Study Protocol

ProspectIve, SingLe-Arm, Global MuLti-Center Study to EvalUate TreatMent of Obstructive SupErficial Femoral Artery and/or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon and in In-Stent Restenosis

ILLUMENATE Global and ISR

Version 11.0

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CP-1005

Sponsor: Spectranetics Corporation
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Colorado Springs
CO 80921
USA

Study Protocol Acceptance

Study Title: Prospect**I**ve, Sing**L**e-Arm, Global Mu**L**ti-Center Study to Eval**U**ate Treat**M**ent of Obstructive Sup**E**rficial Femoral Artery and/or Popliteal Lesio**N**s With **A** Novel Pacli**T**axel-Coat**E**d Percutaneous Angioplasty Balloon and in **I**n-**S**tent **R**estenosis

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 Standard ISO 14155:2011, 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

ILLUMENATE Global and In-Stent Restenosis (ISR)	
Protocol Number	CP-1005
Device	Cohort 1: CVI Paclitaxel-Coated, Percutaneous Transluminal Angioplasty (PTX PTA) Balloon Catheter In-Stent Restenosis ISR (Cohort 2): The same device now commercially available with CE Mark renamed to: Stellarex 0.035" OTW drug-coated angioplasty balloon (Stellarex 035 DCB)
Primary Purpose	Cohort 1: The purpose of this single arm study is to continue to assess safety and performance of the CVI Paclitaxel-Coated PTA Balloon Catheter in the treatment of de novo or restenotic lesions in the superficial femoral (SFA) and/or popliteal arteries. Cohort 2: A second cohort is being added to evaluate this patient population for treatment of in-stent restenotic lesions.
Study Design	Cohort 1: Prospective, multi-center, single-arm study. Cohort 2: Prospective, multi-center, single-arm study compared to a historical control patients.
Follow-Up Schedule	Cohort 1: Follow-up assessments will occur at discharge, 1 month, 6 months, 12 months, 24 months,36 months, 48 months, and 60 months following the study procedure. Cohort 2: Follow-up assessments will occur at discharge, 1 month, 6 months, 12 months, 24 months and 36 months following the study procedure.
Number of Subjects	Cohort 1: Up to 500 subjects Cohort 2: Up to 130 subjects
Number of Sites	Cohort 1: Up to 65 study sites globally Cohort 2: Up to 25 study sites globally

Primary Safety Endpoint	Freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (TLR) through 12 months post-procedure.
Primary Efficacy Endpoint	Primary patency at 12 months post-procedure. Primary patency is defined as the absence of target lesion restenosis per duplex ultrasound (peak systolic velocity ratio [PSVR] ≤ 2.5) and freedom from clinically-driven target lesion revascularization.
Secondary Endpoints	The following secondary outcomes will be summarized in this study: **1.** Major Adverse Event (MAE) rate defined as a composite rate of cardiovascular death, major target limb amputation, and clinically-driven target lesion revascularization (TLR): i. Cohort 1: through discharge and at 1, 6, 12, 24, 36, 48, and 60 months post-procedure. ii. Cohort 2: through discharge and at 1, 6, 12, 24, and 36 months post-procedure. **2.** Rate of adverse events: i. Cohort 1: through discharge and at 1, 6, 12, 24, 36, 48, and 60 months post-procedure. ii. Cohort 2: through discharge and at 1, 6, 12, 24, and 36 months post-procedure. **3.** Rate of clinically-driven TLR at: i. Cohort 1: 6, 12, 24,36, 48 and 60 months post-procedure. ii. Cohort 2: 6, 12, 24, and 36 months post procedure. **4.** Rate of clinically-driven target vessel revascularization (TVR) at: i. Cohort 1: 6, 12, 24,36, 48, and 60 months post-procedure. ii. Cohort 2: 6, 12, 24, and 36 months post procedure. **5.** Rate of major amputation of the target limb at: i. Cohort 1: 6, 12, 24, 36, 48 and 60 months post-procedure. ii. Cohort 2: 6, 12, 24, and 36 months post procedure. **6.** All-cause mortality rate at: i. Cohort 1: 6, 12, 24, 36, 48 and 60 months post-procedure. ii. Cohort 2: 6, 12, 24, and 36 months post procedure. **7.** Rate of occurrence of arterial thrombosis of the treated segment at i. Cohort 1: 1, 6, 12, 24,36, 48 and 60 months post-procedure. ii. Cohort 2: 1, 6, 12, 24, and 36 months post procedure.

	8. Rate of ipsilateral embolic events of the study limb within 30 days post-procedure. **9.** Primary patency rate at 6, 24, and 36 months post-procedure. Primary patency is defined as the absence of target lesion restenosis per duplex ultrasound (peak systolic velocity ratio [PSVR] ≤ 2.5) and freedom from clinically-driven TLR. **10.** Alternative patency rate at 6, 24 and 36 months post-procedure. Alternative patency is defined as the absence of target lesion restenosis per duplex ultrasound PSVR < 2.4 and < 2.0 and freedom from clinically-driven TLR. **11.** Lesion success, defined as achievement of a final in-lesion residual diameter stenosis of ≤ 50%, after using the study device. **12.** Technical success, defined as achievement of a final in-lesion residual diameter stenosis of ≤ 50% (per angiographic core lab), using the paclitaxel-coated PTA balloon catheter without a device malfunction. **13.** Clinical success (per subject) defined as technical success without the occurrence of major adverse events during procedure. **14.** Procedural success (per subject) defined as lesion success without the occurrence of major adverse events during procedure. **15.** Change in Ankle-Brachial Index (ABI) from baseline to 6, 12, 24, and 36 months post-procedure in subjects with: i. Cohort 1: compressible arteries and baseline ABI < 0.9. ii. Cohort 2: compressible arteries. **16.** Change in Walking Impairment Questionnaire (WIQ) score from baseline to 6, 12, 24, and 36 months post-procedure. **17.** Change in Rutherford Clinical Category (RCC) from baseline to 6, 12, 24, and 36 months post-procedure. **18.** Change in EQ-5D from baseline to 6, 12, 24, and 36 months post-procedure.

	Inclusion/ Exclusion Criteria COHORT 1
Cohort 1 - General Inclusion Criteria	**1.** Has symptomatic leg ischemia, requiring treatment of the SFA and/or popliteal artery. **2.** Has a Rutherford Clinical Category of 2 - 4. Note: Rutherford Clinical Category 2 subjects should be entered into the study if conservative treatment has been unsuccessful. **3.** Is ≥ 18 years old. **4.** Has life expectancy > 1 year. **5.** Is able and willing to provide written informed consent prior to study specific procedures. **6.** Is willing and capable of complying with the required follow-up visits, testing schedule and medication regimen.
Cohort 1 - Angiographic Inclusion Criteria	**1.** Has evidence at the target lesion(s) of clinically and hemodynamically significant de novo stenosis or restenosis, or occlusion, in the SFA (1 cm distal to the ostium of the profunda) and/or popliteal artery (proximal to the popliteal trifurcation), confirmed by angiography. **2.** Has target limb with at least one patent (<50% stenosis) tibio-peroneal run-off vessel to the foot confirmed by baseline angiography or magnetic resonance angiography (MRA) or computed tomography angiography (CTA). Note: Treatment of outflow disease is NOT permitted. **3.** Has 1 or 2 target lesion(s) with a cumulative lesion(s) length of no more than 20 cm. NOTE: A maximum of two (2) lesions can be treated if the cumulative total lesion length (i.e. the combined length of both lesions) is less than or equal to 20cm. **4.** Has target lesion(s) located >2 cm from any stent if the target vessel was previously stented. **5.** Has a reference vessel diameter of 4 - 6 mm by visual estimate. **6.** Has a successful exchangeable guidewire crossing of the lesion(s).
Cohort 1 - General Exclusion Criteria	**1.** A female who is pregnant, of childbearing potential not taking adequate contraceptive measures, or nursing; or a male intending to father children during the study. **2.** Has significant gastrointestinal bleeding or any coagulopathy that would contraindicate the use of anti-platelet therapy **3.** Has known intolerance to study medications, paclitaxel or contrast agents that in the opinion of the investigator cannot be adequately pre-treated. **4.** Is currently participating in another investigational device or drug study that would interfere with study endpoints. **5.** Has history of hemorrhagic stroke within 3 months. **6.** Has surgical or endovascular procedure of the target limb within 14 days

	prior to the index procedure. **7.** Has any planned surgical intervention (requiring hospitalization) or endovascular procedure within 30 days after the index procedure. **8.** Has had a previous peripheral bypass affecting the target limb. **9.** Has unstable angina pectoris, myocardial infarction, liver failure, renal failure or chronic kidney disease (dialysis dependent, or serum creatinine ≥ 2.5 mg/dL) within 30 days of the index procedure.
Cohort 1 - Angiographic Exclusion Criteria	**1.** Has significant stenosis (≥ 50%) or occlusion of inflow tract that is not successfully revascularized (< 30% residual stenosis without death or major vascular complication) prior to treatment of the target lesion(s). Only treatment of target lesion(s) is acceptable after successful treatment of inflow iliac artery lesion(s). **2.** Has an acute or sub-acute intraluminal thrombus within the target vessel. **3.** Has in-stent restenosis or restenosis of the target lesion following previous treatment with a drug-coated balloon. **4.** Has an aneurysm (at least twice the reference vessel diameter) located in the target vessel, abdominal aorta, iliac, or popliteal arteries. **5.** Has perforation, dissection or other injury of the access or target vessel requiring stenting or surgical intervention prior to enrollment. **6.** Has no normal arterial segment proximal to the target lesion in which duplex ultrasound velocity ratios can be measured. **7.** Requires use of adjunctive therapies (i.e., laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy). **8.** Has severe calcification that precludes adequate PTA treatment.
	Inclusion/ Exclusion Criteria COHORT 2
Cohort 2 - General Inclusion Criteria	**1.** Has symptomatic leg ischemia, requiring treatment of the SFA and/or popliteal artery. **2.** Has a Rutherford Clinical Category of 2 - 4. Note: Rutherford Clinical Category 2 subjects should be entered into the study if conservative treatment has been unsuccessful. **3.** Is between 18-85 years old. **4.** Has life expectancy > 1 year. **5.** Is able and willing to provide written informed consent prior to study specific procedures. **6.** Is willing and capable of complying with the required follow-up visits, testing schedule and medication regimen. **7.** History of previous femoropopliteal nitinol stenting which is suspect for in-stent restenosis. **8.** The patient has a resting ankle-brachial index (ABI) <0.9 or an abnormal exercise ABI (<0.9) if resting ABI is normal. Patient with incompressible

	arteries (ABI>1.2) must have a toe-brachial index (TBI) <0.7 in target limb.
Cohort 2 - Angiographic Inclusion Criteria	**1.** Has angiographic evidence of significant restenosis (≥50% by visual estimate) within a previously deployed femoropopliteal bare nitinol stent(s) including ISR Class I, II or III. **2.** Has target limb with at least one patent (<50% stenosis) tibio-peroneal run-off vessel to the foot confirmed by baseline angiography or magnetic resonance angiography (MRA) or computed tomography angiography (CTA). Note: Treatment of outflow disease is NOT permitted. **3.** Total target treatment length of in-stent restenosis must be ≥ 4.0 cm in length and may include a single lesion or a multifocal lesion within the femoropopliteal segment (This includes the proximal, mid, and/or distal SFA and P1, P2 and/or P3 segment of the popliteal artery). Edge restenosis may be treated provided the lesion extends no more than 3 cm outside the margin of the stent (proximal and/or distal margin). **4.** Has a reference vessel diameter of 4 - 6 mm by visual estimate. **5.** Has a successful exchangeable guidewire crossing of the lesion(s).
Cohort 2 - General Exclusion Criteria	**1.** A female who is pregnant, of childbearing potential not taking adequate contraceptive measures, or nursing; or a male intending to father children during the study. **2.** Has significant gastrointestinal bleeding or any coagulopathy that would contraindicate the use of anti-platelet therapy **3.** Has known intolerance to study medications, paclitaxel or contrast agents that in the opinion of the investigator cannot be adequately pre-treated. **4.** Is currently participating in another investigational device or drug study that would interfere with study endpoints. **5.** Has history of hemorrhagic stroke within 3 months including those within <60 days with an unresolved walking impairment. **6.** Has surgical or endovascular procedure of the target limb within 3 months prior to the index procedure. **7.** Has any planned surgical intervention (requiring hospitalization) or endovascular procedure within 30 days after the index procedure. **8.** Has had a previous peripheral bypass affecting the target limb. **9.** Has unstable angina pectoris, myocardial infarction within 60 days, liver failure, renal failure or chronic kidney disease (dialysis dependent, or serum creatinine ≥ 2.5 mg/dL) within 30 days of the index procedure. **10.** History of previous femoropopliteal stenting in the target lesion with drug eluting stents or covered stents (endografts).

Cohort 2 - Angiographic Exclusion Criteria	**1.** Ipsilateral and/or contralateral iliac (or common femoral) artery stenosis ≥50% Diameter Stenosis (DS) that is not successfully treated prior to index procedure (e.g. where a perforation occurred requiring a covered stent) or with final residual stenosis ≥ 30% documented by angiography. **2.** Identification of any lesion of the native vessel (excludes ISR) above the target stent in the femoropopliteal segment >50% that is not successfully treated prior to index procedure (e.g. complication requiring additional treatment) or with final residual stenosis > 30% documented by angiography. DES and DCB will not be allowed. The lesion length must be treatable with a single stent (if required). The lesion must not be contiguous with the target lesion; at least 2 cm of normal appearing vessel between the lesion and target lesion/ target stent or between deployed stent (if required) and the target lesion/ target stent. **3.** Has an acute or sub-acute intraluminal thrombus within the target vessel. **4.** Has an aneurysm (at least twice the reference vessel diameter) located in the target vessel, abdominal aorta, iliac, or popliteal arteries. **5.** Has perforation, dissection or other injury of the access or target vessel requiring stenting or surgical intervention prior to enrollment. **6.** Has no normal arterial segment proximal to the target lesion in which duplex ultrasound velocity ratios can be measured. **7.** Requires use of adjunctive therapies (i.e., laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy). **8.** Grade 4 or 5 stent fracture affecting target stent or proximal to the target stent, or where evidence of stent protrusion into the lumen is noted on angiography in 2 orthogonal views.

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1.0 INTRODUCTION

1.1 Purpose

The purpose of this study is to continue to assess the safety and performance of the CVI Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTX PTA) Balloon Catheter in the treatment of de novo or restenotic lesions in the superficial femoral (SFA) and/or popliteal arteries. In Cohort 2 – ISR, the study is expanded to include treatment of in-stent restenotic lesions.

1.2 Device Name

The CVI Paclitaxel-Coated PTA Balloon Catheter will be used in this study. In Cohort 1, the device is investigational.

For Cohort 2, the CE Marked device commercially available in Europe, Stellarex 0.035" OTW drug-coated angioplasty balloon, will be used with an investigational Instructions for Use (IFU). For regions outside of Europe, the device will be marked for investigational use only.

An investigational IFU will be used for Cohort 2 as there will be changes within the body of the commercial IFU including the following main changes (see IFU attachment for all details): deletion of maximum of 2 balloons per lesion, detailed paclitaxel dosing chart, and specification of total maximum paclitaxel dose per lesion treated.

1.3 Intended Use

Cohort 1:

The CVI Paclitaxel-coated PTA Balloon Catheter is intended to be used for the treatment of de-novo or restenotic lesions (excluding in-stent lesions) in the superficial and/or popliteal arteries to establish blood flow and to maintain vessel patency.

Cohort 2 – ISR:

The Stellarex 0.035" OTW drug-coated angioplasty balloon (DCB) is indicated for the treatment of de-novo or restenotic lesions in the lower extremities to establish blood flow and to maintain vessel patency.

1.4 Study Overview

1.5 Duration of the Study

The estimated duration of the study is approximately six to seven years from the time of first subject enrollment to the last study protocol-required follow-up visit for each cohort of the study. Each subject of Cohort 1 will be followed for five years. Each subject of Cohort 2 will be followed for three years.

1.6 Number of Sites and Subjects

In Cohort 1, up to 500 subjects are planned for enrollment into the study at up to 65 study sites globally. Cohort 2 has been added and will include up to 130 subjects with in-stent restenosis at up to 25 sites.

1.7 Sponsor Contact Information

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2.0 DEVICE DESCRIPTION

The CVI PTX PTA balloon catheter (Spectranetics Corporation, formerly Covidien, formerly CV Ingenuity Corporation, Fremont, CA 94555 USA) is an over-the-wire dual lumen catheter with a distally mounted semi-compliant inflatable balloon and an atraumatic tapered tip. The balloon is coated with a proprietary coating containing the drug paclitaxel.

The catheter accommodates a 0.035" (0.89 mm) guidewire. The shaft is 135 cm in length. The catheter is available in balloon lengths of 40, 80, and 120 mm with balloon diameters of 4, 5 and 6 mm. It is compatible with a 6 French or greater sheath. Each device has a protective sheath over the drug-coated balloon portion of the catheter. A compliance chart is included on the product label for each device.

The balloon has two radiopaque makers for positioning the balloon relative to the treatment area. The radiopaque maker bands indicate the working length of the balloon and facilitate fluoroscopic visualization during delivery and placement.

The CVI PTX PTA balloon catheter utilizes a CE-marked, commercially available PTA balloon catheter (EverCross® 0.035" PTA Balloon Catheter, Medtronic, formerly Covidien, formerly ev3, Plymouth, MN 55441, USA) coated with paclitaxel using a proprietary carrier. The paclitaxel coating is a formulation consisting of paclitaxel as the active pharmaceutical agent. The paclitaxel coating covers the working length of the balloon catheter.

The nominal dose density of paclitaxel on the CVI PTX PTA Balloon Catheter is 2.0 µg/mm^2. The nominal dose of paclitaxel on a specific catheter size is listed in Table 1.

Table 1: Nominal Paclitaxel Dose (µg) per Catheter Length/Diameter

Balloon Diameter (mm)	Balloon Length (mm)		
	40	80	120
4	1124 µg	2211 µg	3307 µg
5	1335 µg	2636 µg	3880 µg
6	1619 µg	3174 µg	4721 µg

In Cohort 1, the CVI Paclitaxel-coated PTA Balloon Catheter is an investigational device and may only be used if the patient has provided study informed consent. Use is restricted to investigators who are experienced in the clinical and technical aspects of angioplasty. The investigational device is provided sterile with the device packaged in a foil pouch and contained within a single unit box. Each balloon catheter is intended for single patient use.

For Cohort 2, the CE Marked, commercially available in Europe Stellarex 035 DCB (formerly CVI PTX PTA Balloon Catheter) will be used with an investigational IFU. For regions outside of Europe, the device will be marked for investigational use only. There are no design changes between the investigational device used in Cohort 1 and the CE Marked device in Cohort 2.

For specific information on device components and steps on how to operate the catheter, refer to the most current *Instructions for Use* (IFU).

3.0 BACKGROUND AND SIGNIFICANCE

3.1 Disease Overview

Peripheral Arterial Disease (PAD), atherosclerosis in vessels outside of the heart and brain, is a common ailment affecting an estimated 27 million adults in Europe and North America and is associated with significant morbidity and mortality.[1] Peripheral Arterial Disease is associated with a significant reduction in health-related quality of life, and in extreme cases, the disease can result in debilitating symptoms (including loss of limbs). Total disease prevalence has been estimated at between 3% and 10%, increasing to 15% to 20% in patients over 70 years.[2] Only approximately 25 percent of patients undergo treatment for the disease.[3] Deterioration or progression of PAD occurs in one-third to one-fourth of all patients.[4] One to five percent will eventually require amputation.[4-6]

Peripheral Arterial Disease is associated with substantial morbidity and reduced health status measures. The most common symptom of PAD is difficulty walking (intermittent claudication); less common is critical limb ischemia (CLI) which includes severe persistent rest pain requiring treatment with analgesics, ulceration or gangrene on the distal extremity. Lower extremity arterial disease can lead to reduced mobility, limb pain, gangrene, and amputation, as well as increased mortality.[2,7,8] Physical function, pain, and general health perception is similar or worse than in patients with congestive heart failure or recent myocardial infarction. In addition, patients with PAD generally also present with cardiovascular disease (CVD), which may explain the increased risk of mortality from myocardial infarction (MI) and stroke,[7,9,10] with mortality rates at five years ranging from 30% to 44%.[11,12]

The superficial femoral artery (SFA) is the most commonly diseased artery in the peripheral (lower limb) vasculature, with PAD presenting as intermittent claudication. Patients with intermittent claudication report increased pain and limitations in physical functioning compared with published norms, which are expected based on the nature of their disease. They also report significant deficits in energy, emotional reactions, sleep, and normal activities of daily living due to emotional stress. These limitations have been reported to occur at a relatively low level of exercise.[4-6]

Available therapies for patients with PAD include: risk factor modification, including diabetes control, smoking cessation, and hyperlipidemia control; exercise therapy; pharmacological therapy; and surgical or endovascular revascularization. Risk factor modification therapy is recommended to improve claudication and decrease the morbidity and mortality associated with the progression of PAD.[13-15] Exercise therapy can produce clinical improvements in walking ability and reductions in claudication pain.[16-18] Pharmacological options include antiplatelet and anticoagulant therapies.[19-21] Surgery is typically reserved for patients with critical limb ischemia and is associated with risks such as wound complications, death, MI, infection and leg edema.[21,22] Patency rates for surgical revascularization of the lower extremities have been reported to be 23-74%.[5,21,22]

Multiple published studies report on the short and long-term results of performing percutaneous angioplasty interventions and/or stenting for PAD. Patency rates have been reported to range between 29-93%.[23-42] A meta-analysis of percutaneous angioplasty with provisional stenting compared to stenting alone for treatment of SFA lesions showed similar rates of target vessel revascularization (TVR), making both reasonable choices as endovascular treatments.[43]

However, restenosis remains a major limitation of the clinical usefulness of PTA and stenting. Poor long-term results, especially after the treatment of longer lesions in the femoropopliteal region, have been reported.[44-54]

The local application of anti-proliferative drugs (e.g., sirolimus, zotarolimus, everolimus, and paclitaxel) for prevention of restenosis in coronary arteries via a stent delivery system has shown that these therapies successfully inhibit or reduce restenosis.[55-66] The use of drug-eluting stents in the superficial femoral and proximal popliteal arteries had promising early results that have not been sustained over time. The SIROCCO I and SIROCCO II trials evaluated the local application of sirolimus for prevention of restenosis in the superficial femoral artery in 95 patients comparing use of an uncoated to a drug-coated nitinol self-expanding stent. At 24 months there were no significant differences in Ankle Brachial Index (ABI) or in-stent restenosis as measured by peak systolic velocity ratio using duplex ultrasound. Both groups showed an improvement in Rutherford classification post-procedure which was sustained over 24 months.[67] The STRIDES trial evaluated 104 patients with superficial femoral or proximal popliteal artery lesions treated with an everolimus self-expandable nitinol stent with disappointing results at 12 months.[68] The Zilver PTX peripheral stent with the use of paclitaxel has shown positive results at 12 months but long-term results are currently unknown.[69]

3.2 Paclitaxel-Coated Angioplasty Balloons

Paclitaxel is an antineoplastic drug that has demonstrated sustained inhibition of smooth muscle cell proliferation in several pre-clinical studies.[70-73] Recent publications related to effectiveness of local administration of paclitaxel on restenosis through use of drug-coated balloons in the femoropopliteal artery have highlighted promising results with reduction of neointimal proliferation in the peripheral arteries. [74,75]

The THUNDER (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) trial[74] was a prospective, multicenter study that randomized 154 patients with femoropopliteal disease to treatment with standard PTA (control, n=54), paclitaxel dissolved in the contrast medium (PTX-contrast, n=54), or PTA with a PTX-coated balloon catheter (PTX PTA, n=48). The primary endpoint was late lumen loss (LLL) at 6 months. The mean lesion length was 7.4±6.5 cm; 27% of lesions were total occlusions and 36% were restenotic. There were no adverse events related to the drug-coated balloons. During the study procedure, 17 patients required stent implantation for suboptimal outcomes (12 in the control arm, 2 in the PTX PTA arm, and 3 in the PTX-contrast arm). At 6 months the mean LLL was significantly less in the PTX PTA group compared to the control group ($p<0.001$, 0.4±1.2 mm vs. 1.7±1.8 mm). The group treated with PTX-contrast had a mean LLL of 2.2±1.6 mm ($p=0.11$ vs. control). The rate of TLR at 6 months was 37% (20/54) in the control group and 4% (2/48) in the PTX PTA group ($p<0.001$ vs. control) and 29% (15/52) in the PTX-contrast group ($p=0.41$ vs. control). At 24 months the TLR rate was lower for the PTX PTA group in comparison to the control or the PTX-contrast arms (15% versus 52% and 40% respectively).[74] At 5 years, the angiographic follow-up showed mean LLL lower, but not statistically significant, for the group treated with PTX PTA compared to the control group (0.7±1.9 mm vs. 1.5±1.3 mm, $p=0.54$). The authors concluded the use of PTX PTA was associated with significant reductions in LLL and TLR, while PTX-contrast did not show a significant benefit.

An analogous study published by Werk et al,[75] called Femoral Paclitaxel (FemPac), reported results similar to those seen in the THUNDER study. The trial enrolled 87 patients who were randomized to treatment with paclitaxel-coated balloons (n=45) or to uncoated balloons (n=42). To achieve optimal outcomes, 6 patients in the control arm and 4 patients in the PTX PTA arm required adjunctive stent implantation during the study procedure. The 6-month LLL was significantly less in the group treated with PTX PTA (0.5±1.1) as compared to the control group (1.0±1.1, $p = 0.031$). Restenosis occurred in 19% of patients in the paclitaxel-coated arm and 47% of the control arm.[75]

The rate of TLR at 6 months was 31% (14/45) in the control group and 8.8% (4/45) in the PTX PTA group (P=0.007). There were no adverse events related to the drug-coated balloons. The authors concluded that PTX PTA reduces restenosis without causing any apparent adverse events (AEs).

The PACIFIER trial evaluating the use of paclitaxel-coated PTA catheters to reduce restenosis of femoral and popliteal artery stenosis and occlusions compared to standard PTA showed mean LLL by angiography at 6 months was significantly lower for the group treated with PTX PTA than the control group (-0.01 mm vs. 0.65 mm, p=0.001). The binary stenosis rate was 8.6% for the PTX PTA group and 32.4% for the control group (p=0.01).[76] Additionally, the major adverse event rates, including deaths, amputations, and target lesion revascularizations, were significantly lower for the PTX PTA group at both 6 and 12 months (7.1% vs. 26.2% at 6 months, p=0.04, and 7.1% vs. 34.9% at 12 months, p<0.01, for the PTX PTA group vs. the control group). The authors conclude that drug-coated balloons are "associated with significant reductions in late lumen loss and restenosis at 6 months, and reinterventions after femoro-popliteal percutaneous transluminal angioplasty up to 1 year of follow-up."

Fanelli et al. reported on the independent, prospective, randomized trial, DEBELLUM (Drug-Eluting Balloon Evaluation for Lower Limb MUltilevel TreatMent), comparing angioplasty with drug-eluting balloons to conventional angioplasty.[77] The study included 50 patients with 122 lesions (25 patients with 57 lesions randomized to treatment with PTX PTA and 25 patients with 65 lesions randomized to control). Lesions in the femoropopliteal arteries (75.4%) and below-the-knee (BTK) arteries (24.6%) were included. The late lumen loss at 6 months was significantly less in the PTX PTA group (0.5±1.4 mm) in comparison to control (1.6±1.7 mm; p<0.01). Similarly, the binary restenosis rate at 6 months was significantly lower in the PTX PTA group (9.1% vs. 28.9% control, p=0.03). Target lesion revascularization rates were 6.1% for the PTX PTA group and 23.6% for the control group at 6 months (p=0.02). Thrombosis rates and amputation rates were lower in the PTX PTA group in comparison to control (3.0% vs. 5.2% for thrombosis and 3.0% vs. 7.9% for amputation) but the differences were not statistically significant. No adverse events were noted. The authors concluded that "the DEBELLUM trial confirmed the ability of paclitaxel-eluting balloons to reduce restenosis vs. conventional balloons at 6 months after treatment of multilevel (femoropopliteal and BTK) arterial disease in patients affected by claudication and CLI [critical limb ischemia]."[77]

Three publications by Micari et al. summarized results from a multicenter, Italian registry including treatment with paclitaxel-coated balloons for femoropopliteal stenoses and occlusions.[78-80] The initial publication reported on 66 patients (74 lesions) treated with the IN.PACT Admiral paclitaxel-coated balloon.[79] The mean lesion length was 7.4±3.8 cm with the majority of lesions being *de novo* (95.9%). Stent placement was required in 10.8% of cases due to vessel wall recoil or flow limiting dissection, resulting in a technical success of 89.2% and a procedural success rate of 100%. The mean ankle-brachial index (ABI) improved from 0.58±0.13 pre-procedure to 0.82±0.25 at 3 months post-procedure. No serious adverse events or target lesion revascularizations occurred within the initial 3 month follow-up period.[79] The other two publications reported on 12-month and 2-year results from 105 patients with 114 treated lesions enrolled in the registry.[78,80] The overall technical success rate was 89.6% with 12.3% of lesions stented. At 12-months, the primary patency rate was 83.7% and the target lesion revascularization rate was 7.6%.[78] The ABI remained high at 0.86±0.15 at the 12 month follow-up. Two deaths occurred which were unrelated to the device or procedure. Improvements in quality of life, as measured with the EQ-5D questionnaire, included improved mobility, activity, pain, and anxiety/depression starting at 3 months post-procedure and continuing

through 12 months ($p<0.01$).[78] At 2 years, the primary patency was 72.4% and secondary patency was 84.7%. Improvements in ABI and quality of life seen at 12 months continued through the 2-year follow-up.[80] Overall, the major adverse event rate through 2 years was 17.5%, with 2 deaths, 1 amputation, and 14 target lesion revascularizations. The authors concluded that treatment with paclitaxel-coated balloons is "associated with favorable functional and clinical outcomes at 2 years in patients with femoropopliteal artery disease requiring percutaneous revascularization."[80]

LEVANT I[81] was a first-in-human study of a low-dose PTX-coated angioplasty balloon (Lutonix™ DCB, coated with 2 $\mu g/mm^2$ versus the typical 3 $\mu g/mm^2$ of PTX). The study included 101 patients randomized to treatment with the PTX PTA or uncoated PTA. Randomization occurred after patients were stratified by whether balloon-only (n = 75) treatment or stenting (n = 26) was anticipated. The primary endpoint was LLL at 6 months. There were 8 deployment malfunctions caused by twisting of the balloon, which confounded the outcomes. There were no procedural complications. The mean lesion length was 8.1 cm and 42% of lesions were total occlusions. LLL at 6 months was 0.46 mm in the DCB arm and 1.09 mm in the PTA arm. The rates of major adverse events were similar between groups. It was 39% in the DCB group, including 15 TLRs, 1 amputation and 4 deaths. The MAE rate was 46% in the PTA group which included 20 TLRs, 1 thrombosis and 5 deaths. The primary patency rates at 12 months were 67% in the DCB arm and 55% in the PTA arm. At 24 months, the patency rates were 57% in the DCB arm and 40% in the PTA arm. When the 8 patients with balloon twist malfunctions were excluded, the 12- and 24-month patency rates were 76% and 66%, respectively. Further, the data showed that use before or after provisional stenting did resulted in similar outcomes out to 24 months. The authors concluded treatment with the Lutonix DCB reduced LLL and had a comparable safety profile as PTA.

The DEBATE-SFA Randomized Trial was designed to compare PTX PTA with PTA followed by stent placement (DCB + BMS vs. PTA+BMS) in patients at risk of restenosis.[82] A total of 104 patients with 110 lesions were enrolled and randomized. Procedural success, defined as technical success without procedural complications, was met in all patients. The primary endpoint was 12-month binary restenosis which occurred significantly less ($p=0.008$) in the DCB + BMS arm [9 (17%) vs. 26 (47.3%) of lesions in the DCB + BMS and PTA+BMS groups, respectively]. The freedom from TLR rate was 83% in the DCB+BMS group and 66.7% in the PTA + BMS group ($p=0.07$); a near-significant difference. The authors concluded that pre-dilation with a DCB prior to BMS placement reduces restenosis and TLR at 12 months.

The use of atherectomy prior to delivery of the drug-coated balloon has been explored. [83,84] Use of laser debulking in a CLI population was reported by Gandini et al.[83] Forty-eight (48) patients with SFA in-stent occlusions were randomized to treatment with DCB alone or laser prior to DCB use. The patency rates the in the Laser + DCB group were significantly higher ($p=0.01$) at 6 and 12 months (91.7% and 66.7%) as compared to the in the DCB only group (58.3% and 37.5%). No adverse events were related to laser or the drug coating in either group. Sixt et al. reported on their experience treating restenotic lesions with directional atherectomy (DA) followed by a drug-coated balloon. This retrospective study included 89 lesions; 60 treated with DA + PTA and 29 treated with DA+DCB. There were 2 (3.3%) device-related complications (perforations at the treatment site in the DA + PTA cohort). The freedom from restenosis rates at one year were 84.7% and 43.8% in the DA + DCB and DA + PTA groups, respectively.

The use of DCBs to treat SFA in-stent-restenosis (ISR) has also been assessed. The first report came from a single-center study of 39 patients. There were no procedure-related adverse events reported and the primary patency at one year was 92.1% and 70% at 2 years.[85] [86]. The DEBATE ISR trial assessed DCB treatment of SFA ISR in patients with diabetes [87,88]. The study included 44 patients and compared outcomes to historical data on diabetic ISR patients treated with POBA. The mean lesion length was 13.2 cm in the DCB group and 13.7 in the POBA group. More than half of the lesions were classified as Tosaka class 3 in both groups. Two patients (1 in each group) experienced distal embolisation after one dilation of occlusive ISR, which was treated with aspiration. Procedural success was obtained in all patients. At one year, the TLR rate was significantly lower in the DCB group (13.6% vs. 31%, p=0.045). At the 3 year follow-up however, the TLR rates in the DCB group was 40%, similar to the 43% rate observed in the historical data set.

The first randomized trial assessing POBA vs. DCB for ISR was recently published.[89] The trial randomized 119 patients (62 in the DCB group and 57 in the POBA group) with SFA ISR. The mean lesion length was 8.2 cm and 28.6% were totally occluded. Procedure-related complications included one late stent thrombosis in the DCB group and one subacute stent thrombosis after TLR with DCB in a POBA patient. Two distal embolizations in the DCB group resolved without intervention. The primary endpoint was binary recurrent restenosis assessed by duplex ultrasound and adjudicated by a core lab at 6 months. This was observed in 15.4% (8/52) in the DCB group and 44.7% (21/47) in the POBA group (p=0.002). At 12 months, the rates were 29.5% (13/44) and 62.5% (25/40), respectively (p=0.004). The authors concluded that treatment of ISR with DCB is associated with lower rates of recurrent restenosis, without an apparent difference in safety.

Two articles have been recently published on the cost effectiveness of drug-coated balloons (DCB).[90,91] Diehm and Schneider[90] created a decision-analytic model based on reported TLR rates and applied that data to associated costs over one year (Swiss Francs and Swiss DRG reimbursement figures). After one year, use of DCB was associated with substantially lower costs when compared to PTA, despite the higher cost during the initial treatment. However, because DCBs do not have a dedicated reimbursement, DCBs were less financially favorable for the provider. The authors concluded a specific DRG reimbursement structure for the use of DCBs would benefit everyone. A group from the United Kingdom performed an economic evaluation of endovascular interventions (PTA, PTA + stent, drug-eluting stents, DCB). The model assessed the relative cost-effectiveness from a health service prospective over a patient lifetime.[91] Patients with CLI and claudication were evaluated separately. In both populations, DCBs had a lower lifetime cost and greater effectiveness than all other treatment options.

CVI developed a paclitaxel-coated PTA balloon catheter that addresses some of the limitations of first generation paclitaxel-coated PTA balloon catheters relative to coating integrity while maintaining an excellent safety profile and possible therapeutic advantages as demonstrated in series of pre-clinical evaluations in swine and rabbit animal models. The extensive bench and pre-clinical studies conducted demonstrated that the CVI Paclitaxel-coated PTA Catheter is safe for its intended use with no adverse reactions associated with drug delivery for the treated vessel segment at 30 days post-treatment in the animal model. The presence of paclitaxel in the vessel up to 30 days post-procedure, as demonstrated by pharmacokinetic studies, was associated with the possible prevention of restenotic reaction, characterized by signs of drug effects in the histopathology studies at the time point in the animal model.

A First-in-Human (FIH) investigation using the CVI Paclitaxel-coated PTA Catheter has been conducted to establish the safety profile of the device.[92] A total of eighty (80) subjects were treated with the CVI Paclitaxel-coated PTA Catheter in two cohorts. The first fifty (50) patients were treated with pre-dilatation prior to treatment with the CVI Paclitaxel-coated PTA Catheter: the second thirty (30) patients were treated without the pre-dilatation step (direct cohort). The primary safety endpoint was 6-month MAE rate, defined as a combined rate of cardiovascular death, amputation and target lesion revascularization. The observed rate was 4% (95% CI: 0.5%-13.7%). The lower bound (13.7%) was below the objective performance criterion of 30%, therefore, the endpoint was met. The primary effectiveness endpoint was 6-month late lumen loss (LLL), which was 0.54mm (95%CI:0.28-0.81). The historical control was 1.1mm, which is greater than the upper bound of 0.82mm, therefore the effectiveness endpoint was also met. The primary patency rate, defined as PSVR $\leq$ 2.5, per Kaplan-Meier estimate, was 89.5% at 12 months and 80.3% at 24 months. The freedom from clinically-driven target lesion revascularization rate, per Kaplan-Meier estimate, was 90.0% at 12 months and at 85.8% at 24 months. Additionally, there were no amputations or cardiovascular deaths reported through 24 months.

The two-year results from the direct cohort were recently presented.[93] Twenty-eight patients, with 37 lesions, were included in the direct cohort analysis; two patients were excluded because they were pre-dilatated. The mean lesion length was 6.4cm and calcification was present in 48.6% of lesions. At 6 months, the mean LLL was 0.03 mm, indicating a good drug effect. The MAE rate was 14.5% at 12 motnsh and 18.5% at 24 months, primarily driven by CD-TLR. There was one index limb amputation observed in a patient who had a stent placed during the procedure within 6 months in conjunction with lower limb vessel thrombosis. The primary patency rate was 86.2% at 12 months and 78.2% at 24 months, similar to the rates observed in the pre-dilatation cohort. The freedom from clinically-driven target lesion revascularization rate, per Kaplan-Meier estimate, was 85.4% at 12 months and 81.7% at 24-months. This early data suggests that the CVI Paclitaxel-coated PTA Catheter is a safe and effective treatment option.

No long-term studies have been performed to evaluate the carcinogenic potential of the CVI PTX-coated PTA Catheter. Paclitaxel is a known genotoxin. The CVI PTX-coated PTA Catheter should not be used in women who are pregnant or intending to become pregnant, or in men intending to father children.

4.0 METHODOLOGY

4.1 Study Design

This is a prospective, international, multi-center, single-arm study. All subjects will be treated with paclitaxel-coated balloon angioplasty. Subjects meeting the definition of Rutherford Clinical Category (RCC) 2, 3 or 4 with atherosclerotic lesion(s) ≤20 cm located in the superficial femoral artery (SFA) and/or popliteal artery are eligible for enrollment.

A second cohort (Cohort 2-ISR) is being added to the study to evaluate patients with in-stent restenosis as compared to a historical control. Subjects meeting the definition of Rutherford Clinical Category (RCC) 2, 3 or 4 with in-stent restenosis in the superficial femoral artery (SFA) and/or popliteal artery are eligible for enrollment.

4.2 Study Purpose

The purpose of this single-arm study is to continue to assess the safety and performance of the CVI Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter in the treatment of de novo or restenotic lesions in the superficial femoral (SFA) and/or popliteal arteries in a broad patient population.

A second cohort (Cohort 2-ISR) is being added to compare the safety and performance of the Stellarex 0.035" DCB to a historical control (the PTA control arm of the Spectranetics EXCITE Study; Dippel JACC CV Interv. Vol 8, No 1, Jan 2015) in restenotic lesions in the SFA and/or popliteal arteries in a broad patient population.

4.3 Primary Safety Endpoint

The primary safety endpoint is freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 12 months post-procedure.

4.4 Primary Efficacy Endpoint

The efficacy endpoint is primary patency at 12 months post-procedure. Primary patency is defined as the absence of target lesion restenosis per duplex ultrasound (peak systolic velocity ratio [PSVR] ≤ 2.5) and freedom from clinically-driven target lesion revascularization.

4.5 Secondary Endpoints

The following secondary outcomes will be summarized in this study:

1. Major Adverse Event (MAE) rate, defined as a composite rate of cardiovascular death, major target limb amputation, and clinically-driven target lesion revascularization (TLR):
    i. Cohort 1: through discharge and at 1, 6, 12, 24, 36, 48 and 60 months post procedure.
    ii. Cohort 2: through discharge and at 1, 6, 12, 24, and 36 months post procedure.
2. Rate of adverse events:
    i. Cohort 1: through discharge, and at 1, 6, 12, 24, 36, 48, and 60 months post-procedure.

ii. Cohort 2: through discharge and at 1, 6, 12, 24, and 36 months post procedure.

3. Rate of clinically-driven TLR at:

i. Cohort 1: 6, 12, 24, 36, 48 and 60 months post-procedure.

ii. Cohort 2: 6, 12, 24, and 36 months post-procedure.

4. Rate of clinically-driven target vessel revascularization (TVR) at:

i. Cohort 1: 6, 12, 24, 36, 48 and 60 months post-procedure.

ii. Cohort 2: 6, 12, 24, and 36 months post-procedure.

5. Rate of major amputation of the target limb at:

i. Cohort 1: 6, 12, 24, 36, 48 and 60 months post-procedure.

ii. Cohort 2: 6, 12, 24, and 36 months post-procedure.

6. All-cause mortality rate at:

i. Cohort 1: 6, 12, 24, 36, 48 and 60 months post-procedure.

ii. Cohort 2: 6, 12, 24, and 36 months post-procedure.

7. Rate of occurrence of arterial thrombosis of the treated segment at:

i. Cohort 1: 1, 6, 12, 24, 36, 48 and 60 months post-procedure.

ii. Cohort 2: 1, 6, 12, 24, and 36 months post-procedure.

8. Rate of ipsilateral embolic events of the study limb within 30 days post-procedure.

9. Primary patency rate at 6, 24, and 36 months post-procedure. Primary patency is defined as the absence of target lesion restenosis per duplex ultrasound (peak systolic velocity ratio [PSVR] ≤ 2.5) and freedom from clinically-driven target lesion revascularization.

10. Alternative patency rate at 6, 24 and 36 months post-procedure. Alternative patency is defined as the absence of target lesion restenosis per duplex ultrasound PSVR < 2.4 and < 2.0 and freedom from clinically-driven TLR.

11. Lesion success, defined as achievement of a final in-lesion residual diameter stenosis of $\leq 50\%$ after using the study device.

12. Technical success, defined as achievement of a final in-lesion residual diameter stenosis of $\leq$ 50% (per angiographic core lab), using the paclitaxel-coated PTA balloon catheter without a device malfunction.

13. Clinical success (per subject) defined as technical success without the occurrence of major adverse events during procedure.

14. Procedural success (per subject) defined as lesion success without the occurrence of major adverse events during procedure.

15. Change in Ankle-Brachial Index (ABI) from baseline to 6, 12, 24, and 36 months post-procedure in subjects with:

i. Cohort 1: compressible arteries and baseline ABI < 0.9.

ii. Cohort 2: compressible arteries.

16. Change in Walking Impairment Questionnaire (WIQ) score from baseline to 6, 12, 24, and 36 months post-procedure.

17. Change in Rutherford Clinical Category (RCC) from baseline to 6, 12, 24, and 36 months post-procedure.

18. Change in EQ-5D from baseline to 6, 12, 24, and 36 months post-procedure.

4.6 Subject Selection Criteria

The study population includes those subjects with documented symptomatic stenosis of the superficial femoral artery (SFA) and/or popliteal artery. Assessment of eligibility is based on data available to the Investigator at the time of subject enrollment.

Cohort 2-ISR will allow the treatment of in-stent restenosis.

4.6.1 Inclusion/ Exclusion Criteria Cohort 1

Cohort 1 - General Inclusion Criteria

Subject must meet all of the following general inclusion criteria.

1. Has symptomatic leg ischemia, requiring treatment of the SFA and/or popliteal artery.
2. Has a Rutherford Clinical Category of 2 - 4. Note: Rutherford Clinical Category 2 subjects should be entered into the study if conservative treatment has been unsuccessful.
3. Is ≥ 18 years old.
4. Has life expectancy > 1 year.
5. Is able and willing to provide written informed consent prior to study-specific procedures.
6. Is willing and capable of complying with the required follow-up visits, testing schedule and medication regimen.

Cohort 1 - Angiographic Inclusion Criteria

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

1. Has evidence at the target lesion(s) of clinically and hemodynamically significant *de novo* stenosis or restenosis, or occlusion, in the SFA (1 cm distal to the ostium of the profunda) and/or popliteal artery (proximal to the popliteal trifurcation), confirmed by angiography.
2. Has target limb with at least one patent (<50% stenosis) tibio-peroneal run-off vessel to the foot confirmed by baseline angiography or magnetic resonance angiography (MRA) or computed tomography angiography (CTA). *Note: Treatment of outflow disease is NOT permitted.*
3. Has 1 or 2 target lesion(s) with a cumulative lesion(s) length of no more than 20 cm. NOTE: A maximum of two (2) lesions can be treated if the cumulative total lesion length (i.e. the combined length of both lesions) is less than or equal to 20cm.
4. Has target lesion(s) located >2 cm from any stent if the target vessel was previously stented.
5. Has a reference vessel diameter of 4 - 6 mm by visual estimate.

6. Has a successful exchangeable guidewire crossing of the lesion(s).

Cohort 1 - General Exclusion Criteria

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

1. A female who is pregnant, of childbearing potential not taking adequate contraceptive measures, or nursing; or a male intending to father children during the study.
2. Has significant gastrointestinal bleeding or any coagulopathy that would contraindicate the use of anti-platelet therapy
3. Has known intolerance to study medications, paclitaxel or contrast agents that in the opinion of the investigator cannot be adequately pre-treated.
4. Is currently participating in another investigational device or drug study that would interfere with study endpoints.
5. Has history of hemorrhagic stroke within 3 months.
6. Has surgical or endovascular procedure of the target limb within 14 days prior to the index procedure.
7. Has any planned surgical intervention (requiring hospitalization) or endovascular procedure within 30 days after the index procedure.
8. Has had a previous peripheral bypass affecting the target limb.
9. Has unstable angina pectoris, myocardial infarction, liver failure, renal failure or chronic kidney disease (dialysis dependent, or serum creatinine ≥ 2.5 mg/dL) within 30 days of the index procedure.

Cohort 1 - Angiographic Exclusion Criteria

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

1. Has significant stenosis (≥ 50%) or occlusion of inflow tract that is not successfully revascularized (< 30% residual stenosis without death or major vascular complication) prior to treatment of the target lesion(s). Only treatment of target lesion(s) is acceptable after successful treatment of inflow iliac artery lesion(s).
2. Has an acute or sub-acute intraluminal thrombus within the target vessel.
3. Has in-stent restenosis or restenosis of the target lesion following previous treatment with a drug-coated balloon.
4. Has an aneurysm (at least twice the reference vessel diameter) located in the target vessel, abdominal aorta, iliac, or popliteal arteries.
5. Has perforation, dissection or other injury of the access or target vessel requiring stenting or surgical intervention prior to enrollment.
6. Has no normal arterial segment proximal to the target lesion in which duplex ultrasound velocity ratios can be measured.
7. Requires use of adjunctive therapies (i.e., laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy).
8. Has severe calcification that precludes adequate PTA treatment.

4.6.2 Inclusion/ Exclusion Criteria Cohort 2

Cohort 2 - General Inclusion Criteria

Subject must meet all of the following general inclusion criteria.

1. Has symptomatic leg ischemia, requiring treatment of the SFA and/or popliteal artery.
2. Has a Rutherford Clinical Category of 2 - 4. Note: Rutherford Clinical Category 2 subjects should be entered into the study if conservative treatment has been unsuccessful.
3. Is between 18-85 years old.
4. Has life expectancy > 1 year.
5. Is able and willing to provide written informed consent prior to study-specific procedures.
6. Is willing and capable of complying with the required follow-up visits, testing schedule and medication regimen.
7. History of previous femoropopliteal nitinol stenting which is suspect for in-stent restenosis.
8. The patient has a resting ankle-brachial index (ABI) <0.9 or an abnormal exercise ABI (<0.9) if resting ABI is normal. Patient with incompressible arteries (ABI >1.2) must have a toe-brachial index (TBI) <0.7 in target limb.

Cohort 2 - Angiographic Inclusion Criteria

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

1. Has angiographic evidence of significant restenosis (≥50% by visual estimate) within a previously deployed femoropopliteal bare nitinol stent(s) including ISR Class I, II or III.
2. Has target limb with at least one patent (<50% stenosis) tibio-peroneal run-off vessel to the foot confirmed by baseline angiography or magnetic resonance angiography (MRA) or computed tomography angiography (CTA). *Note: Treatment of outflow disease is NOT permitted.*
3. Total target treatment length of in-stent restenosis must be ≥ 4.0 cm in length and may include a single lesion or a multifocal lesion within the femoropopliteal segment (This includes the proximal, mid, and/or distal SFA and P1, P2 and/or P3 segment of the popliteal artery). Edge restenosis may be treated provided the lesion extends no more than 3 cm outside the margin of the stent (proximal and/or distal margin).
4. Has a reference vessel diameter of 4 - 6 mm by visual estimate.
5. Has a successful exchangeable guidewire crossing of the lesion(s).

Cohort 2 - General Exclusion Criteria

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

1. A female who is pregnant, of childbearing potential not taking adequate contraceptive measures, or nursing; or a male intending to father children during the study.

2. Has significant gastrointestinal bleeding or any coagulopathy that would contraindicate the use of anti-platelet therapy
3. Has known intolerance to study medications, paclitaxel or contrast agents that in the opinion of the investigator cannot be adequately pre-treated.
4. Is currently participating in another investigational device or drug study that would interfere with study endpoints.
5. Has history of hemorrhagic stroke within 3 months including those within <60 days with an unresolved walking impairment.
6. Has surgical or endovascular procedure of the target limb within 3 months prior to the index procedure.
7. Has any planned surgical intervention (requiring hospitalization) or endovascular procedure within 30 days after the index procedure.
8. Has had a previous peripheral bypass affecting the target limb.
9. Has unstable angina pectoris, myocardial infarction within 60 days, liver failure, renal failure or chronic kidney disease (dialysis dependent, or serum creatinine ≥ 2.5 mg/dL) within 30 days of the index procedure.
10. History of previous femoropopliteal stenting in the target lesion with drug eluting stents or covered stents (endografts).

Cohort 2 - Angiographic Exclusion Criteria

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

1. Ipsilateral and/or contralateral iliac (or common femoral) artery stenosis ≥ 50% Diameter Stenosis (DS) that is not successfully treated prior to index procedure (e.g. where a perforation occurred requiring a covered stent) or with final residual stenosis ≥ 30% documented by angiography.
2. Identification of any lesion of the native vessel (excludes ISR) above the target stent in the femoropopliteal segment > 50% that is not successfully treated prior to index procedure (e.g. complication requiring additional treatment) or with final residual stenosis > 30% documented by angiography. DES and DCB will not be allowed. The lesion length must be treatable with a single stent (if required). The lesion must not be contiguous with the target lesion; at least 2 cm of normal appearing vessel between the lesion and target lesion/target stent or between deployed stent (if required) and the target lesion/target stent.
3. Has an acute or sub-acute intraluminal thrombus within the target vessel.
4. Has an aneurysm (at least twice the reference vessel diameter) located in the target vessel, abdominal aorta, iliac, or popliteal arteries.
5. Has perforation, dissection or other injury of the access or target vessel requiring stenting or surgical intervention prior to enrollment.
6. Has no normal arterial segment proximal to the target lesion in which duplex ultrasound velocity ratios can be measured.

7. Requires use of adjunctive therapies (i.e., laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy).
8. Grade 4 or 5 stent fracture affecting target stent or proximal to the target stent, or where evidence of stent protrusion into the lumen is noted on angiography in 2 orthogonal views.

4.7 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.

4.8 Informed Consent Process

Prior to conducting any study-related assessments and prior to administration of any pre-procedure medications or sedation, the principal investigator, or qualified designee, will explain to each subject all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study including, but not limited to, the following: purpose and nature of the study, study procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment. The principal investigator, or qualified designee, shall avoid any coercion or undue improper influence on, or inducement of, the subject to participate and will not waive or appear to waive the subject's legal rights. Subjects will be given a copy of the informed consent form and will be provided ample time to read and understand the document and the opportunity to ask questions. Subjects will be informed of their right to withdraw from the study at any time without prejudice; consent forms will use local non-technical language and be provided in a language understandable to the subject. After this explanation, and before any study-specific procedures have been performed, the subject and the principal investigator, or qualified designee, responsible for conducting the informed consent process will voluntarily sign and personally date the informed consent form. Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent and any other written information provided to the subject.

The principal investigator or qualified designee will document in the medical records and/or on the informed consent document the informed consent process, including the date of consent and name of the person conducting the consent process. Documentation of the time of consent is recommended if the informed consent process occurs on the same day as the index procedure. The principal investigator or qualified designee shall ensure important new information is provided to new and existing subjects throughout the clinical investigation.

4.9 Subject Enrollment

The subject is enrolled in the study after he/she has signed the subject informed consent, it has been determined that he/she meets all of the inclusion criteria and none of the exclusion criteria, and the pre-dilatation has been completed. The point of enrollment is defined as the moment the study device enters the vasculature.

4.10 Overview of Study Conduct

Table 2 provides an overview of the assessment requirements for the study. All testing and assessments should be conducted at the study site

Follow-up visits at 48 and 60 Months (Cohort 1) can be conducted via a telephone call to assess adverse events and record concomitant medication (name, dose, duration).

Table 2: Study Assessment Requirements

				Follow-Up Visits						
	Baseline (within 30 days prior to enrollment)	**Procedure**	**Discharge**	**1-Month** (15-45 days)	**6-Month** (150 – 210 days)	**12-Months** (335 – 395 days)	**24-Months** (670 – 790 days)	**36-Months** (1035-1155 days)	**48-Month** (1400-1520 days)***	**60-Month** (1765-1885 days)***
Informed Consent	X									
Medical History and Physical Exam	X									
Laboratory Tests**	X									
Concomitant Medication Use (anticoagulants and antiplatelet only)	X		X	X	X	X	X	X	X	X
Rutherford Clinical Category Assessment	X		X*		X	X	X	X		
Walking Impairment Questionnaire (WIQ)	X				X	X	X	X		
EQ-5D Questionnaire	X				X	X	X	X		
Ankle Brachial Index (ABI)/Toe Brachial Index (TBI)+	X		X*		X	X	X	X		
Angiogram		X								
Duplex Ultrasound			X*		X	X	X	X		
Adverse Event Evaluation		X	X	X	X	X	X	X	X	X
Stent Fracture Assessment (Cohort 2 only)		X								

*One Duplex Ultrasound, RCC and ABI occurring prior to 45 days post-procedure can occur at either the discharge visit or 1 month visit.
** Within 7 days prior to enrollment
*** 48 and 60 month follow-up visit only applicable for Cohort 1
+ TBI if applicable only for Cohort 2

4.11 Required Assessments and Tests

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

4.11.1 Medical History and Physical Examination

The subject's clinical history and pre-existing conditions will be assessed and documented at baseline.

4.11.2 Medication Use

The subject's medication use will be documented at baseline and all follow-up visits. Medication collection will include only anticoagulants and antiplatelet medications.

4.11.3 Laboratory Testing

Serum creatinine will be obtained and documented within 7 days prior to enrollment. Note: Chronic renal disease to be assessed in the exclusion criteria is defined as dialysis dependent, or sCr ≥ 2.5 mg / dL.Pregnancy test will be completed as appropriate.

4.11.4 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 beginning at pre-discharge or 1 month. Refer to the Manual of Operations for complete instructions on determining RCC.

4.11.5 Ankle-Brachial Index (ABI)/ Toe-Brachial Index (TBI) (Cohort 2 only)

The subject's ABI will be measured and documented at baseline and all follow-up visits beginning at pre-discharge or1 month. An ABI is the ratio of the highest ankle systolic pressure to the highest brachial systolic pressure. Refer to the Manual of Operations for complete instructions on measuring ABI and TBI (Cohort 2 only).

4.11.6 Walking Impairment Questionnaire (WIQ)

Each subject will undergo a WIQ assessment and the results will be documented at baseline and all follow-up visits beginning at 6 months. The WIQ is an interviewer-administered subject-reported functional assessment focused on difficulty in walking. Refer to the Manual of Operations for complete instructions on the WIQ.

4.11.7 EQ-5D Questionnaire

Each subject will complete an EQ-5D questionnaire and the results will be documented. The EQ-5D is a self-reported quality of life assessment used to measure health outcomes. EQ-5Ds questionnaire must be completed at baseline and all follow-up visits beginning at 6 months. Refer to the Manual of Operations for complete instructions on completing the EQ-5D questionnaire.

4.11.8 Angiogram

For procedural angiogram requirements see Section 4.13.1. Angiograms will be obtained per the Angiographic Protocol located in the Manual of Operations.

4.11.9 Duplex Ultrasound (DUS)

The subject will undergo a DUS, the results will be documented and copies of the scan will be sent to the core laboratory. DUS is required prior to 45 days post-procedure (completed at either discharge or 1 month visit), 6 months, 12 months, 24 months, and 36 months post-procedure. Refer to the Manual of Operations for the Duplex Ultrasound Protocol.

4.11.10 Stent Fracture Assessment (Cohort 2 only)

Pre-intervention radiographs of the target leg must be taken in two orthogonal views to assess stent fractures, and will be done according to the Angiographic Core Lab protocol. The operator must assess the stent(s) in the target lesion for stent fracture and grade prior to procedure to determine if the subject meets Angiographic Inclusion Criteria, of stent fracture Grade 0-3. Stent fractures Grade 4-5 are an Angiographic Exclusion

4.11.11Adverse Event (AE) Evaluation

For enrolled subjects, all adverse events will be collected, starting at the point of enrollment and throughout the duration of the study. Refer to Section 4.24 for AE definitions.

4.12 Baseline Requirements

Informed consent must be obtained from each subject prior to obtaining any study-related assessments (not standard of care for the institution) into the study in accordance with ISO 14155:2011, Declaration of Helsinki, and pertinent individual country laws/regulations.

Table 3 summarizes the list of all assessments and tests that are required at baseline.

Table 3: Baseline Requirements

Baseline Requirements	Timeframe Window
Informed consent	Within 30 days prior to enrollment
Medical history and physical exam	
Laboratory testing*	
Concomitant medication use	
Rutherford Clinical Category assessment	
Walking Impairment Questionnaire (WIQ)	
EQ-5D questionnaire	
Ankle Brachial Index (ABI)**/ Toe Brachial Index (TBI)+	

*Labs collected within 7 days prior to enrollment.

**Not required if subject has non-compressible arteries.

+ TBI if applicable only for Cohort 2

4.13 Procedure Requirements

The subject will undergo percutaneous revascularization of the superficial femoral and/or popliteal arteries. The target lesion(s) must be at least 1 cm distal to the ostium of the profunda.

See Section 4.14 for the required pre-procedure anticoagulation/antiplatelet therapy.

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

4.13.1 Angiogram

A sheath will be inserted and after insertion the subject should receive anticoagulation medications as indicated by the Investigator to maintain appropriate clotting time. Selective angiography of the limb to be treated including the distal aorta, bilateral iliac, ipsilateral femoral, popliteal and tibial-peroneal vessels (to the pedal level) will be performed to identify the anatomical characteristics of the vasculature and to best isolate and define the lesion. If a pre-procedure assessment has been completed with CTA/MRA or DUS including imaging of the distal aorta, the angiography can be limited to the target vessel, with a baseline assessment of run-off. Angiography must be conducted according the Angiographic Core Laboratory Protocol (refer to Manual of Operations). Gadolinium and CO_2 are not allowed for use as contrast medium.

During angiography the Investigator performing the procedure will assess the subject for the angiographic inclusion and exclusion criteria. The presense of severe calcification (defined as radioopacities noted on both sides of the arterial wall and extending more than 1cm in length prior to contrast injection or digital subtraction angiography), which may preclude an adequate PTA treatment, must be assessed to determine subject eligibility for Cohort 1 only. A radiopaque ruler will be used to define lesion length and define anatomical measurement references. If the subject meets all the inclusion criteria and does not meet any of the exclusion criteria, the subject is enrolled when the study device enters the vasculature.

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

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

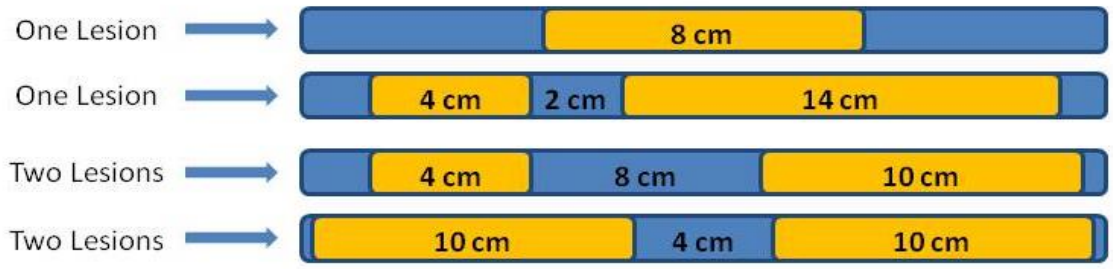
4.13.2 Treatment of Target Lesions

Cohort 1:

The lesion(s) intended for treatment at the time of the index procedure that meet the inclusion criteria and none of the exclusion criteria will be considered the “target lesions”. Each subject can have up to 2 target lesions as long as the maximum cumulative lesion length is no more than 20 cm.

If there are 3 cm or less between diseased segments needing treatment in the SFA and/or popliteal artery of the target limb (i.e., target vessel), then it can be considered one lesion if the total length is no more than 20 cm (see examples below). If there are more than 3 cm between diseased segments, they will be considered separate lesions and count as two lesions.

Examples of 1 or 2 Lesions:



Cohort 2:

One lesion of length ≥ 4cm meeting the inclusion and none of the exclusion criteria may be considered for enrollment.

4.13.3 Treatment of Non-Target Lesions

Prior to Study Procedure:

Any lesions in the non-target limb may be treated up to 1 day prior to target lesion treatment. Lesions in the target limb may be treated up to 14 days (Cohort 1) or 3 months (Cohort 2) prior to the target lesion treatment.

During Study Procedure:

Cohort 1:

Lesions in the iliac arteries, in either limb, that require treatment may be revascularized during the index procedure (prior to target lesion treatment). No other non-target lesions in the ipsilateral or contralateral limb may be treated during the index procedure. Iliac artery treatment must be successful, per Inclusion/Exclusion criteria, in order to enroll the subject except for stent placement. If stent placement is required, the stent placement in the iliac arteries may occur after the treatment of the target lesion(s).

Cohort 2:

Non-target lesions may be treated according to the following guidelines. Ipsilateral and/or contralateral iliac, common femoral artery and/ or proximal target vessel stenoses ≥ 50% DS may be treated prior to the target lesion by local standard of care; however, unsuccessful treatment (e.g. where a perforation occurred requiring a covered stent) or final residual stenosis ≥ 30% documented by angiography) would constitute an angiographic exclusion to participation in the Study. Treatment of in-flow lesions with DES and DCB is not allowed Angiographic exclusions to enrollment include: the need for any other cardiac or vascular surgical or interventional procedure, planned or predicted, prior to completion of the 30–day follow–up (including, but not limited to aortic, renal, cardiac, carotid, contralateral femoro-popliteal, and contralateral below the knee); and/or identification of any lesion below the target stent in the treated leg >50% that will require preplanned or predicted treatment during the index procedure or within 30 days of follow up.

The non-target lesions should be treated and complete run-off to the distal foot performed prior to completion of Angiographic Criteria assessment and target lesion treatment.

Following Study Procedure:

Treatment of other non-target lesions (ipsilateral or contralateral limb) following the index procedure must not occur within 30 days of the index procedure.

4.13.4 Vessel Preparation

Target lesion must be crossed by an exchangeable guidewire in an antegrade manner and without using a re-entry device. Retrograde access and/or re-entry devices are not permitted.

Pre-dilatation of the target lesion(s) is required with a non-drug coated balloon prior to study treatment. A lower profile balloon (i.e., at least 1 mm smaller diameter than necessary for the study balloon) should be used for pre-dilatation. In the event a subject has two target lesions, it is required that both lesions be pre-dilated prior to treatment with the study device (Cohort 1 only).

4.13.5 PTX PTA (DCB) Procedure

The diameter of the study balloon will be selected based on the vessel reference diameter distal to the target lesion. The balloons should be sized to ensure the full length of the lesion is treated and the balloon has full apposition to the arterial wall without oversizing. The length of the balloon will be selected in lengths approximately 10 mm longer than the target treatment area to allow the balloon to extend approximately 5 mm beyond the proximal and distal edges of the target lesion (per Investigator's visual estimate). In the event the target lesion length cannot be treated with a single catheter, a second treatment catheter is allowed. The second study balloon will be placed such that there is approximately 1 cm of overlap (marker to marker) between the coverage areas (per Investigator's visual estimate) to maintain continuous coverage of the target lesion. A maximum of two study balloons may be used for each target lesion treated.

The PTX PTA balloon catheters will be delivered and deployed per the *Instructions for Use* (IFU). All balloon inflations will be maintained for at least one minute.

If a study balloon enters the vasculature but isn't used to treat the subject, the subject is considered enrolled in the study and must complete the 30 day follow-up period and AE reporting through 30 days.

4.13.6 Adjunctive Procedures

Cohort 1:

For post-treatment residual stenosis >50% or flow-limiting dissection (grade D or greater), after study treatment, post-dilation must be performed using a commercially available bare balloon with prolonged inflations(s) (minimum 2 minutes) Thereafter, stent implantation, using a commercially available, non-drug eluting, bare metal stent, is allowed if residual stenosis remains >50%, a flow-limiting dissection (grade D or greater) is present, or there is a translesional pressure gradient >10 mmHg. The translesional pressure gradient can be measured using a pressure wire and simultaneously measuring pressures proximal and distal to the target lesion.

Cohort 2:

If upon completion of prescribed treatment, the Investigator determines that there is a suboptimal angiographic result (>50% residual stenosis in target treatment segment post assigned treatment), Provisional PTA with conventional balloons and/or stenting may be performed. Bailout stenting is only allowed to manage occurrence of flow-limiting dissection (grade D or greater), or threatened or

acute closure of target lesion. **Elective use of stents is a protocol deviation**. Additional procedures may be performed as medically necessary.

4.13.7 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.

4.13.8 Adverse Event Evaluation

For enrolled subjects, all adverse events will be collected, starting at the point of enrollment. See Section 4.24 for the AE definitions. Adverse event evaluations will also occur prior to discharge and at all follow-up visits.

4.14 Medical Anticoagulant/Antiplatelet Therapy

4.14.1 Pre-Procedure

All subjects are required to receive dual antiplatelet therapy with aspirin and clopidogrel (preferred medication), prasugrel, or ticlopidine per hospital standard of care prior to the procedure. The following doses for aspirin and clopidogrel are recommended:

- Aspirin (may be enteric-coated): ≥81 mg every day. If not currently taking aspirin, a bolus of 500 mg can be given the day before or the day of the procedure.
- Clopidogrel: 75 mg every day for 7 days prior to procedure, or 300 mg every day for 3 days prior to procedure, or 600 mg within 24 hours prior to or immediately after the procedure (while the subject is still on the table).

If prasugrel is administered, the recommended dose is 10 mg daily.

Ticlopidine should only be administered if the subject has a known allergy to clopidogrel or prasugrel. Recommended dose for ticlopidine is 250 mg twice a day. If a subject is prescribed ticlopidine, a complete blood cell count and differential is required prior to administration.

4.14.2 Peri-Procedure

The subject should receive anticoagulation as indicated by the Investigator to maintain appropriate clotting time. Medications provided during the study procedure do not need to be reported on the Case Report Forms.

4.14.3 Post-Procedure

The optimal duration of antiplatelet therapy for each subject is to be determined by the investigator. All subjects are recommended to receive antiplatelet therapy with aspirin and/or clopidogrel after the procedure. The following doses are recommended:

- Aspirin (may be enteric-coated): ≥81 mg every day indefinitely.
- Clopidogrel: 75 mg every day for a minimum of 4 weeks after the procedure. If the subject is intolerant of clopidogrel and prasugrel, ticlopidine may be used.

Recommendation Note: Subjects receiving ticlopidine should have a complete blood cell count and differential blood count completed.

4.15 Follow-Up requirements

All enrolled subjects are required to complete all follow-up visits.

4.16 Discharge Follow-up Requirements

All subjects are required to have a discharge assessment. Discharge assessment requirements are listed in Table 4.

Table 4: Discharge Assessment Requirements

Discharge Requirements	Timeframe
Concomitant medication use	Prior to discharge
Adverse event evaluation	
Duplex Ultrasound*	
Rutherford Clinical assessment*	
Ankle-brachial index*/ Toe brachial index+	

*One Duplex Ultrasound, RCC and ABI occurring prior to 45 days post-procedure can occur at either the discharge visit or 1 month visit.
+ TBI if applicable only for Cohort 2

4.17 Follow-up Visit Requirements

Following hospital discharge, all subjects are required to have follow-up visits at pre-determined time points during the study. Table 5 lists the requirements and visit windows for the 1-Month visit (One Duplex Ultrasound, RCC and ABI occurring prior to 45 days post-procedure can occur at either the discharge visit or 1 month visit), *One Duplex Ultrasound, RCC and ABI occurring prior to 45 days post-procedure can occur at either the discharge visit or 1 month visit. *Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.*
+ TBI if applicable only for Cohort 2

Table 6 for the 6-Month visit,

Table 7 for the 12-Month visit,

Table 8 for the 24-Month visit, and Table 9 for the 36-Month visit. The visit windows are specified according to number days following the index procedure.

The 1-Month follow-up visit can be conducted via a telephone call or a physician office visit. If a Duplex Ultrasound, RCC or ABI is required at the 1 month visit, the visit will be conducted in office. The 6, 12, 24, and 36 Month follow-up visits require a physician office visit and in-person evaluation.

For Cohort 1, the 48 and 60 Month follow-up visits (Tables 10 and 11) may be conducted via a telephone call or a physician office visit to assess adverse events and record concomitant medication (name, dose, duration).

Table 5: 1-Month Follow-Up Visit Requirements

Follow-up Requirements	Target	Window
Concomitant medication use	30 Days	15-45 Days
Adverse event evaluation		
Duplex Ultrasound*		
Rutherford Clinical assessment*		
Ankle-brachial index*/ Toe-brachial index+		

*One Duplex Ultrasound, RCC and ABI occurring prior to 45 days post-procedure can occur at either the discharge visit or 1 month visit. *Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.*

+ TBI if applicable only for Cohort 2

Table 6: 6-Month Follow-Up Visit Requirements

Follow-up Requirements	Target	Window
Concomitant medication use	180 Days	150-210 Days
Rutherford Clinical Category assessment		
Ankle-brachial index/ Toe Brachial index+		
WIQ		
Duplex Ultrasound*		
EQ-5D questionnaire		
Adverse event evaluation		

**Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.*

+ TBI if applicable only for Cohort 2

Table 7: 12-Month Follow-up Visit Requirements

Follow-up Requirements	Target	Window
Concomitant medication use	365 Days	335-395 Days
Rutherford Clinical Category assessment		

Ankle-brachial index/ Toe Brachial index[+]		
WIQ		
Duplex Ultrasound*		
EQ-5D questionnaire		
Adverse event evaluation		
**Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.* [+] *TBI if applicable only for Cohort 2*		

Table 8: 24-Month Follow-up Visit Requirements

Follow-up Requirements	Target	Window
Concomitant medication use	730 Days	670-790 Days
Rutherford Clinical Category assessment		
Ankle-brachial index/ Toe Brachial index[+]		
WIQ		
Duplex Ultrasound*		
EQ-5D questionnaire		
Adverse event evaluation		
**Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.* [+] *TBI if applicable only for Cohort 2*		

Table 9: 36-Month Follow-up Visit Requirements

Follow-up Requirements	Target	Window
Concomitant medication use	1095 Days	1035-1155 Days
Rutherford Clinical Category assessment		
Ankle-brachial index/ Toe Brachial index[+]		
WIQ		
Duplex Ultrasound*		
EQ-5D questionnaire		
Adverse event evaluation		
**Must be conducted per Duplex Ultrasound Protocol. Copies must be sent to the Duplex Ultrasound Core Laboratory for review.* [+] *TBI if applicable only for Cohort 2*		

Table 10: 48-Month Follow-up Visit Requirements (Cohort 1 only)

Follow-up Requirements	Target	Window
Concomitant medication use	1 460 Days	1 400-1 520 Days
Adverse event evaluation		

Table 11: 60-Month Follow-up Visit Requirements (Cohort 1 only)

Follow-up Requirements	Target	Window
Concomitant medication use	1 825 Days	1 765-1 885 Days
Adverse event evaluation		

4.18 Unscheduled and Re-intervention Visits During Follow-up

Completion of study assessments at unscheduled follow-up visits prior to the 60-month (Cohort 1) or 36 month (Cohort 2) 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 a target lesion prior to the 60-month follow-up (Cohort 1) or 36-month follow-up (Cohort 2) 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, EQ-5D and duplex ultrasound, even if the re-intervention and angiogram are declined. Copies of any angiographic or duplex ultrasound results must be sent to the appropriate core laboratory. These data will be collected and used for adjudication by the Clinical Event Committee for "clinically-driven" reintervention.

4.19 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 in the subject's medical records. Reasons for termination include but are not limited to: study completion, subject withdrawal, physician-directed subject withdrawal, lost-to-follow-up or death.

4.20 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 and sites must send at least one certified letter. 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).

4.21 Subject Withdrawal

All study subjects have the right to withdraw their consent at any time during the study. 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.

4.22 Deviations to the Study

Principal Investigators and site support staff must avoid protocol deviations. Any deviations from clinical protocol requirements will be considered protocol deviations and need to be reported to the sponsor. The sponsor will not make any exceptions to the protocol and will not provide waivers to subjects with any protocol deviations. 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.

4.23 Device Deficiency

A device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling. All device malfunctions must be reported to the sponsor.

If a device deficiency results in an adverse event for the subject, this adverse event (AE) will be considered reportable and must be reported as an adverse event. Device deficiencies that do not result in an adverse event for the subject do not need to be recorded as an AE, as they are not considered an AE.

If a device malfunction occurs with the Stellarex 035 DCB catheter, return the device as per the device return procedure .

4.24 Adverse Events

Adverse event reporting requirements and time frames are provided in Table 12 of Section 9.2.

4.24.1 Adverse Event Definitions[1]

Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device.

Serious Adverse Event (SAE) is defined as an adverse event that:

- Led to a death,
- Led to a serious deterioration in the health of the subject that either resulted in:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or body function,

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

  Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

For purposes of reporting within this protocol, pre-existing conditions and/or planned procedures for pre-existing conditions do not need to be reported as an adverse event or a SAE in the CRF unless there is an increase in severity or frequency during the course of the study. If a procedure is planned prior to enrollment and it is documented in the medical record as planned then an AE or a SAE does not need to be reported in the eCRF.

Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

4.24.2 Adverse Event Classifications

In addition to the definitions above, adverse events will be classified as a **major adverse event** defined as any clinically-driven TLR, major amputation of treated limb, or cardiovascular death.

4.24.3 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequalae.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

4.24.4 Adverse Event Relationships

The Investigators will evaluate whether or not the adverse events were related to the procedure, study requirements, and/or study device according to the following categories:

Not Related: The event is definitely not associated with the study device or procedure. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.

Unlikely: An adverse event has little or no temporal relationship to the study device or procedure and/or a more likely alternative etiology exists.

Possible: The temporal sequence between device application and or study procedure and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.

Probable: The temporal sequence between device application or study procedure and the event is relevant or the event abates upon device application completion/removal or procedure completion or the event cannot be reasonably explained by the subject's condition.

Highly Probable: The temporal sequence between device application or study procedure and the event is relevant and the event abates upon device application completion/removal or procedure completion, or reappearance of the event on repeat application or on repeat interventional procedures (re-challenge).

4.25 Deaths

Each subject death must be reported to the Sponsor. A death must be reported to the Sponsor or representative as soon as possible after the site's knowledge of the event. A written report will be provided to the Sponsor within 3 calendar days after the Investigator learns of a death and will be provided to the ethics committee according to the committee's 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.

4.26 Core Laboratory Requirements

4.26.1 Angiographic Core Laboratory

An independent Angiographic Core Laboratory will review all scheduled and unscheduled angiographic procedure data. See Angiographic Core Laboratory Protocol in the Manual of Operations.

4.26.2 Ultrasound Core Laboratory

An independent Ultrasound Core Laboratory will review all scheduled and unscheduled duplex scans. See Duplex Ultrasound Protocol in the Manual of Operations.

4.27 Committees

4.27.1 Clinical Events Committee

The Clinical Events Committee (CEC) is made up of angiologists, interventional radiologists, interventional cardiologists or vascular surgeons who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on the protocol.

At the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the CEC will be blinded to the primary results of the trial during the period of primary endpoint data collection.

The CEC is responsible for reviewing all reported adverse events (Cohort 1 only). The CEC will adjudicate and classify all primary and secondary endpoint events as defined in the clinical protocol. In addition, the CEC will be responsible for adjudicating and classifying any site reported device related or procedure related adverse events. The CEC will determine if any device related adverse event is an unanticipated serious adverse device effect. The committee will rule on all deaths that occur throughout the trial.

4.27.2 Study Steering Committee

The Steering Committee (SC) is the main policy and decision making committee of the study and has final responsibility for the scientific conduct. The specific tasks of the SC are to:

- Ensure proper design and conduct of the trial
- Verify ethical and professional standards of the trial
- Ensure that the results of the clinical trial and the scientific accomplishments are arrived at in the most efficient manner possible
- Enforce the publication policy

The steering committee will be composed of the global principal investigator and the international principal investigator from each geographic region (European Union, Asia Pacific and the Americas).

4.27.3 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will consist of at least 5 members with 3 members representing a quorum. Membership will include a biostatistician and independent representatives in relevant fields of clinical expertise, including but not limited to, physicians with one of the following specialties: interventional cardiology, vascular surgery, or interventional radiology. DSMB members will be not part of the study or committees related to the study. The DSMB will advise the sponsor regarding the continuing safety of trial subjects, including those to be recruited, as well as the continuing validity and scientific merit of the trial.

4.28 Case Report Forms

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

Case report forms related to the index procedure should be completed within two weeks following subject discharge. The follow-up forms must be completed in a timely manner after the follow-up visit.

Study monitors designated by the sponsor will review the information documented in the eCRFs and verify the information recorded is consistent with medical records and other source documents. Errors or incomplete entries will be rectified.

The sponsor will use the study data for statistical and tracking purposes and will treat the information as confidential. A regulatory representative may review or copy study records during an audit.

5.0 STATISTICAL METHODS

5.1 Statistical Methods – Cohort 1

5.1.1 *Sample Size*

This study is designed to continue to assess the safety and performance of the PTX PTA balloon catheter in a broad patient population. The predefined statistical analysis of the outcomes is detailed

below; however, no formal statistical success criteria are proposed. Therefore, the sample size of the study is not based on statistical formulas for hypothesis testing of the primary outcome.

5.1.2 *General Principles*

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.1 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software. Unless otherwise specified, data for all enrolled study subjects will be presented.

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.

5.1.3 *Analysis of Baseline Demographics and Procedural Characteristics*

All clinically relevant baseline demographics and procedure characteristics will be tabulated.

5.1.4 *Analysis of Outcomes*

Descriptive statistics will be provided for all study endpoints including the primary safety endpoint, the efficacy endpoint and all secondary endpoints. Categorical variables will be analyzed using frequency tabulation and event rate. For continuous variables, analysis will include mean, median, standard deviation, and ranges. Time-to-event variables including the primary safety endpoint will be analyzed using survival analysis and reported at 1 year (365 days), 2 years (730 days) 3 years (1095 days), 4 years (1,460 days) and 5 years (1,825 days) with Kaplan-Meier plots provided.

Prior to receipt of all 12 month data, results may be reviewed for submission to regulatory bodies. In these circumstances, data cut-off dates will be determined and documented prospectively.

5.1.5 *Handling Discontinued Subjects*

The primary endpoints will be analyzed using Kaplan-Meier survival analysis. This method includes each patient's data through evaluable time periods in order to predict event rates and rates of freedom from events. Since all patients contribute to the analysis regardless of whether they had the event of interest, discontinued subjects will not be analyzed with methods common to randomized controlled clinical trials, including simulations and last-event-carried-forward. The reasons for mortality and other study exits will be provided in a tabular format, and the number of patients analyzed at each study interval will be clearly listed.

5.1.6 *Analysis of Ability to Pool Data across Investigational Sites*

This is a multicenter 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 could be pooled. The following variables will be completed to assess the appropriateness of pooling data from across all sites:

- Baseline demographics such as age and gender
- Lesion characteristics such as lesion length and percent stenosis

The distributions of the above variables across the sites will be tabulated. To detect site differences, t-tests or Wilcoxon's rank-sum test will be used for continuous variables and Fisher's exact test for categorical variables.

5.2 Statistical Methods – Cohort 2

5.2.1 *Statistical Overview*

The ISR cohort study design is that of a single-arm trial in which there are two co-primary endpoints. The Stellarex 035 DCB treated group (Cohort 2) will be compared to historical control patients. The historical control patients include 68 patients who were randomized to the Spectranetics EXCITE ISR PTA control arm. The two endpoints and their corresponding statistical hypotheses are:

- Non-inferior Safety: Freedom from device and procedure related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 12 months post-procedure. (label π the probability of an event for the corresponding treatment group).
    - H_0: $\pi_{\text{Stellarex}} \leq \pi_{\text{EXCITE PTA}} + \delta$
    - H_1: $\pi_{\text{Stellarex}} > \pi_{\text{EXCITE PTA}} + \delta$ where δ is the non-inferiority margin of 0.05.
- Superior Effectiveness: Patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from target lesion revascularization. (label θ the probability of an event for the corresponding treatment group).
    - H_0: $\theta_{\text{Stellarex}} \leq \theta_{\text{EXCITE PTA}}$
    - H_1: $\theta_{\text{Stellarex}} > \theta_{\text{EXCITE PTA}}$

The analysis populations are Intention-to-Treat (ITT) , modified ITT (mITT), and Per-Protocol (PP); they are fully defined below in the next subsection.

5.2.2 *Analysis Populations*

The Intention-to-Treat (ITT) population will be comprised of all subjects who successfully complete the preliminary qualification procedures and are subsequently enrolled to receive the Stellarex 035 DCB.

The Modified Intention-to-Treat (mITT) will be comprised of all subjects in the ITT population who do not receive a bailout stent and did not receive provisional treatment for >50% residual stenosis post all assigned treatment or bailout stenting. The primary analysis for both safety and efficacy will be based on the mITT population.

The Per-Protocol (PP) population will consist of ITT subjects who had no bail-out stenting and no major protocol deviations defined by the study management team. The data for each subject will be reviewed by an independent angiographic core laboratory.

All trial endpoints will be analyzed using both the Intention-to-Treat, Modified Intention-to-Treat, and Per-Protocol populations, with the mITT analysis *a priori* designated as the primary analysis population.

5.2.3 *Statistical Analyses*

General Statistical Considerations

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Continuous variables that are recorded using approximate values (e.g., < or >) will be replaced by the closest exact value for the calculation of summary statistics. Categorical variables will be summarized using frequency counts and percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

The statistical analysis plan (SAP) should be referred to for further information on intended statistical methods. The SAP will be finalized and approved prior to study database lock. The SAP will detail the analytical methodology and assumptions beyond those presented below.

Analyses of Primary Endpoints

The primary analysis of the primary safety endpoint will be performed on the mITT analysis set. The primary efficacy and safety endpoints will be analyzed as dichotomous endpoints (success/failure) based on each subject's observed status at their 12 month followup visit. Patients who had an event prior to their 12 month follow-up will be considered as an event at the 12 month follow-up visit.

For the primary safety endpoint, the probability of non-inferiority is the probability the ILLUMENATE Global DCB Cohort 2 12-month rate is within the 0.05 non-inferiority margin from the EXCITE PTA 12-month rate. For the primary efficacy endpoint, the probability of superiority is defined as the probability the 12-month rate in the ILLUMENATE Global DCB Cohort 2 is greater than the EXCITE PTA 12-month rate. The 12 month rates will be estimated with multiple imuptation for missing values.

At the final analysis, study success will be declared if there is at least a 97.6% probability of superiority for the primary efficacy endpoint and at least a 97.5% probability of non-inferiority for

the primary safety endpoint. If non-inferiority is declared for the safety endpoint at the final analysis, a test of superiority will be conducted. Superiority in terms of safety will be declared if there is at least a 97.5% probability of superiority.

Because the treatments being compared are based on patients from two different clinical studies, a propensity score for membership in each patient group will be constructed as a function of baseline covariates. The primary analyses of efficacy and safety will be stratified according to the quantiles of the propensity scores. For the primary efficacy endpoint the probability of superiority and for the primary safety endpoint the probability of non-inferiority based on 5% non-inferiority margin will be determined across the strata. The final analysis will be conducted when all enrolled patients have had the opportunity to complete 12 months of follow-up. Missing data will be imputed by multiple imputation. If non-inferiority is declared for the safety endpoint at the final analysis with complete 12-month data, a test of superiority will be conducted. Superiority in terms of safety will be declared if there is at least a 97.5% probability of superiority. All tests are similar to a one-sided test at the 2.5% alpha level

Interim Analysis

There will be one interim analysis during the enrollment of the ISR cohort, to be conducted approximately 6 months from the date the last patient is enrolled. At this time, all enrolled ISR patients will have completed 6 months of follow-up. Based on the interim data, we will determine the predictive probability of success at the final analysis with complete 12 month data for the primary efficacy and primary safety endpoints. If, at the interim analysis, there is at least a 95% predictive probability of success on the primary efficacy endpoint and at least a 95% predictive probability of success on the primary safety endpoint, early trial success will be declared. If early trial success is not declared, the trial will continue to the final analysis with complete 12 month data. Even if early success is declared, follow-up of patients will continue to be followed in order to further refine the estimated efficacy and safety at 12 months. The critical values for early success and for declaring success at the final analysis have been calibrated to ensure the overall one-sided Type I error rate is controlled to ≤2.5% for each primary endpoint independently.

Study Operating Characteristics

The interim and final analyses for the ISR Cohort 2 will be characterized by simulation across varying assumptions of the efficacy and safety for the ISR cohort. For the purpose of simulation, efficacy and safety endpoints were considered as independent of each other. While the primary analysis will stratify by propensity score, propensity scores have not been included in the simulations to determine the trial's operating characteristics. Operating characteristics are based on 1,000 simulations per scenario.

In the EXCITE historical control patients, the 12-month rate for the primary efficacy endpoint is 66.6% (95% CI = 53.8%, 78.7%). Similarly, for the primary safety endpoint, the 12 month rate is 51.0% (95% CI = 38.2%, 63.8%). The one-sided simulated Type I error rate for the primary efficacy endpoint was 2.50% and the one-sided simulated Type I error rate for the primary safety endpoint was 2.23%. Type I error is based on 10,000 simulations. Assuming a fixed underlying true rate, if the I Global ISR Cohort 2 has equivalent 12-month efficacy and safety to that of the EXCITE historical control patients, there is essentially a 0% probability of declaring superiority on efficacy, and a 0% probability of declaring non-inferiority on safety.

If 12-month rate for the primary efficacy endpoint in the I Global ISR Cohort 2 is 46%, a 20% absolute improvement over the EXCITE historical control patients, there is an 83% probability of declaring success on the efficacy endpoint and a 41% probability of declaring an early success on efficacy. If 12-month rate for the primary safety endpoint in the Global ISR cohort is 36%, a 15% absolute improvement over the EXCITE historical control patients, there is an 83% probability of declaring success on the safety endpoint and a 38% probability of declaring an early success on safety.

Analysis of Secondary Endpoints

All secondary endpoints will be analyzed descriptively without hypothesis-testing.

For binary variables such as MAE or technical success, counts, percentages and exact 95% confidence intervals using Clopper-Pearson's method will be calculated. For continuous variables, means, standard deviations and 95% confidence intervals will be calculated.

Analysis of Subgroups

Subgroup analyses will be performed separately for subgroups defined by the following baseline characteristics; sex, race, age (< 65 versus ≥ 65), lesion length ≤ 180 mm versus ≥ 180 mm , lesion length < 200 mm versus ≥ 200 mm and reference vessel diameter (< 4 mm, 4 up to 5 mm, 5 mm up to 6 mm, and ≥ 6 mm). Separately for each subgroup, a time-to-event analysis will be performed. A Cox proportional hazards model through 12 months (365 days) will be fit with terms for study (EXCITE ISR PTA versus ILLUMINATE Global ISR DCB), subgroup membership, and the interaction between study and subgroup. This model will be stratified by the propensity score quartile to account for the non-randomized nature. If the p-value associated with the interaction term is less than 0.15, additional analyses will be performed to further understand these results. Results comparing study groups will also be presented for each level of each subgroup. Subgroup analyses will be descriptive in nature and are intended to examine possible heterogeneity of the treatment effect.

Analysis of Other Data

The clinical laboratory analyses may be analyzed by tabulating the number and percentage of subjects with clinically significant changes from baseline for each parameter at each time point.

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.

6.1 Potential Benefits

There are no guaranteed benefits from participation in this study; however, it has been shown that treatment with a PTX PTA balloon catheter 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 - Cohort 1 (PTX PTA Balloon Catheter)

Potential complications which may be associated with a peripheral balloon dilatation procedure include, but may not be limited to, the following:

- Abnormal heart rhythms
- Abrupt closure
- Allergic reaction to contrast medications
- Amputation
- Aneurysm
- Arrhythmias (bradycardia, tachycardia)
- Arterial dissection
- Arterial perforation or rupture
- Artery spasm
- Arterio-venous (AV) fistula
- Bleeding
- Bypass graft surgery
- Chest pain
- Coagulopathy
- Congestive heart failure
- Death
- Discomfort during procedure
- Embolism/Device embolism
- Endocarditis
- Femoral nerve compression with associated neuropathy
- Fever
- Groin bruising/discomfort
- Hematoma
- Hemorrhage
- Hypertension
- Hypotension
- Infection or pain at insertion site
- Injury to groin blood vessel
- Inflammation
- Ischemia
- Leucopenia
- Lymphocele
- Myocardial infarction
- Nausea
- Pseudoaneurysm
- Renal failure
- Respiratory failure
- Restenosis
- Sepsis
- Seizure
- Shock
- Stroke/CVA
- Thrombocytopenia
- Thrombus
- Total occlusion
- Unstable/stable angina
- Vessel trauma that may require intervention or surgical repair
- Vomiting
- Wound complication

Potential complications which may be associated with the addition of paclitaxel to a PTA balloon catheter include, but may not be limited to, the following:

- Abdominal pain
- Abnormal liver function
- Acne
- Allergic reaction to paclitaxel
- Alopecia
- Anemia
- Coagulopathy
- Edema (non-pulmonary)
- Gastrointestinal symptoms (e.g., diarrhea, nausea, pain, vomiting)
- Hemolysis
- Hematologic dyscrasia (including neutropenia)
- Hypercholesterolemia
- Hyperlipidemia
- Hypertension
- Hypertriglyceridemia
- Leucopenia
- Male hypogonadism
- Myalgia
- Pain
- Peripheral neuropathy

- Pneumonia
- Pyelonephritis
- Rash
- Renal tubular necrosis
- Sepsis
- Thrombocytopenia
- Transfusion
- Urinary tract infection
- Viral, bacterial, fungal infections

6.3 Potential Risks - Cohort 2 (CE-marked Stellarex 035 DCB)

Potential complications which may be associated with the addition of paclitaxel to a PTA balloon catheter include, but may not be limited to, the following:

- Abnormal heart rhythms
- Allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (drug, excipients, and materials)
- Amputation / loss of limb
- Aneurysm
- Arrhythmias
- Arterio-venous fistula (AVF)
- Bleeding
- Death
- Embolism/device embolism
- Fever
- Hematoma
- Hemorrhage
- Hypertension / hypotension
- Infection or pain at insertion site
- Inflammation
- Ischemia
- Occlusion
- Pain or tenderness
- Pseudoaneurysm
- Renal failure
- Restenosis
- Sepsis / Infection
- Shock
- Stroke/CVA
- Thrombosis
- Vessel dissection, perforation, rupture
- Spasm

Potential complications which may be associated with the addition of paclitaxel to a PTA balloon catheter include, but may not be limited to, the following:

- Allergic / immunologic reaction to paclitaxel
- Alopecia
- Anemia
- Gastrointestinal symptoms (Diarrhea, nausea, pain, vomiting)
- Hemolysis
- Hematologic dyscrasia (including neutropenia, leucopenia, thrombocytopenia)
- Histologic changes in vessel including inflammation, cellular damage, or necrosis
- Myalgia / arthralgia
- Peripheral neuropathy
- Rash
- Transfusion

As with any device requiring mechanical deployment and retraction, such as the Stellarex DCB catheter, there exists a risk of mechanical failure of the device resulting in potential surgical intervention to remove the device.

It is expected that the fluoroscopy time of the index procedure will be similar to that required for similar procedures conducted outside of a clinical study and will not pose additional risks to the subject or laboratory personnel.

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

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

While some of the potential risks identified have occurred in prior PTX PTA studies, and while Spectranetics believes that the risk for significant injury or death due to the study device is quite low, these risks have yet to be adequately and fully quantified. Eligibility criteria that exclude subjects who are at higher risk for experiencing an anticipated adverse event have been selected in order to reduce the potential risks to subjects that participate in this study.

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 substantial experience treating the superficial femoral artery in the past 12 months
- Currently treating subjects who meet the inclusion/exclusion criteria
- Ability to enroll an adequate number of subjects in the study
- Ability to perform required clinical testing, including: fluoroscopy, 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 compliance with all aspects of the study
- Adequate staffing to conduct the study. This includes:

Principal Investigator — 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 protocol, applicable laws, and applicable regulations; ensures informed consents are signed, and reviews and signs CRFs indicating documents are accurate and complete.

Sub-Investigator(s) Responsible for study activities in coordination with Principal Investigator and in accordance to the investigational plan. A site is not required to have a sub-investigator.

Study/Research Coordinator 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 CRFs to the sponsor in a timely manner.

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 protocol, and supporting documentation, including but not limited to, the *Instructions for Use* of the study device, CRFs, the informed consent process, Ethics Committee involvement, responsibilities and obligations, reporting requirements and general guidelines for good clinical practices.

Prior to enrolling subjects at an investigational site, the following documentation must be provided to the sponsor:

- EC and CA (if applicable) approval for the study protocol
- EC and CA (if applicable) approval for the principal investigator to conduct the study
- EC and Sponsor approved informed consent form for the study
- Investigator(s') *curriculum vitae* (CV)
- Financial disclosure documentation from the principal investigator, sub-investigators, and study staff, as applicable
- Signed Clinical Study/Trial Agreement and if applicable, Sub-Investigator Agreement(s)
- Completed training documentation form (provided by Sponsor or representative) to verify each physician conducting the procedure has been trained on the study device and the appropriate study staff has been trained on the protocol, device, CRFs, and study conduct, accordingly

8.0 MONITORING PROCEDURES

8.1 Monitoring Procedures

Spectranetics as the sponsor will be responsible for ensuring that adequate monitoring at each site is completed to ensure protection of the rights of subjects, the safety of subjects, and the quality and integrity of the data collected and submitted. Appropriately trained personnel appointed by Spectranetics will conduct monitoring at each site. Monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, investigational device accountability (if applicable), compliance with applicable laws and regulations, compliance with the 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 sent to the sponsor. The report will include the date of the monitoring visit, the site name, the name of the monitor, the name of the investigator, the names of other individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up. 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 study supplies shipped to the principal investigator/site, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study.

9.0 RESPONSIBILITIES, RECORDS and REPORTS

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/ Competent Authority approvals
- Informed Consent Forms
- Electronic Case Report Forms (eCRFs)
- Adverse event forms (and source documents)
- Subject termination information
- Protocol deviations
- Correspondence file regarding study
- Device disposition

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

9.2 Compliance with Protocol and Protocol Amendments

A protocol deviation is defined as any divergence from the study protocol. The investigator is responsible for promptly reporting protocol deviations to their Ethics Committee per Ethics Committee policy and to the sponsor. The sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and subject safety and determine if additional reports or actions are required. Additional action may include site re-training, removal of the devices, and/or site termination.

The investigator will not implement any changes to the protocol without first obtaining a written agreement from the sponsor and documented approval from the Ethics Committee, except in the event of an immediate hazard to the subject. The investigator will report the deviation in accordance with the applicable regulations.

9.3 Reports

Reports that are the sponsor or the principal investigator's responsibility to generate are listed in Table 12. 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 12: Reporting Responsibilities

Type of Report	Reporting Responsibilities	
	Report Prepared For	Reporting Time Frame
Adverse Events, observed device deficiencies and malfunctions with assessment	PI to Sponsor	Recorded as of point of subject enrollment; report within 10 business days of the investigator learning of the event.
Serious Adverse Events (SAE) or device deficiencies (including malfunctions) that could have led to a SAE	PI to Sponsor and Ethics Committee.	Recorded as of point of enrollment, (immediately), but not later than 3 calendar days, to Sponsor or representative after the principal investigator is first aware of the event. To Ethics Committee according to local guidelines.
Serious Adverse Events (SAE) or device deficiencies (including malfunction) that could have led to a SAE	Sponsor to all competent authorities of the participating Member States.	Immediately, but not later than 2 calendar days after awareness by the Sponsor, for SAEs with imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other subjects, users or other persons; or a new finding. Immediately, but not later than 7 calendar days after awareness by the Sponsor, for all other SAEs and device deficiencies that could have led to a SAE.
All SAEs in a multi-center study	Sponsor to all participating sites. PI to Ethics Committee if required by national regulations or Ethics Committee.	All SAE must be reported to all investigational sites.
Withdrawal of Ethics Committee approval (or other action on the part of the Ethics Committee that affects the study)	PI to Sponsor	Written - Within 5 working days of Ethics Committee decision.
Progress reports	PI to Sponsor and Ethics Committee	At intervals dictated by the Ethics Committee, but no less than yearly.
Emergency protocol deviations	PI to Sponsor and Ethics Committee	ASAP, but to Sponsor no later than 5 working days after the deviation occurs. To Ethics Committee according to local guidelines.
Inappropriate Informed Consent	PI to Sponsor and Ethics Committee	To Sponsor within 5 working days after the deviation occurs. To Ethics Committee according to local guidelines.
Final report	PI to Sponsor and Ethics Committee	To Sponsor within 3 months after termination or completion of study or Investigator's participation. To Ethics Committee according to local guidelines.

Type of Report	Reporting Responsibilities	
	Report Prepared For	Reporting Time Frame
Other	As Required	Upon request by the Ethics Committee to provide accurate, complete, and current information about any aspect of the study.

9.4 Device Accountability

Cohort 1:
This trial is an investigational trial and devices may not be used for the treatment of subjects not qualified for the study per the required entrance criteria. The Principal Investigator will maintain adequate records of the receipt and disposition of the investigational devices, including lot numbers, date used, subject identification (ID) number and treating physician. A device accountability log supplied by the Sponsor will be used. The device accountability log will be reviewed by the monitor during regular monitoring visits.

Use of any investigational device outside of the protocol is strictly forbidden and may constitute grounds for removal of the investigator/site from the clinical investigation.

Cohort 2:
This cohort will use Stellarex 0.035" OTW drug-coated angioplasty balloon commercially available devices with an investigational IFU (in Europe). In regions outside Europe, the device will be investigational use only. The Principal Investigator will maintain adequate records of the receipt and disposition of these devices, including lot numbers, date used, subject identification (ID) number and treating physician. A device accountability log supplied by the Sponsor will be used. The device accountability log will be reviewed by the monitor during regular monitoring visits.

9.5 Use of Information and Publication

All information and data generated in association with this study will be held in strict confidence until the study completion. The investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from the sponsor.

At the conclusion of each follow-up time point and the entire study, an abstract reporting the primary results may be prepared and presented in an appropriate international forum. A manuscript may also be prepared for publication in a scientific journal. The data and results from the study are the sole property of the sponsor. The sponsor shall have the right to access and use all data and results generated during the study. The sponsor acknowledges that the Principal Investigator(s) might desire to publish a multi-center publication regarding the trial results. The sponsor must receive any proposed publication and/or presentation materials at least 60 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the sponsor in compliance with the sponsor's publication policy set forth in the clinical study agreement or Investigator's Agreement

9.6 Records Custody

An Investigator may withdraw from the study. If the Principal Investigator withdraws from the study, responsibility for follow-up and maintaining the records must be transferred to a responsible

party (such as another study Investigator). Notice of transfer must be provided in writing by the Principal Investigator to the Sponsor and the EC no later than 10 working days after transfer occurs.

10.0 TRIAL TERMINATION

The Sponsor, DSMB and Steering Committee will monitor the progression of the study. If warranted, the study may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the study population.

Notification of suspension or termination will occur no later than five (5) business days after Sponsor makes the determination. In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the Ethics Committees, health authorities and all investigators. A suspended or terminated study may not be reinitiated without approval of the reviewing Ethics Committees (where applicable). The investigator should follow any subjects as standard of care at the institution.

The Sponsor has the right to terminate the trial at any time for any reason.

11.0 ABBREVIATIONS AND DEFINITIONS

Abbreviations

ABI	Ankle-Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
ASAP	As Soon As Possible
AV	Arterio-venous
BBC	Bare balloon catheter
BMI	Body Mass Index
CBC	Complete Blood Count
CE	Conformité Européene
CEC	Clinical Events Committee
CLI	Critical Limb Ischemia
CRF	Case Report Form
CTA	Computed Tomography Angioplasty
CV	Curriculum Vitae
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CVI	CV Ingenuity
DCB	Drug Coated Balloon
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasound
EC	Ethics Committee
ID	Identification
IFU	Instructions for Use
ISO	International Organization for Standardization
ISR	In-stent Restenosis
ITT	Intent-to-Treat
IV	Intravenous
LLL	Late Lumen Loss
MAE	Major Adverse Event
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
MRA	Magnetic Resonance Angioplasty
O.U.S.	Outside the United States
PAD	Peripheral Artery Disease
PI	Principal Investigator
PP	Per Protocol
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
PTX PTA	Paclitaxel-Coated Percutaneous Transluminal Angioplasty
QA	Quantitative Angiography
QALY	Quality-adjusted Life Year
RCC	Rutherford Clinical Category
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event

SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SC	Steering Committee
SFA	Superficial Femoral Artery
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect
WIQ	Walking Impairment Questionnaire

Definitions

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

Adjunctive Treatment: A procedure performed after treatment with the protocol-defined treatment

Adverse Event Definitions[2]

Adverse Event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Serious Adverse Event (SAE)	An adverse event that a) led to a death or b) led to a serious deterioration in the health of the subject that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life – threatening illness or injury or permanent impairment to a body structure or body function. c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event. For purposes of reporting within this protocol, pre-existing conditions

	and/or planned procedures for pre-existing conditions do not need to be reported as an adverse event or a SAE in the CRF unless there is an increase in severity or frequency during the course of the study. If a procedure is planned prior to enrollment and it is documented in the medical record as planned then an AE or a SAE does not need to be reported in the eCRF.
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (see definition above).
Unanticipated Serious Adverse Device Effect (USADE)	Any serious device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Adverse Event Relationship Categories (procedure, study device, or study requirement):

Not Related: The event is definitely not associated with the study device or procedure. The adverse event is due to an underlying or concurrent illness or effect of another device or drug.

Unlikely: An adverse event has little or no temporal relationship to the study device or procedure and/or a more likely alternative etiology exists.

Possible: The temporal sequence between device application and or study procedure and the event is such that the relationship is not unlikely or subject's condition or concomitant therapy could have caused the AE.

Probable: The temporal sequence between device application or study procedure and the event is relevant or the event abates upon device application completion/removal or procedure completion or the event cannot be reasonably explained by the subject's condition.

Highly Probable: The temporal sequence between device application or study procedure and the event is relevant and the event abates upon device application completion/removal or procedure completion, or reappearance of the event on repeat application or on repeat interventional procedures (re-challenge).

Amputation:

Major Amputation: Surgical removal of a limb or a part of a limb above the ankle .

Minor Amputation: Surgical removal of toes at or below the ankle.

Aneurysm: A localized, pathological, blood-filled dilatation of a blood vessel at least twice the reference vessel diameter caused by a weakening of the vessel wall.

Angina Pectoris

Braunwald Classification of Unstable Angina:

New onset of severe or accelerated angina. Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Canadian Cardiovascular Society (CCS) Classification of Stable Angina:

Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.

Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

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

Anticipated Adverse Event: An undesirable health related experience occurring to a subject whether or not considered related to the investigational device or drug regimen prescribed as part of the protocol that is predefined in the protocol and/or Instructions for Use that occurs or worsens during a clinical study.

Arterial Dissection:

Intimal disruption of the vessel wall with or without medial or adventitial contrast staining.

National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System: (0, A, B, C, D, E, F)

0: No dissection

A: Minor radiolucent areas in the lumen without impairment of flow or persistent dye staining after contrast runoff

B: Luminal flap that is radiolucent and that runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff

C: Contrast appears outside of the vessel lumen as an "extra-luminal cap". The staining appears even after contrast clears the lumen

D: Spiral radiolucent luminal filling defects. Often persistent staining after contrast clears from the vessel.

E: New and persistent filling defects in the vessel lumen.

F: Lesions that progress to impaired flow or total occlusion.

Arterial Flow:

During and following deployment, each vessel will be evaluated and graded, according to the following arterial flow parameters. These findings will be recorded and included in the study records.

Flow 0: No antegrade flow beyond the point of occlusion or target site.

Flow 1: Contrast passes the point of obstruction but "hangs up" and fails to opacify the entire distal vasculature during the duration of the cine-angiographic filming sequence.

Flow 2: Antegrade filling of contrast with complete filling of the artery and its major and minor branches, but with visually determined decreased rate of flow compared to flow rate observed during pretreatment angiogram. Alternatively, delayed contrast washout in the target site territory may occur.

Flow 3: Antegrade flow of contrast with complete filling of the artery and its major and minor branches with visually determined flow rate from equal to the flow rate observed during pretreatment angiogram.

Arterial Inflow:

For a lesion in the superficial femoral artery (femoro-popliteal level) inflow refers to the aorto-iliac level. Good inflow implies that vessels proximal to a target treatment site are free of hemodynamically significant lesions (≥ 50%).

Arterial Outflow:

For a lesion in the superficial femoral artery (femoro-popliteal level) outflow refers to combined levels distal to the lesion, including the following arteries: distal popliteal, tibioperoneal trunk, anterior tibial, posterior tibial, peroneal, dorsalis pedis, plantar and pedal. Good outflow implies that the distal popliteal, tibioperoneal trunk and at least one of the infrapopliteal arteries (anterior tibial, posterior tibial, peroneal) is free of hemodynamically significant lesions (≥ 50%) and that there is in-line flow into the foot.

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

Arterial 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.

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

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

Compressible Artery[1]: An artery without significant calcification that can be evaluated by duplex ultrasound or an artery that results in an ABI value < 1.3.

Clinical Success (per subject): Defined as technical success without the occurrence of major adverse events during procedure.

Chronic Kidney Disease: Dialysis dependent, or serum creatinine ≥ 2.5 mg/dL.

Death: When possible, death will be classified according to underlying cause. Death within 30-days of the study procedure will be classified as procedure related unless demonstrated otherwise.

Cardiovascular death:

Any death due to proximate cardiac cause (eg, myocardial infarction (MI), low-output failure, fatal arrhythmia), unwitnessed death, or death of unknown cause.

Device Deficiency: An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device Malfunction: A malfunction is a failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled.

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

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

Enrollment: The subject is enrolled in the study after he/she has signed the subject informed consent, it has been determined that he/she meets all of the inclusion criteria and none of the exclusion criteria, and the pre-dilatation has been completed. The point of enrollment is defined as the moment the investigational device enters the vasculature. **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.

[1] Creager Mark, Victor Dzau, and Joseph Loscalzo, eds. Vascular Medicine: A Companion to Braunwald's Heart Disease. Philadelphia, PA: Saunders Elsevier, 2006.

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

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

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

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

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

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

In-Stent Restenosis Classifcation:

Class I: Focal ISR (≤ 50 mm in length)

Class II: Diffuse ISR (> 50 mm in length)

Class III: Totally occluded ISR

Tosaka et al. Journal of the American College of Cardiology; Vol. 59, No. 1, 2012.

Intraluminal thrombus: A blood clot within a vessel.

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.

Lesion Success: Defined as achievement of a final in-lesion residual diameter stenosis of ≤ 50% (per angiographic core lab), after using the investigational device.

Major Adverse Event (MAE): Defined as clinically-driven target lesion revascularization, major amputation of the treated limb, or cardiovascular death.

Multilevel Disease: Presence of obstructive lesions at more than one level in the same extremity as the treatment lesion.

Myocardial Infarction

Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB,but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.[3]

National Heart, Lung and Blood Institute (NHLBI) Classification of Dissection[2]:

Dissection	Description
Type A	Small radiolucent area within the lumen of the vessel disappearing with the passage of contrast material
Type B	Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles
Type C	Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
Type D	Spiral shaped filling defect with delayed runoff of the contrast material in the distal vessel
Type E	Persistent luminal filling defect with delayed runoff of the contrast material in the distal vessel

[2] Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. Am J Cardiol 1991; 68: 467-71.
[3] Third universal definition of myocardial infarction. Thygesen K, et al. Eur Heart J. 2012 Oct;33(20):2551-67

Dissection	Description
Type F	Filling defect accompanied by total coronary occlusion

Occlusion: An obstruction within an artery.

Patency Rate:

Patency rate defined as the absence of target lesion restenosis determined by duplex ultrasound peak systolic velocity ratio (PSVR) of ≤ 2.5 and freedom from clinically-driven target lesion revascularization.

Ultrasound evidence will be used first to determine patency.

- Ultrasound images showing a PSVR of ≤ 2.5 will be considered patent by the core laboratory. In the event that the core laboratory cannot determine the PSVR, the core laboratory will make an assessment as to whether or not the lesion is patent, 50-99% stenosed or occluded.
- If ultrasound images are not available at a follow-up or analysis time point, and if an angiogram evaluation is available, the angiogram will be used to determine patency. A result of ≤ 50% residual stenosis will be considered patent.
- If both ultrasound and angiographic images are available at a given time point, and there is a conflict with respect to patency, the images will be provided to the Clinical Events Committee for adjudication.

Peak Systolic Velocity Ratio: In-lesion duplex ultrasound measurement that measures the peak velocity of blood (cm/second) within a lesion or stented vessel segment divided by the peak velocity of blood (cm/second) proximal to the lesion or stented vessel segment.

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.

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

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 ILLUMENATE Global outcomes of interest, or the physician deems it in the best interest for the safety or welfare of the subject to withdraw.

Popliteal Artery: Defined as the vessel located between Hunter's canal and the trifurcation of the anterior tibial, posterior tibial and peroneal arteries.

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

Protocol Deviation: Any divergence from the Study Protocol

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

Primary 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 without clinically-driven revascularization within the target lesion.

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 Success (per subject): Defined as lesion success without the occurrence of major adverse events during procedure.

Protocol Deviation: Any divergence from the Study Protocol.

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

Reference Vessel Diameter (RVD)

An approximation of the diameter of the vessel at the location of the target lesion. RVD is the average of vessel diameters proximal and distal to the target lesion. It will be estimated or measured by the investigator and also measured by the angiographic core lab.

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

Restenosis: Re-narrowing of the artery following the reduction of a previous narrowing. It is defined as the presence of a PSVR > 2.5 by duplex ultrasound or of a hemodynamically significant restenosis (≥ 50%), as determined by angiography.

Restenotic Lesion: A lesion in a vessel segment that had undergone a prior percutaneous treatment.

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

Rutherford Clinical Category[3]: 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 Calcification: Radiopacities noted on both sides of the arterial wall and extending more than one cm of length prior to contrast injection or digital subtraction angiography.

Stenosis: An abnormal narrowing of an artery.

[3] Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997 Sep;26(3):517-38.

Stent Integrity: Assessed by fluoroscopy or radiography, using two orthogonal views – AP and lateral) for subject eligibility using a 5 point scoring system.

Category	Clinical Description
0	No Strut Fractures
I	Single Tine Fracture
II	Multiple Tine Fracture
III	Stent fracture(s) with preserved alignment of the components
IV	Stent fracture(s) with mal-alignment of the components
V	Stent fracture(s) in a trans-axial spiral configuration

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

Superficial Femoral Artery (SFA)

The SFA connects to the popliteal artery at the opening of adductor magnus or hunter's canal towards the end of the femur.

Tandem Lesions: Two distinct lesions with 3 cm or less of healthy vessel separating the diseased areas.

Target Limb: The entire limb in which the target lesion is located.

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 (Cohort 2).

Target Lesion Revascularization (TLR):

Re-treatment by an invasive procedure, including atherectomy, angioplasty, stenting, endarterectomy, bypass, or thrombolysis, performed to open or increase the lumen diameter of the target lesion. TLRs will be classified as clinically-driven or non-clinically driven through an adjudication process. Diameter stenosis will be determined per Angiographic Core Laboratory assessment.

Clinically-Driven Target Lesion Revascularization:

A revascularization of the target lesion is considered clinically-driven if the PSVR $\geq$ 2.5 by duplex ultrasound or if angiography shows a percent diameter stenosis >50% and there is worsening of the Rutherford Clinical Category or ABI that is clearly referable to the target lesion. [Worsening is defined as deterioration (an increase) in the Rutherford Clinical Category by more than 1 category (>1 category) from the earliest post-procedural measurement, or

deterioration in the Ankle Brachial Index (ABI) by more than 0.15 from the maximum early post-procedural level])

TASC: See Trans-Atlantic Inter-Society Consensus

Target Vessel: The entire vessel in which the target lesion is located.

Target Vessel Revascularization (TVR): Any reintervention in the target vessel.

Clinically Driven Target Vessel Revascularization

A repeat revascularization procedure (percutaneous or surgical) of a lesion in the target vessel, exclusive of the target lesion site. A revascularization of the target vessel is considered clinically-driven the PSVR ≥ 2.5 by duplex ultrasound or if angiography shows a percent diameter stenosis >50% and there is worsening of the Rutherford Becker Clinical Category or ABI that is clearly referable to the target lesion. (Worsening is defined as deterioration (an increase) in the Rutherford Becker Clinical Category by more than 1 (>1) category from the earliest post-procedural measurement or deterioration in the Ankle Brachial Index (ABI) by > 0.15 from the maximum early post-procedural level.)

Technical Success: Defined as achievement of a final in-lesion residual diameter stenosis of ≤ 50% (per angiographic core laboratory), using the CVI paclitaxel-coated PTA balloon catheter without a device malfunction.

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 (TASC)[4]: A classification scheme for the assessment and management of peripheral arterial disease published in 2000.

Trans-Atlantic Inter-Society Consensus II (TASC II)[5]: A classification scheme for the assessment and management of peripheral arterial disease published in 2007.

Transient Ischemic Attack (TIA): Brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 24 hours, and without evidence of infarction.

Vascular Complications:

Access Site Occlusion:

Access site occlusion is defined as total obstruction of the artery usually by thrombus (but may have other causes) usually at the site of access requiring surgical repair.

Arteriovenous Fistula

A communication between an artery and a vein in which the arterial blood flows directly into a neighboring vein.

[4] Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg.* Jan 2000;31(1 Pt 2):S1-S296

[5] Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33 Suppl 1:S1-75

Peripheral Embolization

Peripheral embolization is defined as a loss of distal pulse, pain and/or discoloration (especially the toes). This can include cholesterol emboli. Indicate whether a peripheral embolization occurred distal to the arterial access site during the procedure or after lab visit but before any subsequent lab visits, requiring therapy.

Pseudoaneurysm

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

Retroperitoneal Bleed

An accumulation of blood in the retroperitoneal space.

Peripheral Ischemia

Inadequate blood supply in the study limb due to a blockage of blood vessels.A restriction in arterial blood flow by stenosis, restenosis or occlusion that, if prolonged, can lead to tissue damage.

Walking Impairment Questionnaire (WIQ): A disease-specific instrument utilized to characterize walking ability through a questionnaire as an alternative to treadmill testing. It is a measure of patient-perceived walking performance for patients with PAD and/or intermittent claudication.

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