If maximum bailout stent occurs (20%), this allows a 2 % amputation/death rate within 1 month before the study is stopped i.e. total events of 22%, or freedom from events of 78%).
Secondary endpoints	**1.** **Device Outcome:** Categorized by < 50% residual stenosis following JS atherectomy alone and without additional adjunctive PTA or bail out procedures as determined by the Angiographic Core Laboratory. **2.** **Procedural Outcome:** Categorized by < 30% residual stenosis following the protocol-defined treatment (JS + PTA) with provisional or bail out procedures as determined by the Angiographic Core Laboratory. **3.** **Procedural Success:** Defined as ≤30% residual diameter stenosis following JS + PTA without provisional or bailout procedures. **4.** **Target Lesion Revascularization (TLR) at 6 months (with no bailout stent included)**: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 6 months. Intra-procedural bail out stenting of the index lesion is NOT considered meeting a TLR endpoint. (ITT analysis) **5.** **Target Lesion Revascularization (TLR) at 1 year**: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 1 year ITT (bail out stent in the Lab is considered as TLR) ITT (bail out stent in the Lab is not considered as TLR) **6.** **Target Lesion Patency at 6 months and 1 year:** Defined as PSVR ≤ 2.5 at the treated site or < 50% stenosis by angiography as determined by the Angiographic Core Laboratory in the absence of TLR, amputation, and/or surgical bypass (the evaluation of patency is extended to one cm proximal and one cm distal to the target lesion) **7.** **Clinically Driven Target Lesion Revascularization at 6 months and 1 year**: Defined as any re-intervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis (Peak Systolic Velocity Ratio (PSVR) > 3.5 or on

	angiography) 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 *in the Lab is* considered as TLR) ITT (bail out stent *in the Lab is* not considered as TLR) Routine angiography in an asymptomatic patient at 6 months or 1 year is not required in this protocol. **8. Target Vessel Failure at 6 months and 1 year:** Defined as major unplanned amputation related to the treated limb, vascular mortality related to treated limb and target vessel revascularization at 6 months and 1 year (stenting in the lab is not considered a TLR/TVR) **9. Target Lesion failure at 6 months and 1 year:** Defined as major unplanned amputation related of the treated limb, vascular mortality related to treated limb and target lesion revascularization at 6 months and 1 year (stenting in the lab is not considered a TLR) **10. Major Adverse Events (MAE) as individual endpoints in-hospital and up to 30 days :** Include device-induced vascular injury as reported by the operator, amputation (major and minor unplanned), death, significant distal embolization requiring the use of pharmacologic or mechanical means to treat (other than a vasodilator), perforation (extravasation of blood outside the vessel wall), major bleeding, non-fatal myocardial infarction (defined as the occurrence of more than 20 minutes of chest pain post procedure with an increase in troponin), stroke, access complications (AV fistula and pseudoaneurysm), bail out stenting, acute renal failure (drop in crcl by > 25% from baseline), acute (≤ 24 hours) or subacute (≤ 1 month , > than 24 hours) vessel closure. **11. Major Adverse Event Rate at 6 months and 1 Year:** Defined as major unplanned amputation of the treated limb, all-cause mortality or TLR at 6 months and 1 year (bail out stent in the Lab is included as TLR) **12. 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. **13. 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). **14. 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 and baseline ABI < 0.9.

	15. **Assisted Primary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR ≤ 2.5 at 1 year, maintained by repeat percutaneous intervention of a restenotic but not occluded index lesion **16.** **Secondary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR ≤ 2.5 at 1 year, maintained by repeat percutaneous intervention of a restenotic or occluded vessel

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
PTA	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

PURPOSE

The purpose of this single arm, prospective multicenter study is to test the hypothesis that JetStream atherectomy (JS) with adjunctive balloon angioplasty (PTA) in treating femoropopliteal in-stent restenosis (FP ISR) is superior to PTA alone using core lab, adjudicated historic control, in reducing the primary outcome of target lesion revascularization (TLR) at 6 months follow-up.

DEVICE NAMES

The JetStream XC rotational and aspiration atherectomy device (JS device).

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.

JS application in treating FP ISR is off label and considered investigational

DURATION OF THE STUDY

The estimated duration of the study is approximately two years from the time of first subject enrollment to the last Study Protocol required follow-up visit. Subjects will be followed for 6 months for the primary endpoint and 1 year for the secondary endpoints.

NUMBER OF SITES AND SUBJECTS

One hundred and 40 patients (140) subjects are planned for enrollment into this prospective registry at up to 14 study sites in the United States.

PARTICIPATING INVESTIGATORS

The study National Principal Investigators are Dr. Nicolas W. Shammas, MD, MS, FACC, FSCAI and Dr Subhash Banerjee, MD, FACC, FSCAI

SPONSOR CONTACT INFORMATION

Sponsor: Midwest Cardiovascular Research Foundation
1622 E Lombard Street
Davenport, IA 52803
Phone: +1 563 3242828
Fax: +1 563 3230217

Contact: Gail Shammas, BSN, RN
Clinical Research Manager
Phone: +1 563 3200264
Email: shammasg@mcrfmd.com

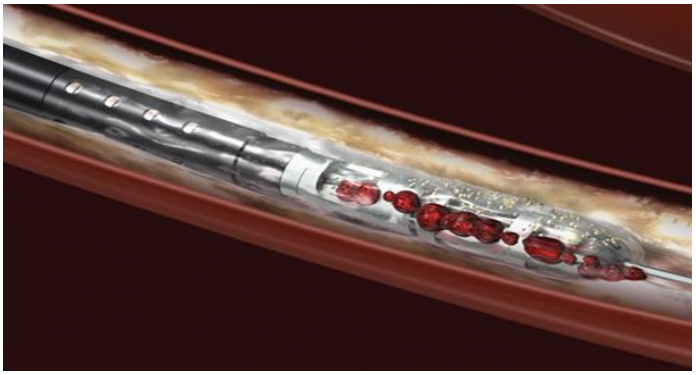
2.0 DEVICE DESCRIPTIONS

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.



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3.0 BACKGROUND AND SIGNIFICANCE

3.1 DISEASE OVERVIEW

In 2001, in the United States alone, the prevalence of peripheral arterial disease (PAD) is estimated to be 8-12 million people. Endovascular therapy has exponentially increased over the past decade and is now applied in the majority of patients undergoing PAD treatment with revascularization. The tool box to treat infrainguinal PAD has expanded significantly and includes plain old balloon angioplasty (PTA), atherectomy, stenting, specialized balloons, drug coated balloons (DCB) and Drug coated stents (DCS). In univariate analysis, PAD is more prevalent with age, men and Black population and less prevalent in Hispanic and Asians. Multivariate analysis continues to indicate that older age and Blacks are at a higher risk of PAD than the younger population or non-Hispanic Whites respectively even when adjusting for traditional risk factors such as diabetes, hypertension, hyperlipidemia, smoking and history of coronary artery disease (2b).

Several studies have shown that stenting of the femoropopliteal artery (FP) leads to higher long term patency. Bare metal stents have not shown conclusively to reduce target lesion revascularization (TLR) which is in contrast to DCB and DCS[3,4,5,6]. Irrespective, stenting has several disadvantages including a continued high rate of restenosis and stent fractures that is progressive with time[7,8]. FP ISR occurs in more than one third of patients at 1 year and up to 49% at 2 years[3-8]. Complex lesions (long, Trans-Atlantic Inter-Society Consensus II C/D lesions, total occlusions), certain demographics (female gender, diabetes mellitus), critical limb ischemia and significant stent fractures are associated with a higher rate of restenosis[9]. Also the majority of occluded stents are restenotic-thrombotic and generally are more challenging to treat.

3.2 Therapies in Treating FP ISR

Several methods have been proposed to treat FP-ISR including plain old balloon angioplasty (PTA), cryoplasty (PolarCath, Boston Scientific, Natick, Mass) , cutting balloons, drug-eluting self-expanding stents (Zilver X) (Cook Medical, Bloomington, IN, USA), rotational and aspiration atherectomy including the Rotarex S (Staub Medical AG, Wangs, Switzerland) and JetStream (Boston Scientific, Maple Grove, MN), directional atherectomy with SilverHawk (MDT, USA)), laser ablation (Excimer laser, Spectranetics, Colorado Springs, Co, USA), Viabahn covered stents (W.L.Gore and Associates, Newark, DE) and DCB[10-20].

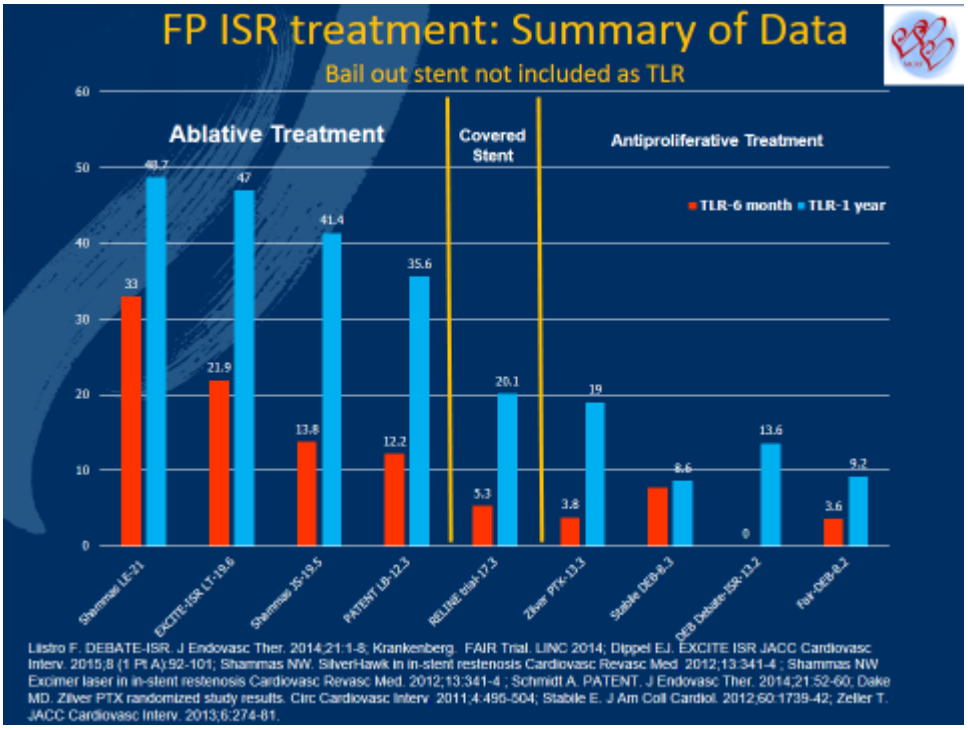
Early observational data attempted debulking of FP ISR to reduce restenotic tissue burden and theoretically delay or reduce the rate of repeat revascularization. Silingardi et al[21] reported their experience with the Rotarex S device in treating 32 patients with subacute or chronic FP (n=26) or iliac (n=6) ISR. Although technical success was 100%, primary patency at 6 months and 12 months was 75% and 58.1% respectively. On the other hand, Wissgott et al.[22] reported on 78 patients with ISR treated with the Rotarex S catheter (lesion length 147 mm). Technical success was high at 97.4% and restenosis at 1

year was remarkably low at 18.4%. SilverHawk atherectomy also showed mixed results. In a cohort of 43 patients with FP ISR (mean lesion length of 131 mm), Zeller et al[12] showed patency and TLR rates of 54% and 53% respectively at one year with the SilverHawk catheter (currently contraindicated in treating FP ISR). Given the approximate same mean lesion length (mean of 126.2 mm), Shammas et al[10], showed a TLR rate of 31.7% in 41 consecutive patients treated for FP ISR at one year with SilverHawk. Laird et al.[23]recently reported the results of the SALVAGE trial with the use of the excimer laser and the Viabahn (W.L.Gore and Associates, Newark, DE) covered stent in treating FP ISR. The primary patency at 12 months was measured by duplex ultrasonography. Twenty-seven patients were enrolled. The mean lesion length was 200.7 mm and the majority of lesions were TASC C/D. Procedural success was achieved in 100% of cases. Primary patency and TLR at 12 months were 48% and 17.4% respectively. This prospective single arm registry does not distinguish, however, between the relative effectiveness of the laser versus the Viabahn endograft stent in reducing restenosis in FP ISR lesions.

Recently 3 randomized trials were presented in treating FP ISR; the EXCITE ISR trial (randomized laser + PTA vs PTA alone), the RELINE trial (randomized Viabahn stent vs PTA) and the Randomized Femoral Artery In-Stent Restenosis (FAIR) Trial.[18,19,34]. In the GORE VIABAHN (W.L Gore and Associates, Newark, Delaware, USA) Versus Plain Old Balloon Angioplasty (PTA) for Superficial Femoral Artery (SFA) In-Stent Restenosis (RELINE) trial[19], Viabhan endograft stent was shown to be superior to PTA leading to significantly better patency rates at 1 year (37% versus 74.8% respectively). In the EXCImer Laser Randomized Controlled Study for Treatment of FemoropopliTEal In-Stent Restenosis (EXCITE ISR) trial[18], a multicenter, prospective, randomized, controlled trial conducted across 40 U.S. centers. A total of 169 ELA + PTA subjects (62.7% male; mean age 68.5 ± 9.8 years) and 81 PTA patients (61.7% male; mean age 67.8 ± 10.3 years) were enrolled. Mean lesion length was 19.6 ± 12.0 cm versus 19.3 ± 11.9 cm, and 30.5% versus 36.8% of patients exhibited total occlusion. ELA + PTA subjects demonstrated superior procedural success (93.5% vs. 82.7%; $p = 0.01$) with significantly fewer procedural complications. ELA + PTA and PTA subject 6-month freedom from TLR was 73.5% versus 51.8% ($p < 0.005$), and 30-day major adverse event rates were 5.8% versus 20.5% ($p < 0.001$), respectively. ELA + PTA was associated with a 52% reduction in TLR (hazard ratio: 0.48; 95% confidence interval: 0.31 to 0.74). This trial showed that debulking with the laser is an important strategy to reduce TLR in treating FP ISR when compared to PTA. Finally, The Randomized Femoral Artery In-Stent Restenosis (FAIR) Trial[34], randomized 119 patients with superficial femoral artery in-stent restenosis to drug coated balloon (DCB) (n=62) versus PTA (n=57). Mean lesion length was 82.2±68.4 mm. and 28.6% of lesions were totally occluded. The primary end point of recurrent in-stent restenosis assessed by ultrasound at 6 months was 15.4% (8 of 52) in the DCB and 44.7% (21 of 47) in the PTA group (P=0.002). Freedom from target lesion revascularization was 96.4% versus 81.0% (P=0.0117) at 6 months and 90.8% versus 52.6% (P<0.0001) at 12 months, respectively. No major amputation was needed. Two patients in the DCB and 3 patients in the PTA group died. No death was procedure related.

Drug coated balloons (DCB)[16,17,24] and drug coated stents (DCS)[15] have emerged as promising technology in the treatment of FP ISR. Data however is mostly applicable for short (less than 10 cm) and intermediate lesions (10-15 cm). Patency with DCB ranged from 70.5 to 92.1% with TLR from 9.2 to 13.6% at 1 year. Also in intermediate lesions, DCS using the Zilver PTX showed patency and TLR rates of 95% and 3.8% and 78.8% and 19% at 6 months and 1 year follow up respectively. Combining atherectomy and DCB may offer a superior treatment modality than either device alone. A small observational study showed that laser with DCB has a patency of 91.7% and TLR of 7.1% at a mean follow up of 19.1 months. Also DCB with directional atherectomy yielded a patency rate of 84.7% at 1 year in mean lesion length of 15.3 cm[25,26]. Studies are currently ongoing to test this hypothesis.

Below is a bar graph summarizing data from trials of FP ISR treatment.



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3.3 JetStream Atherectomy in Treating FP ISR

3.31 Preclinial Studies

Preclinical data was recently presented at CRT 2015 on the application of JetStream atherectomy in ISR and published in JEVT[29]. Below is a description of these **preGLP experiments**.

Preprocedure Animal Care

A Yorkshire swine model was chosen as the experimental animal because of the similarity to humans in terms of the size and anatomy of the cardiovascular system. Furthermore, this model has been validated for the occurrence of restenosis within 1 month of stent/balloon overstretch injury, making it more practical for testing medical devices in treating ISR. All animals were held in quarantine and housed at CBSET (Lexington, MA, USA), a facility accredited by the American Association for Accreditation of Laboratory Animal Care, under conditions that met or exceeded requirements as set forth in the USDA guidelines.[1,2] Standard veterinary practices were performed during quarantine, including physical examinations and clinical pathology to determine health status before assignment to the study. A nutritionally balanced diet appropriate for the species was offered daily to all animals with water ad lib. Animals were released from quarantine by the veterinary staff when deemed healthy.

Animal Preparation

All animals were pretreated 1 day before stent implantation with aspirin 650 orally and clopidogrel 300 mg orally. They were maintained on aspirin (81 mg daily orally) and clopidogrel (75 mg daily orally) thereafter until euthanized. Animals received Telazol (4–6 mg/kg) intramuscularly as a pre-anesthetic. Isoflurane anesthesia was then administered to effect via mask/nosecone, and endotracheal intubation was then performed. Following intubation, the animals were maintained on continuous inhalant isoflurane anesthesia delivered for the remainder of the procedure. Perioperative nifedipine (10 mg/animal placed sublingually) was also administered. The animals were prepared for surgery using accepted veterinary care standards. Electrocardiogram leads, a pulse oximetry sensor, and a temperature probe were placed for continuous monitoring of vital signs. Pre-emptive analgesia (buprenorphine; 0.01–0.03 mg/kg), was administered intramuscularly at anesthesia (prior to surgical incision). The incision site was prepared and appropriately draped for aseptic procedures.

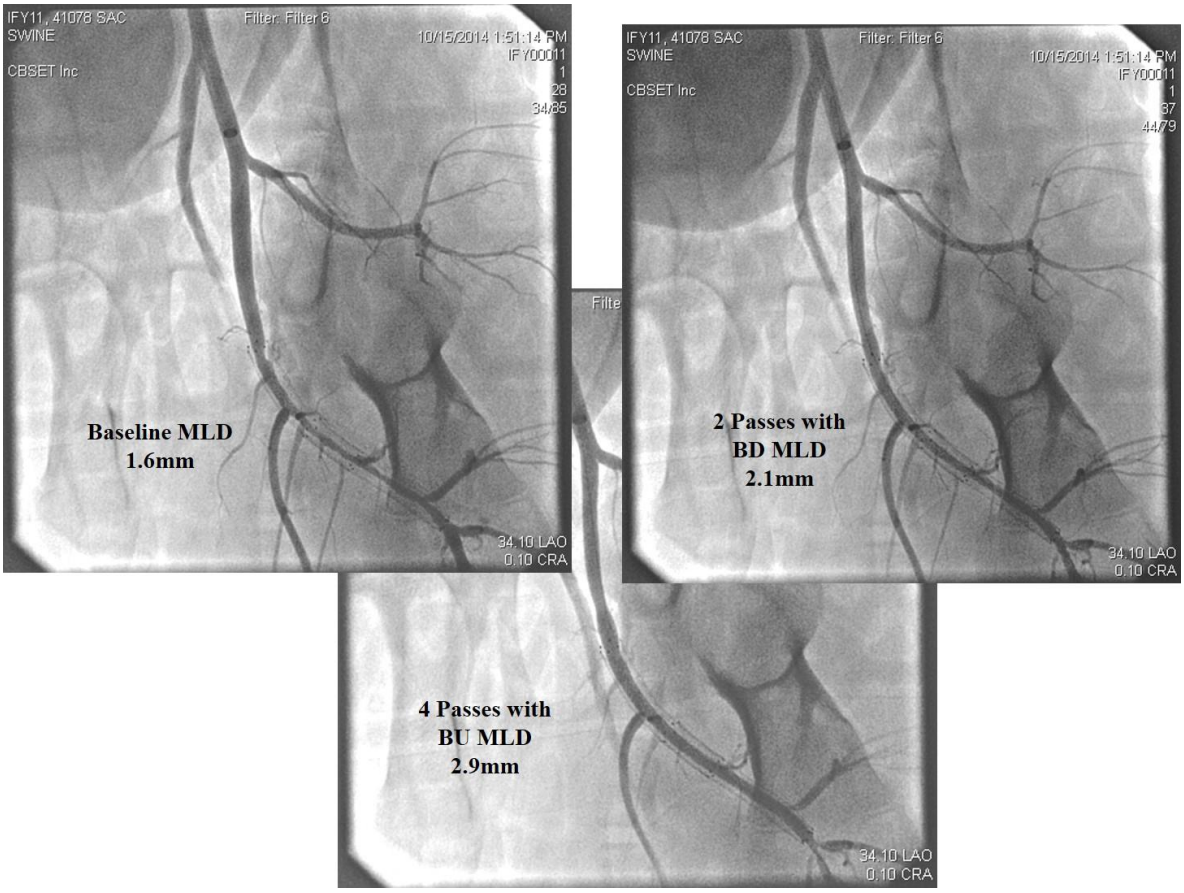
Stent Implantation Procedure

The right carotid artery was accessed using a cutdown approach. An introducer sheath was advanced into the artery and heparin (50–200 U/kg) was administered intravenously to prolong the activated coagulation time to a target of >275 seconds. A guide catheter was then advanced to the iliac arteries under fluoroscopic guidance. The femoral arteries were crossed with a 0.035-inch J-tipped guidewire, and the target segment was dilated 3 times (30 seconds each) with an oversized angioplasty balloon at various pressures and to achieve a 1.2 to 1.5 balloon:artery ratio. Two overlapping 40-mm-long nitinol S.M.A.R.T. self-expanding stents (5.0 and 6.0 mm in diameter; Cordis Corporation, Bridgewater, NJ, USA) were then deployed to the dilated target lesion (sized 1.2:1 stent:artery). The amount of overlap was either 100% (n=2) or 25% to 50% (n=6). The same process was repeated for the contralateral leg. A total of 8 stents were deployed in 4 limbs. Following stent implantation in both left and right femoral arteries, the animal is weaned off the anesthetic and extubated. Buprenorphine 0.01 to 0.03 mg/kg was administered intramuscularly every ~4 to 12 hours to provide analgesic coverage through at least the first 24 postoperative hours

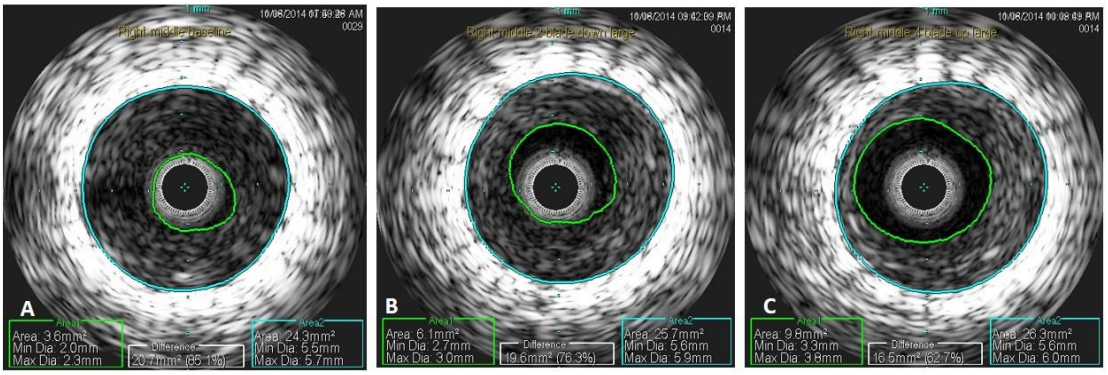
Atherectomy Procedure

Animals were brought back to the fluoroscopy suite approximately 1 month after stent implantation. The anesthesia procedure was repeated as described above. Carotid artery access was obtained using cutdown method. Angiographic images of the target vessel were obtained with contrast media to characterize the degree of ISR. Quantitative vessel angiography (QVA; Centricity Cardiology CA1000 Cardiac Review 2.0 software) was used to measure minimum lumen diameter (MLD), plaque surface area (PSA), and percent stenosis. An optimal residual stenosis after atherectomy alone was defined as a residual percent stenosis <50%.

Atherectomy was then carried on by advancing the cutter at a slow speed of 1 to 2 mm per seconds from the proximal to distal end of the stented segment (one run) over a Spartacore wire (Abbott Vascular, Redwood City, CA, USA). Two atherectomy runs with BD followed by QVA at the lesion site was performed. Atherectomy was then repeated with BU for 4 runs and with QVA of the lesion after each run (Figure 1).



Intravascular ultrasound (IVUS) quantitative measurements were also performed at baseline, after 2 BD runs, and after each BU run (BU1, BU2, BU3, BU4) on a total of 24 locations in the proximal, mid, and distal parts of the stented segments (Figure 2).



Minimum lumen area (MLA) within each the 24 locations was determined. PSA was calculated from the total stented area at each location minus the MLA. Finally, MLA and PSA at baseline were plotted against net MLA gain and PSA reduction (BU MLA or PSA – baseline MLA or PSA), respectively. The minimum MLA and PSA ranges at baseline needed for an increase in MLA by 1 to 2 mm and reduction in PSA by 5% to 10% from baseline were determined.

Device interaction with the implanted stent and subsequent damage of the stent was carefully evaluated under fluoroscopy. The process was repeated for the contralateral limb. After the last treatment, the animal was euthanized. Stents were evaluated postmortem with high resolution radiographs to determine strut damage.

Statistical analysis

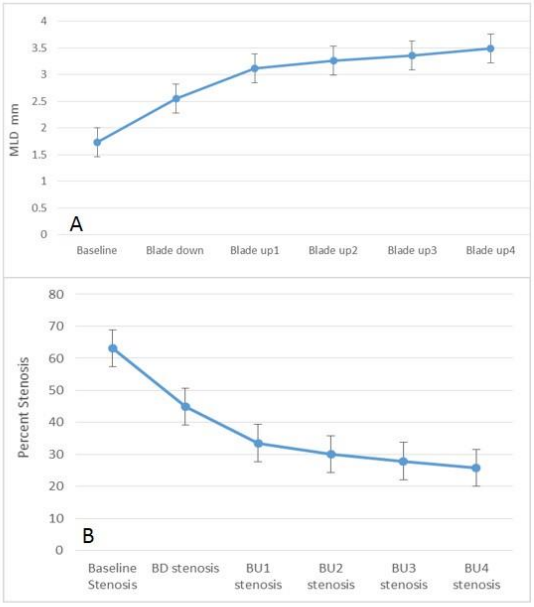
Descriptive analysis was performed on all angiographic variables. Single-sample Wilcoxon signed-rank test was performed between MLA obtained after BU runs and theoretical maximal MLA of the XC 2.4-3.4 cutter with BU model. Line graphs were performed to illustrate the change in MLD, MLA, PSA (with IVUS) and percent stenosis with each treatment. Wilcoxon signed-rank test and paired *t* test (1-tail) were performed to compare baseline, BD, and BU 1 to 4 runs using the statistical package in Minitab 17 (State College, PA, USA).

Results

The mean vessel diameter was 4.7±0.6 mm and mean lesion length was 61.5±12.6 mm. The mean baseline (n=8) MLD was 1.73±0.84 mm. Following 2BD and 1 BU runs, the mean MLDs were 2.6±0.7 mm (p=0.025) and 3.12±0.39 mm (p=0.005), respectively, vs baseline MLD. There was also a significant increase in MLD between 2BD runs and

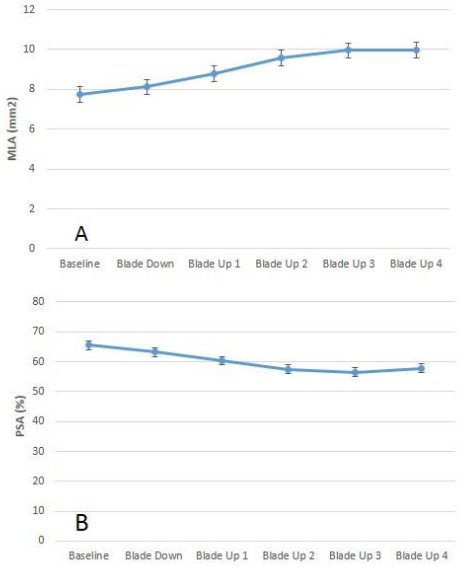
BU1 run (p=0.005). No statistical difference in MLD was seen between BU runs (p>0.05; Figure 3A).

PSA was significantly reduced between baseline (83.9%±14.8%) and 2 BD (67.7%±17.0%, p=0.005) and BU1 (55.4%±9.0%, p=0.005) runs and between BU1 and BU2 runs (50.7%±9.7%, p<0.05). No differences in PSA was seen between the BU2, BU3, and BU4 runs (p>0.05). Percent stenosis was reduced from a mean of 63.13%±16.91% to 44.97%±15.0%8 (p=0.005) with BD runs and to 33.51%±6.73% (p=0.005) with BU1 run. There was also a significant reduction in percent stenosis between 2 BD runs and BU1 run (p=0.01) and between BU1 and BU2 runs (30.1%±7.0%, p=0.05). No difference between percent stenosis was seen between BU 2 to 4 runs (p=0.10; Figure 3B).

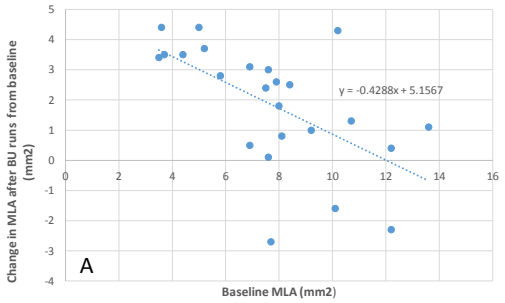


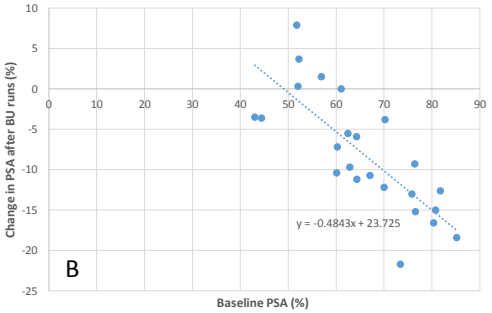
The mean baseline MLA by IVUS was 7.8±2.7 mm^2. Following 2BD and 1 BU runs, the mean MLAs were 8.1±2.5 mm^2 (p<0.044) and 8.7±2.0 mm^2 (p=0.007), respectively, when compared to baseline MLA. There was also a significant increase in MLA between 2BD runs and BU1 run (p=0.033) and between BU1 and BU2 runs (9.4±2.4 mm^2, p=0.007). No statistical difference in MLA was seen between BU 2 to 3 runs (p>0.05; Figure 4A).

PSA was significantly reduced between baseline (65.2%±11.7%) and 2 BD (63.0%±10.5%, p=0.015) and BU1 (60.7%±9.2%, p=0.011) runs and between BU1 and BU2 runs (57.5%±7.5%, p=0.025). No differences in PSA were seen between the BU2, BU3, and BU4 runs (p=0.12; Figure 4B)

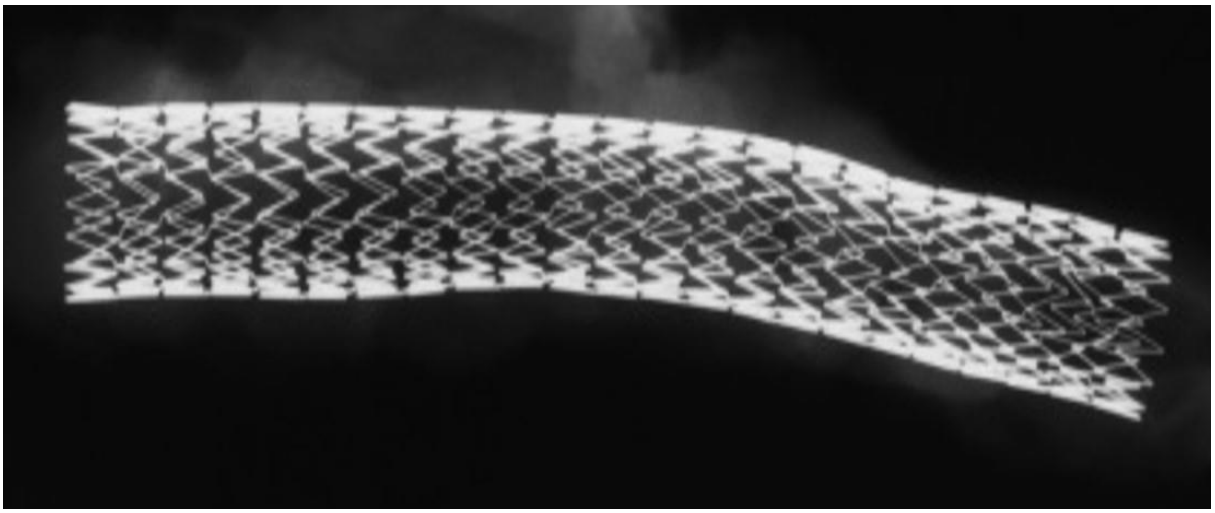


Vessel area measured by IVUS at site of treated stenosis remained unchanged between baseline and BU4 run (23.3±5.8 vs 22.5±4.9 mm^2, respectively; p=0.73). Furthermore, a significant correlation was seen between MLA at baseline and MLA after BU runs (p=0.006; Figure 5A) and between PSA at baseline and PSA after BU runs (p<0.0001; Figure 5B). An approximate baseline MLA of 8.0 to 9.0 mm^2 led to an MLA gain of 1 to 2 mm^2 and an approximate baseline PSA of 60% to 70% led to a reduction in PSA by 5% to 10% using the large cutter BU mode. Finally, theoretical MLA achievable from the XC BU 2.4-3.4 device is 9.08 mm^2 ($A = \pi r2$ using r=3.4/2=1.7mm). No difference was seen between this calculated MLA and the IVUS measured MLAs after BU runs, indicating no orbital effect of the device on tissue cutting.





There were no observed angiographic stent disruptions or stent strut discontinuity with IVUS or high resolution radiography (Figure 6) with JetStream Navitus atherectomy.



Using IVUS, JetStream Navitus is a true debulking device with no Dottering effect. In one study of post JetStream Navitus atherectomy, total vessel volume remained unchanged, but tissue volume is reduced and MLD is increased significantly.[3] IVUS data confirm the same findings by showing that MLA is increased and PSA is reduced, indicating true tissue excision within a nitinol self-expanding stent. Furthermore, the median MLA change seen after BU runs was statistically similar to the theoretical MLA calculated using a BU large cutter, which indicates that effective cutting is limited to the perimeter of the device, with no "wobbling" or "orbital" effect. This is a limitation of the

device in treating femoropopliteal ISR, as suboptimal tissue excision is therefore expected in larger vessel diameter (possibly 7 mm or higher).

In this model, stents were positioned at different overlapping lengths to test the safety of the device in treating short or long overlapping stent segments, particularly when the blades are up. No adverse events or stent-device interaction were seen. Also, there was no angiographic evidence of dissection or distal embolization following JetStream Navitus atherectomy, but it should be noted that these lesions are relatively short and not totally occluded; thus, they have a low potential for embolization.

Finally, adjunctive balloon angioplasty was not performed after the JetStream Navitus as the intention of the study was to test the effectiveness and safety of the device itself rather than the final outcome after adjunctive balloon angioplasty. The residual narrowing post atherectomy was a mean of 30.1%, which is consistent with effective tissue debulking (<50% residual) with the JetStream Navitus alone and without balloon angioplasty. This residual narrowing was accomplished in a mean vessel diameter of 4.7 mm.

References:

1. NRC (National Research Council). Guide for the Care and Use of Laboratory Animals. Washington, DC: The National Academies Press; 2011.

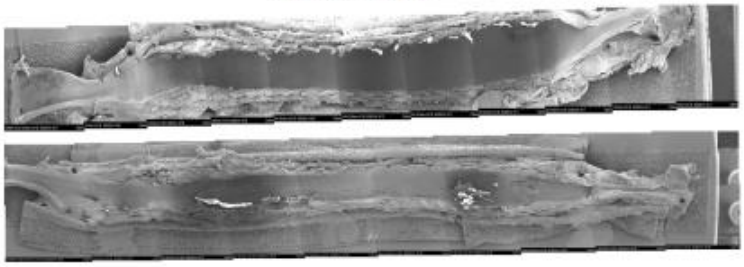
2. American Veterinary Medical Association. AVMA Guidelines for the Euthanasia of Animals: 2013 Edition. Version 2013.0.1. Published March 2013. https://www.avma.org/KB/Policies/Documents/euthanasia.pdf. Accessed May 15, 2013.

3. Singh T, Koul D, Szpunar S, et al. Tissue removal by ultrasound evaluation (the TRUE study): the Jetstream G2 system post-market peripheral vascular IVUS study. J Invasive Cardiol. 2011;23:269-273

Data recently presented at ICI 2015 in Israel from the same above model using SEM and histopathology showed a variable tissue disruption of in-stent restenotic tissue with no evidence of adverse effects on the implanted artery (e.g., thrombosis, dissection) or the implanted stents. High resolution radiographs showed no evidence of strut fracture or displacement. Histology and SEM showed, despite focal exposures of stent struts related to either incomplete neointimal coverage and/or atherectomy, there was no evidence of atherectomy-related damage to the stent in these areas. The degree of neointimal proliferation in this swine femoral artery ISR model was sufficient to evaluate the JetStream atherectomy catheter for safety.

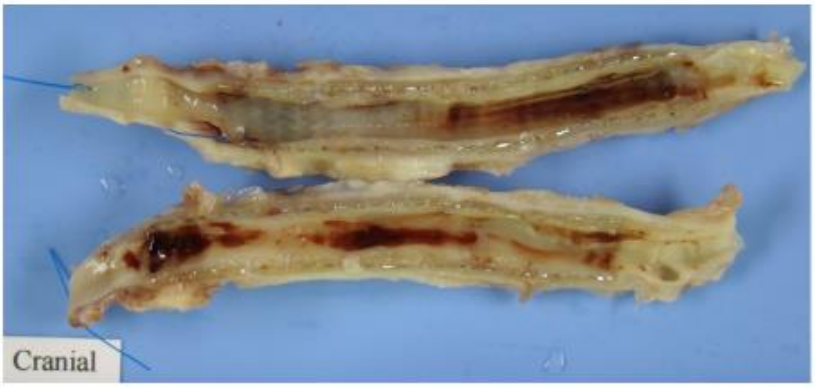
SEM of Left SFA
2BD/3BU (Last BU run 5 times back and Forth)

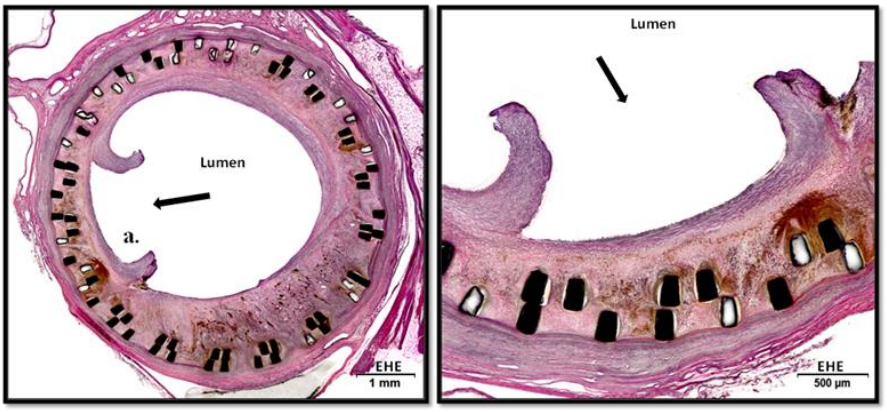
Minimal neointima



Macroscopic Observation of Left SFA
2 BD/2BU with JETSTREAM atherectomy

Eccentric lesion





3.32 Clinical studies

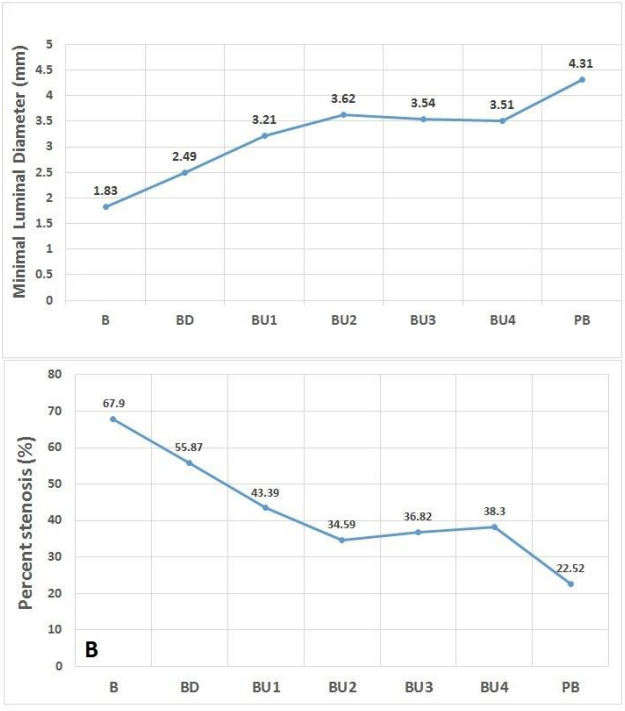
Beschorner et al[35] reported data on 33 patients (40 infrainguinal ISR lesions) treated with the Pathway PV atherectomy system (predecessor of JetStream). Primary patency was 33 % after 12 months and 25 % after 24 months. In this study, the majority of the lesions were FP (90%) but few lesions were in the peroneal, tibioperoneal and others. The vessels had no or mild (<30 degrees) tortuosity. Lesion length was 85.7 mm. Total occlusions were present in 20% of vessels. No serious device-related events were noted. Acute procedural success was accomplished in all lesions with adjunctive balloon/stent treatment. Distal embolization occurred in 6% of lesions treated and required aspiration embolectomy successfully. Bail out stenting was need in one lesion (3%). The Pathway PV system used in this study required 8 F system. Since then, the device (currently the Jetstream XC) was improved upon with more powerful aspiration and cutting abilities and is now compatible with 7 F sheath.

The recently presented final data of the JetStream ISR study at New Cardiovascular Horizon 2015[27] (one year TLR data will be presented at LINC 2016) evaluated acute procedural and 6-month outcomes, and stent-device interaction of the JetStream Navitus in treating FP ISR from 2 U.S. centers (manuscript in Print in JEVT 2016. Copy of accepted manuscript is in **Appendix B**). Demographic, clinical, angiographic and procedural data were collected on 29 patients (32 limbs) included. The primary effectiveness endpoint was acute procedural success (<30% residual narrowing with no serious adverse events). The primary safety endpoint was freedom from major adverse events (MAE). Secondary endpoints include clinically driven target lesion revascularization (TLR) at 6 months and stent integrity as assessed by Angiographic Core Laboratory. Six-month follow-up was completed on 27 patients (29 limbs). Adjunctive balloon angioplasty was performed in 100% at a mean pressure of 11.6 ± 3.3 atm. Total lesion length was 17.4 ± 13.1 cm and total treated length 19.5 ± 12.9 cm. Acute procedural success occurred in 90.6% of limbs. Acute device success (<50% residual narrowing after atherectomy alone) was 75.9%. Embolic filter protection (EFP) was used in 16/32 (50.0%) of limbs. Macrodebris was noted in 2/16 (12.5%) of filters and distal embolization (DE) requiring treatment occurred in 3/32 limbs (9.4%) (2 with no EFP). There were no new stent fractures or deformities (n=24) post JS. On 6-month follow-up TLR occurred in 4/29 patients (13.8%). Patency rate (PSVR<2.4) was 72%. Other non-

procedure related adverse events were total death 3.4% and major bleeding 3.4%. These results were highly encouraging establishing in this feasibility small study the safety and effectiveness of the JetStream in treating FP ISR when compared to historic control.

Observational data also are available from the multicenter xl-PAD registry that provided insight into how JetStream is applied in a real world registry[28]. Jetstream™ atherectomy was performed in 68 procedures. 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%.

Finally, a small feasibility study[36] to assess the role of adjunctive balloon angioplasty after optimal debulking with JetStream was evaluated in 6 patients (total 15 lesions) with femoropopliteal instent restenosis. This demonstrated similar results to the porcine model above where maximum debulking was reached after 2 blades up mode but adjunctive balloon angioplasty added a significant increase in MLD post Jetstream (see figure below)



3.33 Reported Adverse Events

Reported adverse events have been published (presented above). Unpublished AE/SAE can be found on the FDA webpage.

4.0 METHODOLOGY

4.1 STUDY DESIGN

This is a prospective, multicenter (up to 14 sites), single arm study. Patients will be treated with plaque excision using JetStream XC (JS) followed by adjunctive balloon angioplasty (PTA). Each subject must meet all inclusion criteria and no exclusion criteria. A subject will be enrolled in the study only after angiography and confirmation of ISR in the FP segment. All subjects will be followed up to 6 months after enrolment for the primary endpoint and 1 year for several secondary endpoints.

Study Purpose
The purpose of this study is to assess and estimate the effect of treating FP ISR with plaque excision using JS in combination with adjunctive PTA and compare this to historic control of PTA.

4.2 PRIMARY OUTCOME

Effectiveness

Target Lesion Revascularization (TLR) 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. (Intention to treat Analysis 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

1. **Device Outcome:** Categorized by < 50% residual stenosis following JS atherectomy alone and without additional adjunctive PTA or bail out procedures as determined by the Angiographic Core Laboratory.
2. **Procedural Outcome:** Categorized by < 30% residual stenosis following the protocol-defined treatment (JS + PTA) with provisional or bail out procedures as determined by the Angiographic Core Laboratory.
3. **Procedural Success:** Defined as ≤30% residual diameter stenosis following JS + PTA without provisional or bailout procedures.
4. **Target Lesion Revascularization (TLR) at 6 months**: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 6 months. Intra-procedural bail out stenting of the index lesion is NOT considered meeting a TLR endpoint. (ITT analysis)
5. **Target Lesion Revascularization (TLR) at 1 year**: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 1 year

   ITT (bail out stent in the Lab is considered as TLR)
   ITT (bail out stent in the Lab is not considered as TLR)
6. **Target Lesion Patency at 6 months and 1 year:** Defined as PSVR ≤ 2.5 at the treated site or < 50% stenosis by angiography as determined by the Angiographic Core Laboratory in the absence of TLR, amputation, and/or surgical bypass (the evaluation of patency is extended to one cm proximal and one cm distal to the target lesion)
7. **Clinically Driven Target Lesion Revascularization at 6 months and 1 year**: Defined as any re-intervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis (Peak Systolic Velocity Ratio (PSVR) > 3.5 or on angiography) 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 *in the Lab is* considered as TLR)
   ITT (bail out stent *in the Lab is* not considered as TLR)

   Routine angiography in an asymptomatic patient at 6 months or 1 year is not required in this protocol.
8. **Target Vessel Failure at 6 months and 1 year:** Defined as major unplanned amputation related to the treated limb, vascular mortality related to treated limb and target vessel revascularization at 6 months and 1 year (stenting in the lab is not considered a TLR/TVR)
9. **Target Lesion failure at 6 months and 1 year:** Defined as major unplanned amputation related of the treated limb, vascular mortality related to treated limb and target lesion revascularization at 6 months and 1 year (stenting in the lab is not considered a TLR)
10. **Major Adverse Event Rate at 6 months and 1 Year:** Defined as major unplanned amputation of the treated limb, all-cause mortality or TLR at 6 months and 1 year (bail out stent in the Lab is included as 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 RCC at 6 months and 1 year compared to baseline, that is attributable to the treated limb (in cases of bilateral disease).
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 and baseline ABI < 0.9.
14. **Assisted Primary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR ≤ 2.5 at 1 year, maintained by repeat percutaneous intervention of a restenotic but not occluded index lesion
15. **Secondary Patency rate at 1 year:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory, or PSVR ≤ 2.5 at 1 year, maintained by repeat percutaneous intervention of a restenotic or occluded vessel

4.4 SUBJECT SELECTION CRITERIA

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

Patients with symptomatic peripheral arterial disease (Rutherford Becker Class II to IV) will be enrolled if they have been previously treated with stenting in the femoropopliteal segment and now return with suspicion of restenosis. There is no limit on how many times the target in-stent restenotic lesion has been previously treated. Also there is no exclusion based on how the prior treatment was done including if drug eluting balloons or stents have been used. Covered stents cannot be included however including Viabhan stents. There is no limit on the length of the target lesion as long as only one target lesion is treated and enrolled. If there is more than one target lesion per vessel, this will be considered an exclusion. Patients will be considered enrolled in the study following the index angiogram and if they are deemed by the operator to meet the inclusion criteria and none of the exclusion criteria and prior to commencement of any therapeutic intervention. In this study, and in order to ensure adequate representation of minority and ethnic groups affected by PAD, our target for the Black population will be about 15% of all patients enrolled and for females a minimum of 30%

4.4.1 INCLUSION CRITERIA

Subjects must meet all of the following criteria to be eligible to participate in this study:

1. Subject is 18 years of age or older.
2. Subject presents with clinical evidence of peripheral arterial disease with ISR in the femoropopliteal segment (includes common femoral, superficial femoral and popliteal)
3. Subject presents with a Rutherford Classification of 2-4 and has symptoms of rest limb pain or claudication.
4. Target lesion(s) must be viewed angiographically and have ≥50% stenosis.

5. The atherectomy wire must be placed entirely across all lesions to be treated with no visible evidence of clear or suspected subintimal/substent wire passage.
6. The main target vessel reference diameter must be ≥ 5 mm and ≤ 7 mm
7. One patent distal run-off vessel with <70% disease and with brisk flow is required.
8. Intraluminal crossing of the lesion. If this is not certain, IVUS may be used to verify this per operator's discretion
9. Patient has signed approved informed consent.
10. Patient is willing to comply with the follow-up evaluations at specified times.

4.4.2 EXCLUSION CRITERIA

Subjects will not be eligible to participate in the study if any of the following conditions are present:

1. Subject is unable to understand the study or has a history of non-compliance with medical advice.
2. Subject is unwilling or unable to sign the Informed Consent Form (ICF).
3. Subject is currently enrolled in another clinical investigational study that might clinically interfere with the current study endpoints
4. Subject is pregnant or planning to become pregnant within the study period.
5. Subject has a known sensitivity to contrast media and the sensitivity cannot be adequately pre-medicated for.
6. Subject is diagnosed with chronic renal failure or has a creatinine level > 2.5 mg/dl and is not on chronic dialysis.
7. Subject has a known allergy to heparin, ASA, Plavix.
8. Subject has a history of bleeding disorders or platelet count < 80,000 cells/ml.
9. Subject experiences ongoing cardiac problems (e.g., cardiac arrhythmias, congestive heart failure exacerbation, myocardial infarction, etc.) that, per the investigator, would not make the subject an ideal candidate for study procedures.
10. Subject has a CVA or TIA within 4 weeks prior to JetStream procedure.
11. Subject has an anticipated life span of less than 12 months.
12. Subject is suspected of having an active systemic infection.
13. Limited vascular access that precludes safe advancement of the Jetstream XC System to the target lesion(s).
14. Patient has evidence of intracranial or gastrointestinal bleeding within the past 3 months.
15. Patient has had severe trauma, fracture, major surgery or biopsy of a parenchymal organ within the past 14 days.
16. Patient has any planned surgical intervention or endovascular procedure ≤ 30 days after the index procedure.
17. Use of another debulking device during the index procedure prior to the Jetstream XC System.
18. Use of another debulking device after the Jetstream XC system.
19. Class III and IV fractures
20. Stents not fully apposed to vessel wall or overlapping stent segments

21. Target lesion previously treated with a covered stent (such as Viabhan stent)

4.43 STUDY TREATMENT RULES

1. No other debulking devices, cutting/scoring balloons or cryogenic balloons may be used in before or after the Jetstream XC
2. Balloon inflation is per operator's discretion but should not exceed burst pressure and should be at least at nominal pressure. Operators should increase balloon pressure beyond nominal pressure only if balloon full expansion does not occur at nominal pressure. If higher balloon pressure beyond nominal is felt necessary, then pressure is increased at 1 atm every 5 seconds until full balloon expansion occurs.
3. Semi-compliant balloons are recommended
4. The only adjunctive therapies allowed are PTA and bailout stenting:
    - Bailout stenting is allowed if > 30% residual stenosis remains or for perforation
    - Type D dissection leading to flow limitations
    - Self-expanding nitinol stents are recommended if needed
    - Covered stents are allowed only if there is a perforation
    - Bailout stenting is not allowed if the lesion has ≤ 30% residual stenosis
    - Only one leg may be treated per patient. Patient is enrolled only once in the study.
    - Drug coated stents or Drug coated balloons are not allowed.

4.44 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 IFUs.
2. Patient has already been enrolled once in the protocol
3. 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).
4. Has known hypersensitivity to treatment device materials including nitinol.
5. Has known uncontrollable hypercoagulable condition, or refuses blood transfusion.
6. Has surgical or endovascular procedure of the target or non-target vessel within 30 days prior to the index procedure.
7. 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).
8. Has had superficial thrombophlebitis or deep venous thrombus within 30 days prior to index procedure.

9. Has history of significant gastrointestinal bleeding in the past 1 month prior to index procedure, or any history of hemorrhagic diathesis.
10. 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.
11. 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

4.45 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.

4.46 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.

4.47 BLINDING

Blinding is not possible in this one arms study

4.48 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^			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				
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.

^ Cr at 72 hours post procedure +/- 24 hours

4.49 Required Assessments and Tests

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

4.50 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.

4.51 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.

4.52 Creatinine

Creatinine (non-standarized) will be obtained and documented at baseline, 72 hours post procedure (+/- 24 hours) and at 1-year follow-up visit.

4.53 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.

4.54 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.

4.55 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.

4.56 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.

4.57 ANGIOGRAM

For procedural angiogram requirements see Section 4.62. Angiograms will be obtained per the Angiographic Protocol determined by the Angiographic Core.

4.58 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.

4.59 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 4.20 and 4.3 and Definition section for AE definitions.

4.60 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.

4.61 PROCEDURE REQUIREMENTS

The subject will undergo percutaneous revascularization of the superficial femoral and/or popliteal arteries. The JS + adjunctive PTA will be used to treat all lesion. Operators should have at least a minimum experience with 10 Jetstream cases as a primary operator to qualify to enroll patients in this study.

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

4.62 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 then treated with the JS + PTA as per protocol.

Angiographic films, including run-off, will be obtained immediately prior to and after treatment (after JS alone, and after adjunctive PTA or bail out stenting) 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. 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.

The Angiographic core laboratory will also assess stent fracture location and severity at baseline prior to any treatment and post atherectomy to assess for additional/worsening fractures.

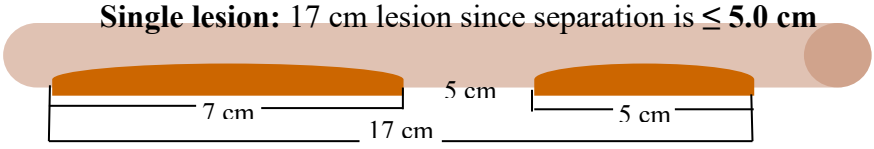
4.63 TREATMENT OF THE TARGET VESSEL

4.641 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, patient not eligible for enrolment

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



4.642 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 during the index procedure, but not within or equal 30 days following the index procedure.

4.643 JS + PTA 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 cm and 2.1 XC for 4-5 cm. The plaque excision procedure will follow the steps described in the published manual by Shammas et al.[2] The Spartacore (Abbott) or JetStream Wire (Boston Scientific) are recommended with the use of the JetStream device. The Grand Slam wire and hydrophilic wires are not recommended. Filters are highly 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 adjunctive PTA.

Dilation of the lesion following JS has to be done with a 1:1 balloon size and avoidance of oversizing. The diameter of the study balloon will be selected based on the vessel reference diameter distal to the target lesion. Balloon inflation should be limited to within the stent. See section 4.43 for details.

If there is a complication during JS, treatment 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.

4.644 ADJUNCTIVE PROCEDURES

Adjunctive procedures besides PTA 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) 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. Adjunctive or primary PTA should be done with a non-compliant or semi compliant balloon sized 1:1 to vessel size. Adjunctive stenting is performed only with self-expanding nitinol stent. Drug coated stents, covered stents, or drug coated balloons are not allowed in the study.

4.645 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.

4.646 ADVERSE EVENT EVALUATION

An AE evaluation will be performed during and at the end of the procedure. See Section 4.20 for the AE definitions. Adverse event evaluations will also occur prior to discharge and at all follow-up visits.

4.647 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 activated clotting time (ACT). For patients receiving bivalirudin, ACT is not necessary. For patients receiving heparin, the ACT goal is 250 seconds (Using iStat) or 300 seconds using Hemochron. If patient is on clopidogrel or other ADP receptor antagonist, this will be continued as prescribed. If patient is on Ticagrelor, only 81 mg of ASA daily should be prescribed. If patient is not on ADP receptor antagonist, he will be loaded with clopidogrel 600 mg po x one dose (or equivalent drug).

Post-Procedure

The subject should be optimally medically-managed for peripheral arterial disease per the standard institutional regimen. Post procedure, patients should be continued on clopidogrel (or an equivalent drug) 75 mg po daily for 3 months and aspirin indefinitely. If patient is on ticagrelor, asa 81 mg po daily is prescribed.

4.648 FOLLOW-UP REQUIREMENTS

All subjects are required to complete all follow-up visits as shown in Figure 2.

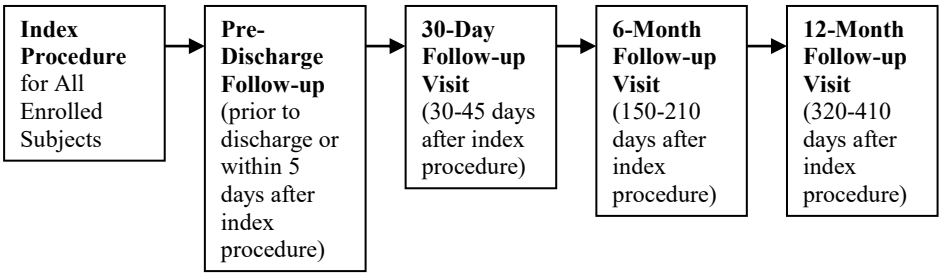


Figure 2: Study Diagram of Follow-up Requirements

4.649 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.*

4.650 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.*		

4.651 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.

The investigator will initially determine the lesion severity by visual estimate prior to re-intervention. The cine angiogram will be sent to angiographic core lab for analysis. Two orthogonal views of the lesion will be required to determine more accurately the lesion severity by the core lab. Core lab evaluation of lesion severity will be used as the more definitive measure and supersedes operator's visual estimate.

The following describes what take precedence (angiogram versus duplex ultrasound) to determine lesion severity:1. Patient has both modalities because of symptoms recurrence prior to 6 months follow up. To be consistent with the 6 months' primary endpoint the Duplex ultrasound will take precedence

2. Patient has angiogram only because of symptom recurrence prior to 6 months. In this case the angiographic finding of loss of patency will be used as no Duplex ultrasound was performed. The Duplex ultrasound at 6 months post reintervention will not be used even if performed as it is post re-intervention.

3. Patient undergoes both modalities at 6 months because of symptoms. Duplex ultrasound will take precedence as long as it has been done prior to the angiogram and re-intervention.

4.652 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.

4.653 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).

4.654 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.

4.655 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.

4.656 ADVERSE EVENTS

4.657 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.

4.658 ADVERSE EVENT CLASSIFICATIONS

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

Major Adverse Events

1. **Major Adverse Events (MAE) as individual endpoints in-hospital and up to 30 days :** Include device-induced vascular injury as reported by the operator, amputation (major and minor unplanned), death, significant distal embolization requiring the use of pharmacologic or mechanical means to treat (other than a vasodilator), perforation (extravasation of blood outside the vessel wall), major bleeding, non-fatal myocardial infarction (defined as the occurrence of more than 20 minutes of chest pain post procedure with an increase in troponin), stroke, access complications (AV fistula and pseudoaneurysm), bail out stenting, acute renal failure (drop in crcl by > 25% from baseline), acute (≤ 24 hours) or subacute (≤ 1 month , > than 24 hours) vessel closure.
2. **Target Lesion failure at 6 months and 1 year:** Defined as major unplanned amputation related of the treated limb, vascular mortality related to treated limb and target lesion revascularization at 6 months and 1 year (stenting in the lab is not considered a TLR)
3. **Major Adverse Event Rate at 6 months and 1 Year:** Defined as major unplanned amputation of the treated limb, all-cause mortality or TLR at 6 months and 1 year (bail out stent in the Lab is included as 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.

4.659 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.

4.660 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.

4.661 CORE LABORATORY REQUIREMENTS

4.662 ANGIOGRAPHIC CORE LABORATORY

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

4.663 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.

4.664 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.

4.665 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.

4.666 CASE REPORT FORMS

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

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

5.0 STATISTICAL METHODS

5.1 SAMPLE SIZE

5.11 Meta-analysis of PTA control arms from randomized trials

Please refer to Appendix A at end of protocol

5.12 Assumptions:

TLR with bailout stenting from historic control from meta-analysis: 37.9%
TLR with bailout stenting from Jetstream ISR feasibility study: 20.7%
Power 80%
Alpha 0.05

We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0.38. If the true failure rate for experimental subjects is 0.21, we will need to study 112 experimental subjects and 112 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 (meta-analysis from published randomized trials provides data on 182 controls). The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. Assumingly a loss of 20% of patients on follow-up a minimum of 134 patients will be enrolled.

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5.2 DATA ANALYSIS PLAN

5.23 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. A maximum of 140 patients will be enrolled.

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.

5.24 ANALYSIS OF BASELINE DEMOGRAPHICS AND PROCEDURAL CHARACTERISTICS

Descriptive analysis will be performed on all clinically relevant baseline demographics and procedural variables using percentages for dichotomous variables and mean +/- Standard deviations for continuous variables

5.25 ANALYSIS OF OUTCOMES

We hypothesize that JetStream atherectomy is superior to plain old balloon angioplasty in treating femoropopliteal in-stent restenosis in regards to the primary effectiveness endpoint of target lesion revascularization at 6 months with bailout stenting considered as a TLR. The Null Hypothesis assumes that the active control (JetStream) and the historic control of TLR (derived from the meta-analysis) have the same TLR at 6 months by intention to treat analysis. We calculated that if TLR is 0.38 for balloon angioplasty and 0.21 for JetStream, we need a total of 112 experimental subject and 112 control to reject the null hypothesis with a power of 0.8 and alpha of 0.05. The meta-analysis has provided data on TLR for balloon angioplasty in more than 112 controls. To account for patient loss to follow up we plan to enroll a maximum number of 140 patients in this study

5.26 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.

6.0 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. The recommendations in the IFU will be used for wire selection.

6.1 POTENTIAL BENEFITS

There are no guaranteed benefits from participation in this study; however, it has been shown that treatment with plaque excision 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.

6.2 POTENTIAL RISKS

6.3 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
- Device getting stuck on stent
- Wire breaking during atherectomy
- 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
- Disruption of previously implanted stent

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. These risks in applying the JS to in-stent restenosis has not been defined in a large trial but early preclinical data and the JetStream ISR feasibility study has shown that the device performed safely with no device-stent interaction**.**

6.4 RISK MITIGATION

The CEC committee will adjudicate every adverse events and unexpected device related events. DSMB will meet at completion of the first 30 patients and at 60 patients to analyze procedural and follow up events. Recommendations will be made to continue or stop the study based on these 2 interim analysis. All investigators will have to prove experience with at least 10 Jetstream cases with no significant events. Also, investigators will be trained on the protocol to ensure adherence to the inclusion and exclusion criteria and for timely reporting of adverse events as recommended by the IRB and FDA. Subjects will learn about the protocol from investigators and designated coordinators. Voluntary participation will be emphasized. Patients will sign informed consent form (see Appendix C for the ICF).

7.0 SITE REQUIREMENTS

7.1 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, 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.

7.2 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) or Institutional Review Board (IRB) 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.

8.0 MONITORING PROCEDURES

8.1 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. The lead coordinator and quality monitor at MCRF will be responsible for the monitoring procedure:

Gail A Shammas, BSN, RN

Lead Coordinator and Quality Monitor

Midwest Cardiovascular Research Foundation

1622 E Lombard Street,

Davenport, IA 52803

shammasg@mcrfmd.com

Monitoring will be conducted as per MCRF SOP and plan and with monitoring documentation per standardized templates

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.

8.2 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.

8.3 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.

9.0 RESPONSIBILITIES, RECORDS and REPORTS

The proposed study will be performed in accordance with all requirements set forth in the U.S. regulations, 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 812, the World Medical Association Declaration of Helsinki, ISO 14155 (1) and (2), current Good Clinical Practices (GCP), International Conference on Harmonization (ICH) and any other applicable local laws and regulations.

9.1 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 approval of the device on the market or 7 years after cessation of the study and must contact the Sponsor prior to disposal of study records.

9.2 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.

9.3 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.

9.4 IRB APPROVALS

IRB written approval will be obtained before being allowed to conduct and participate in the study. This approval letter must identify the study name, approved protocol number (including revision number), the date of the approval as well as the expiration date of such an approval. The investigator is responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, study timing, and for maintaining continuation of the approval during the entire study period. The investigator must also keep on file all correspondence with the IRB and forward copies of such correspondence to MCRF.

9.5 INFORMED CONSENT

MCRF will provide a template ICF for IRB submission prior to the site initiation. This template may be modified to suit the requirements of the individual study site.

A copy of the ICF must be given to each subject enrolled in the study. The investigator or assigned designee must administer this approved ICF to each prospective study subject, and obtain the subject's signature or a legally approved designee's signature along with the date of consent prior to enrollment in the study. The ICF must be obtained in accordance with the applicable guidelines on 21 CFR Part 50, current GCP, the Declaration of Helsinki, ISO 14155 (1) and (2), or local regulations and laws, whichever represents the greater protection of the individual. The subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and also informed that withdrawal from the study will not jeopardize their future medical care. The institutional standard subject consent form does not replace the study ICF.

9.6 INFORMED CONSENT (ICF)

All information and data sent to MCRF concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The investigator consents to audits by the staff of MCRF and its authorized local governmental body to review the study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media.

9.7 AMENDING THE PROTOCOL

The protocol can be amended only by the Sponsor. All changes must be submitted to the IRB for review and approval. Any change that would require alteration of the ICF must receive approval from the IRB prior to implementation. Following approval, the protocol amendment will be distributed to all protocol recipients at the study sites.

9.8 PROTOCOL DEVIATIONS

A Protocol Deviation CRF must be completed for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion/exclusion criteria, not performing required testing, missed follow-up visits, etc.). Investigators must notify the reviewing IRB of any deviation from the Study Protocol that was done to protect the life or physical well-being of a subject (medical emergencies). Such notice should be given within 48 hours where feasible but no later than 5 days after occurrence.

9.9 CASE REPORTS FORMS (CRF)

CRFs for individual subjects will be developed by MCRF or subcontracted by MCRF to a qualified CRO. CRFs are used to record study data and are an integral part of the study and subsequent reports. After the data have been submitted, corrections will be initiated via queries to be completed by study site personnel to investigator. CRFs and queries must be signed by the investigator

10.0 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.

11.0 PUBLICATION STRATEGY

At the conclusion of all 1-year follow-up visits, a multi-site abstract reporting the preliminary results may be prepared and presented at one or more major endovascular meetings by Dr Nicolas Shammas. A multi-site publication may also be prepared for print in a peer-reviewed scientific journal at the conclusion of the study. Following the national PIs (Shammas and Banerjee), additional co-authors will be added to the main manuscript by order of number of patients enrolled in the study. Final number of coauthors will be determined based on patient enrolment, quality of data and lack of significant protocol violation. Investigators with significant protocol deviations that jeopardize data quality may not be considered as authors. The final decision for co-authorship will be determined by the Sponsor.

The publication of results from any single-site experience within the study must not be submitted for publication (by itself or as part of other registries) until approval from the Sponsor is granted and after the publication of the main manuscript. 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 PIs are expected to review, approve and co-author any additional publications prior to submission to Journals or other publications media resulting from this study.

12.0 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 + PTA) 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)	**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.
Major Adverse Events	**Major Adverse Events (MAE) as individual endpoints in-hospital and up to 30 days :** Include device-induced vascular injury as reported by the operator, amputation (major and minor unplanned), death, significant distal embolization requiring the use of pharmacologic or mechanical means to treat (other than a vasodilator), perforation (extravasation of blood outside the vessel wall), major bleeding, non-fatal myocardial infarction (defined as the occurrence of more than 20 minutes of chest pain post procedure with an increase in troponin), stroke, access complications (AV fistula and pseudoaneurysm), bail out stenting, acute renal failure (drop in crcl by > 25% from baseline), acute ($\leq$ 24 hours) or subacute ($\leq$ 1 month , > than 24 hours) vessel closure. **Major Adverse Events (MAE) as composite endpoint at 30 days**: unplanned amputation (major or minor), death or TLR at 30 days (TLR includes bail out stenting) **Major Adverse Event Rate as individual and composite endpoint at**

	6 months and 1 Year: Defined as major unplanned amputation of the treated limb, death or TLR at 6 months and 1 year (bail out stent in the Lab is included as 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 JS atherectomy alone and without additional adjunctive PTA or bail out procedures 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.

Index Lesion: The target lesion treated during the index procedure

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.

JS pass: Movement of the JS across the target area. One pass is the movement of the JS from the proximal to the distal end of the lesion

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:[30]

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

Dissection	Description
	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 ≤ 2.5):** Defined by duplex ultrasound measurement of peak systolic velocity (PSV) ratio ≤ 2.5 at the target lesion.
- **Patency via angiography:** Defined as < 50% stenosis per angiography as determined by the Angiographic Core Laboratory.
- **Assisted primary Patency:** Defined as < 50% stenosis per angiography or duplex as maintained by repeat percutaneous intervention of a non-occluded vessel
- **Secondary Patency:** Defined as < 50% stenosis per angiography or duplex, as maintained by repeat percutaneous intervention of a non-occluded or occluded vessel

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-ISR 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.

Procedural Outcome: Categorized by < 30% residual stenosis following the protocol-defined treatment (JS + PTA) with provisional or bail out procedures as determined by the Angiographic Core Laboratory.

Procedural Success: Defined as ≤30% residual diameter stenosis following JS + PTA without provisional or bailout procedures.

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[31]: 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.

Severe or Moderate Calcification: Grade 2 (moderate) or higher (severe) as defined by the Peripheral Arterial Calcium Scoring System (PACSS)[32]

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) 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).

Target Lesion Revascularization (TLR) 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 secondary endpoint, Intra-procedural bail out stenting of the index lesion is NOT considered meeting a TLR endpoint. (ITT analysis)

Target Lesion Revascularization (TLR) at 1 year: TLR is defined as retreatment of the index lesion (extended 1 cm proximal and distal to the lesion) at 1 year

ITT (bail out stent in the Lab is considered as TLR)
ITT (bail out stent in the Lab is not considered as TLR)

Target Lesion Patency at 6 months and 1 year: Defined as PSVR ≤ 2.5 at the treated site or < 50% stenosis by angiography as determined by the Angiographic Core Laboratory in the absence of TLR, amputation, and/or surgical bypass (the evaluation of patency is extended to one cm proximal and one cm distal to the target lesion)

Clinically Driven Target Lesion Revascularization at 6 months and 1 year: Defined as any re-intervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis (Peak Systolic Velocity Ratio (PSVR) > 3.5 may substitute if a pre-intervention angiogram has not been recorded) 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 *in the Lab is* considered as TLR)
ITT (bail out stent *in the Lab is* not considered as TLR)

Target Vessel Failure at 6 months and 1 year: Defined as major unplanned amputation related to the treated limb, vascular mortality related to treated limb and target vessel revascularization at 6 months and 1 year (stenting in the lab is not considered a TLR/TVR)

Target Lesion failure at 6 months and 1 year: Defined as major unplanned amputation related of the treated limb, vascular mortality related to treated limb and target lesion revascularization at 6 months and 1 year (stenting in the lab is not considered a TLR)

TASC: See Trans-Atlantic Inter-Society Consensus II

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.

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

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.

Treatment interval: Time from JS activation until deactivation (via physician's hand control).

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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Appendix A
JET ISR

Meta-analysis

We completed a meta-analysis for the 3 randomized trials published (1-3) with femoropopliteal in-stent restenosis where the control arm was balloon angioplasty alone. Below is a table of this meta-analysis. This showed that TLR with balloon angioplasty alone was 37.9%.

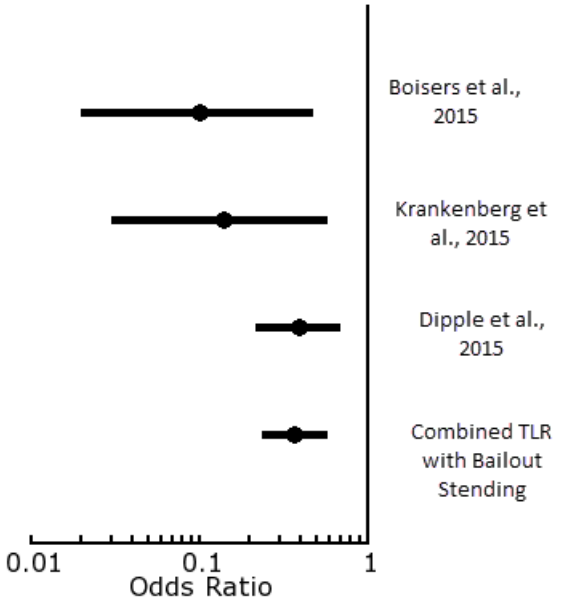
Estimated Counts of TLR with Bailout Stenting at 6-Months

Estimated Counts of TLR with Bailout Stenting at 6-Months			
Author, year	**Treatment**	**Control**	**Total**
Boisers et al., 2015	(2/39) 5.3%	(15/44) 34.2%	(17/83) 20.5%
Krankenberg et al., 2015	(3/62) 5.2%	(15/57) 26.0%	(18/119) 15.1%
Dipple et al., 2015	(45/169) 26.5%	(39/81) 48.2%	(84/250) 33.6%
Total	**(50/270) 18.5%**	**(69/182) 37.9%**	**(119/452) 26.3%**

Meta-Analysis for Estimated TLR with Bailout Stenting at 6-Months

Estimated TLR with Bailout Stenting at 6-Months							
Author, year	**n**	**Weight**	**Treatment**	**Control**	**Risk Difference**	**Risk Ratio**	**Odds Ratio**
Boisers et al., 2015	83	18.4%	5.3%	34.2%	-28.9% [-44.6%, -13.2%]	0.15 [0.04, 0.62]	0.10 [0.02, 0.47]
Krankenberg et al., 2015	119	26.3%	5.2%	26.0%	-20.8% [-33.5%, -8.1%]	0.20 [0.06, 0.65]	0.14 [0.03, 0.57]
Dipple et al., 2015	250	55.3%	26.5%	48.2%	-21.7% [-34.5%, -8.9%]	0.55 [0.39, 0.77]	0.39 [0.22, 0.68]
Total	**452**	**100.0%**	**18.5%**	**37.9%**	**-19.4% [-27.8%, -11.0%]**	**0.49 [0.36, 0.67]**	**0.37 [0.24, 0.57]**

The Breslow- Day test indicates that TLR with Bailout has no heterogeneity and thus can be combined into a meta-statistic (p-value=0.1764) (Figure below).



New Statistical analysis for Jet-ISR

TLR with bailout stenting from historic control from meta-analysis: 37.9%
TLR with bailout stenting from Jetstream ISR feasibility study: 20.7%
(2 bailout stent for suboptimal results + 4 TLR at 6 months/29 limbs)
Power 80%
Alpha 0.025

If one assumes a 1:1 ratio of actual treatment:control (instead of the original 2:1)

We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0.38. If the true failure rate for experimental subjects is 0.21, we will need to study 112 experimental subjects and 112 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 (meta-analysis provides 182 controls which is more than needed for this analysis). The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. Assumingly a loss of 20% of patients on follow-up a minimum of 134 patients will be enrolled.

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Study Protocol MCRF-S-002-2015

JET-ISR Trial

JetStream Atherectomy for the Treatment of In-stent Restenosis of the Femoropopliteal Artery

Version 2
Amendment 1
September 11, 2016

Sponsor

Midwest Cardiovascular Research Foundation

National Principal Investigators

Nicolas W Shammas, MD, MS, FACC, FSCAI
Subhash Banerjee, MD, FACC, FSCAI

Supported by

Boston Scientific

Changes include:

Page 27: Section 4.4.2 Exclusion Criteria 20 is changed from “Stents not fully apposed to vessel wall or overlapping stent segments” to “stents unapposed to either vessel wall or unapposed to overlapping stent segments. Apposed overlapping stents is not an exclusion”

Page 29: Section 4.47 Blinding consists of correction of a grammatical error from "arms" to "arm"

Page 29: Section 4.44 General Exclusion Criteria 9 is changed from “Has a history of gastrointestinal bleeding in the past 1 month prior to index procedure, or any history of hemorrhagic diathesis” to “Has a history of gastrointestinal bleeding in the past 3 months prior to index procedure, or any history of hemorrhagic diathesis.”

Page 30: Table 1 Study Assessment of Hemoglobin A1C is completely removed

Page 30: Table 1 Study Assessment Creatinine draw time Pre-Discharge is changed from 72 hours post procedure +/- 24 hours to 72 hours post procedure +/- 48 hours

Page 30: Table 1 Study Assessment Duplex Ultrasound Pre-Discharge is changed from “The first duplex ultrasound can occur any time within 45 days after the index procedure” to “The first duplex ultrasound is optional and can occur any time within 45 after the index procedure.”

Page 30: Section 4.52 Creatinine
“Creatinine will be obtained and documented at baseline, 72 hours post procedure (+/-) 24 hours, and at 1 year follow-up visit” is change to “Creatinine will be obtained and documented at baseline, 72 hours post procedure (+/-) 48 hours, and at 1 year follow up visit.”

Page 31: Section 4.53 will be completely removed.

Page 31: Section 4.58 Duplex Ultrasound
Second sentence will be changed from “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” to “DUS is optional within 45 days of the index procedure (at either the pre-discharge or 30-Day visit), and required at 6 months, and at 1 year post-procedure.”

Page 35/36: Table 3: Pre-Discharge Assessment Requirements
Duplex Ultrasound* “First duplex ultrasound can occur any time within 45 days of the procedure” will be change to Duplex Ultrasound* “First duplex ultrasound is optional and can occur any time within 45 days of the procedure.”

Page 35: Table 3: Pre-Discharge Assessment Requirements will have the addition of “Creatinine will be obtained and documented at baseline, 72 hours post procedure (+/-) 48 hours, and at 1 year follow up visit.”