A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Moxy™ Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries

LEVANT 2
CLINICAL TRIAL

Investigational Plan

Version 8.0

Sponsor:

LUTONIX®

[redacted]

Investigational Device: Moxy™ Drug Coated Balloon

NCT Number: 01412541*
*NCT Number added post-approval per CT.gov requirement

This study will be conducted in compliance with the protocol and all other applicable regulatory requirements including the archiving of essential documents.

PROTOCOL SIGNATURE PAGE

The LEVANT 2 Trial Investigational Plan

A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Moxy™ Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries.

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital Institutional Review Board/Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to ICH Good Clinical Practice (GCP), ISO 14155, Declaration of Helsinki 21CFR 50, 56 and 812, and any local regulations.

Clinical Site Name_____

_____	_____	
Site Principal Investigator (Print Name)	Site Principal Investigator (Signature)	Date

Received by Sponsor:

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Date

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Initials

The Lutonix LEVANT 2 Trial Protocol Summary

Title	A Prospective, Multicenter, Single Blind, Randomized, Controlled Trial Comparing the Moxy™ Drug Coated Balloon vs. Standard Balloon Angioplasty for Treatment of Femoropopliteal Arteries (LEVANT 2)
Test Device	Moxy™ Drug Coated Balloon
Control Device	Non-coated standard percutaneous transluminal angioplasty balloon catheter (standard PTA catheter)
Study Design	Prospective, Multicenter, Single Blind, Randomized, Safety and Efficacy
Overview	The study will enroll patients presenting with claudication or ischemic rest pain and an angiographically significant lesion in the superficial femoral or popliteal artery and a patent outflow artery to the foot. After successful protocol-defined pre-dilatation, subjects that are determined not to require stenting based on defined angiographic criteria are randomized 2:1 to treatment with either the Moxy Drug Coated Balloon (test arm) or standard PTA catheter (control arm). Subjects that do not meet post-predilatation lesion criteria are excluded (and treated per standard practice) and followed for safety for 30 days. Randomized subjects will have ultrasound and clinical follow-up through 2 years and telephone follow-up through 5 years. An Economic Assessment sub-study (AMORE) will be conducted at sites in the USA.
Purpose	To assess the safety and efficacy of the Moxy Drug Coated Balloon for treatment of stenosis or occlusion of the femoral and popliteal arteries
Objective	To demonstrate the superior efficacy and non-inferior safety of the Moxy Drug Coated Balloon by direct comparison to standard PTA catheter for treatment of stenosis of the femoropopliteal arteries
Randomization	Subjects will be randomized 2:1 to Moxy Drug Coated Balloon or standard PTA catheter
Enrollment	Enrollment will occur at up to 55 global centers. Approximately 750 subjects will be enrolled in order to include a total of 476 randomized subjects. Enrollment will be stopped once 476 subjects are randomized. An additional 55 roll-in subjects may be included for site training purposes. Approximately 50% of randomized enrollment will be in the USA.
Randomized Subject Follow-Up Schedule	*Clinical*: 6, 12, and 24 Months *Duplex Ultrasound (DUS):* 0-30 days, 6 months, 12 months, and 24 months *Telephone:* 1, 36, 48 and 60 Months
Primary Endpoints	<u>Safety</u> Composite of freedom from all-cause peri-operative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death.

	Efficacy Primary Patency of the target lesion at 1 year. Primary Patency is defined as the absence of target lesion restenosis (defined by DUS peak systolic velocity ratio (PSVR) ≥2.5) and freedom from target lesion revascularization (TLR).
Secondary Endpoints	*Efficacy* • Acute Device, Technical and Procedural success The following endpoints will be assessed at 6, 12 and 24 Months: • Primary and Secondary Patency (DUS PSVR <2.5) • Alternative Primary and Secondary Patency based on alternative definitions of DUS PSVR <2.0 and <3.0 • DUS Clinical Patency (DUS PSVR <2.5 without prior Clinically Driven TLR) • Target Lesion Revascularization (TLR) o Clinically-driven o Total *(clinical and DUS/angiography-driven)* • Change of Rutherford classification from baseline • Change of resting Ankle Brachial Index (ABI) from baseline • Change in Walking Impairment Questionnaire from baseline • Change in Six Minute Walk Test from baseline in a subset of patients • Change in quality of life from baseline, as measured by EQ-5D and SF36-v2 surveys *Safety* • Freedom at 30 days from all-cause death, index limb amputation above the ankle and target vessel revascularization (TVR) (VIVA Safety Endpoint) • Composite of freedom from all-cause perioperative (≤30 day) death and freedom from the following at 1, 6, 24, 36, 48, and 60 months: index limb amputation, index limb re-intervention, and index-limb-related death. The following endpoints will be assessed at 1, 6, 12, 24, 36, 48 and 60 months: • All-cause death • Amputation (above the ankle)-Free Survival (AFS) • Target Vessel Revascularization (TVR) • Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature • Major vascular complications

	• Readmission for cardiovascular events *Other* • Target limb related hospital days at 1 and 2 years

Inclusion Criteria	Clinical Criteria 1. Male or non-pregnant female ≥18 years of age; 2. Rutherford Clinical Category 2-4; 3. Patient is willing to provide informed consent, is geographically stable and comply with the required follow up visits, testing schedule and medication regimen; <u>Angiographic Criteria</u> Lesion Criteria 4. Length ≤15 cm; 5. Up to two focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. two discrete segments, separated by several cm, but both falling within a composite length of ≤15 cm); 6. ≥70% stenosis by visual estimate; 7. Lesion location starts ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the TP trunk; 8. *de novo* lesion(s) or non-stented restenotic lesion(s) >90 days from prior angioplasty procedure; 9. Lesion is located at least 3 cm from any stent, if target vessel was previously stented; 10. Target vessel diameter between ≥4 and ≤6 mm and able to be treated with available device size matrix; 11. Successful, uncomplicated (without use of a crossing device) antegrade wire crossing of lesion; 12. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions); NOTE: Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication. 13. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure); 14. Contralateral limb lesion(s) cannot be treated within 2 weeks before and/or planned 30 days after the protocol treatment in order to avoid confounding complications; 15. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment.

Exclusion Criteria	**Patients will be excluded if ANY of the following conditions apply:** 1. Pregnant or planning on becoming pregnant or men intending to father children; 2. Life expectancy of <5 years; 3. Patient is currently participating in an investigational drug or other device study or previously enrolled in this study; NOTE: Enrollment in another clinical trial during the follow up period is not allowed. 4. History of hemorrhagic stroke within 3 months; 5. Previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the index procedure; 6. History of MI, thrombolysis or angina within 2 weeks of enrollment; 7. Rutherford Class 0, 1, 5 or 6; 8. Renal failure or chronic kidney disease with MDRD GFR ≤30 ml/min per 1.73 m^2 (or serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis); 9. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion; 10. Inability to take required study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication; 11. Anticipated use of IIb/IIIa inhibitor prior to randomization; 12. Ipsilateral retrograde access; 13. Composite lesion length is >15 cm or there is no normal proximal arterial segment in which duplex flow velocity can be measured; 14. Significant inflow disease. Successful treatment of inflow disease allowed prior to target lesion treatment; 15. Known inadequate distal outflow (>50 % stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion; 16. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel; 17. Severe calcification that renders the lesion un-dilatable; 18. Use of adjunctive treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).
Primary Analytical Subset	Intent-to-treat (ITT) composite dataset including all randomized subjects. Secondary as-treated and per-protocol analyses will also be performed.

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Sponsor/ Contact:	Lutonix, Inc. [redacted]
US CRO	[redacted]
EU CRO	[redacted]
Electronic Data Capture (EDC)	[redacted]
Angiographic Core Lab	[redacted]
DUS Core Lab	[redacted]
Pharmacokinetic Core Lab	[redacted]
EU Authorized Representative:	[redacted]

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1 INTRODUCTION

The purpose of this investigation is to assess the safety and efficacy of the Moxy™ Drug Coated Balloon for treatment of a stenosis or occlusion of the femoropopliteal arteries.

1.1 CLINICAL BACKGROUND

Peripheral arterial disease (PAD) is estimated to be present in 3% of people in the age range of 40-59 years and in 20% of people over 70 years[1] of age. The femoropopliteal artery is the most commonly diseased artery in the peripheral circulation, and is the site of a larger percentage of lower limb interventions[2]. Because of the vessel's unique characteristics, such as significant shortening, elongation, torsion, flexion, and vulnerability to external compression, superficial femoral artery (SFA) disease can be associated with severe and life threatening complications[3] and a very high frequency of restenoses after percutaneous intervention[4]. The Moxy Drug Coated Balloon may help reduce the rates of restenosis and the need for repeat endovascular or surgical procedures.

Four decades after the first femoropopliteal angioplasty was performed with sequential dilators in 1964[5], a durable endovascular treatment for femoropopliteal disease is yet to be identified. Percutaneous transluminal angioplasty (PTA) has become the most common therapy, but PTA is challenged by a high rate of restenosis and a frequent need for reintervention; the one year patency of PTA without reintervention is estimated to be only 33% in a recent meta-analysis[6]. Bare metal stents (BMS) were successful at preventing recoil and dissection, but stent outcomes in the femoropopliteal artery are complicated by stent fracture, and restenosis rates of BMS are as high as 40-60% in the peripheral vasculature[7]. Restenosis is caused by neointimal hyperplasia, a hyperproliferative response to the vessel injury caused by angioplasty and the foreign body reaction and abnormal vessel geometry caused by stent implantation. In the coronary vasculature, this challenge has largely been mitigated in the last decade by the introduction of drug eluting stents (DES). However, in the peripheral vasculature DES have not proven as beneficial[8],

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[1] Zeller, T. Current state of endovascular treatmet of femoro-popliteal artery disease. *Vas Med* 12 (2007): 223-234.

[2] Levy PJ. Epidemiology and pathology of peripheral arterial disease. *Clin Cornerstone.* 2002; 4(5):1–15.

[3] Murabito JM, et. al. Temporal trends in the incidence of intermittant claudication from 1950 to 1999. *Am J of Epidemiol 2005;162:430-7)*

[4] Smouse, HB, et. al. Biomechanical forces in the femoropopliteal arterial segment. *Endovascular Today.* 2005; June 60.

[5] Dotter, CT. Transluminal recanalization and dilatation in atherosclerotic obstruction of femoral popliteal system. *Am Surg* 31 (1965): 453-59.

[6] Rocha-Singh, KJ, et. al. Performance Goals and Endpoint Assesssments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients with Symptomatic Peripheral Arterial Disease. *Cath and Cardio Inter* 69 (2007): 910.

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

[8] Duda, SH et. al. Drug-Eluting and Bare Nitinol Stents for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery. *J Endovasc Ther* 13 (2006): 701.

although a recent publically presented peripheral study investigating a paclitaxel coated stent has shown benefit over BMS[9].

The introduction of bare nitinol stents improved outcomes over PTA alone and early generation BMS showed a primary patency between 60 and 80% at one year. The recently published RESILIENT study[10] tested a new, flexible nitinol stent and showed a primary patency rate of 81.3% in the stent group vs. 36.7% in the PTA group. Provisional nitinol stent implantation has become the worldwide standard-of-care in the SFA in cases where PTA results are suboptimal (e.g. flow limiting dissection, severe recoil, or unacceptable residual stenosis). Provisional stenting is designated as a 'class IIa' recommendation per the most recent 2005 ACC/AHA guideline for management of peripheral artery disease[11].

Stent outcomes in the femoropopliteal artery are complicated by the vessel's unique physiologic characteristics and possibility of stent fracture, and restenosis remains a clinical challenge. In addition, implantation of a stent can complicate and limit the treatment choices available to the patient in the event repeat intervention or surgery becomes necessary.

A novel therapy that is commercially available in some countries and under investigation in others is the drug coated balloon (DCB), an otherwise standard PTA catheter with a drug coating on the balloon surface. During angioplasty, DCBs are designed to deliver an anti-proliferative drug directly to tissues of the treated vessel wall, thus inhibiting neointimal hyperplasia and restenosis without the need for a permanent foreign body implant. The investigational device of the present study, the Moxy Drug Coated Balloon, is one example of a DCB.

To date, two pilot European clinical trials for treatment of femoropopliteal arteries have been performed by another manufacturer to assess their drug coated balloons using the Paccocath® technology. The Paccocath coating contains the same active pharmaceutical ingredient (API) – paclitaxel - as in the Lutonix drug coating, but a different carrier (iopromide). This same API is currently used in some manufacturers' approved drug eluting stents. Both studies have

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[9] Dake M. The Zilver PTX Randomized Trial: 12 month Results of a Paclitaxel-Eluting Stent Versus Balloon Angioplasty and Bare Metal Stenting in Patients with Femoropopliteal Artery Disease Presentation at 2010 TCT.

[10] Laird, JR, Katzen BT et. al. Nitinol Stent Implantation Versus Balloon Angioplasty for Lesions in the Superficial Femoral Artery and Proximal Popliteal Artery: Twelve-Month Results From the RESILIENT Randomized Trial. *Circ Cardiovasc Interv*. 2010;3:267-276.

[11] Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WRC, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr., White CJ, White J, White RA. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease [Lower Extremity, Renal, Mesenteric, and Abdominal Aortic]). J Am Coll Cardiol. 2006;47:1239–1312.

demonstrated preliminary safety and decreased restenosis of the femoropopliteal lesions in the context of standard-of-care stenting. Both the THUNDER[12] and FemPac[13] studies were prospective, randomized, controlled, multi-center clinical trials that compared the Paccocath coated DCB to control PTA with provisional stenting allowed in both arms. Subject characteristics were similar in both studies, however overall lesion lengths were notably shorter in the FemPac trial. In both studies, DCB-treated subjects had significantly less late lumen loss (the primary endpoint), less restenosis, and a lower rate of reintervention (target lesion revascularization (TLR)) at 6 months than those treated with control PTA. The potential benefit of DCB demonstrated by these pilot studies is tabulated in the Table 1.

TABLE 1: THUNDER AND FEMPAC RESULTS

THUNDER		
Endpoint	DCB (n=48)	PTA (n=54)
Late Lumen Loss (6 month), n±SD - Primary Endpoint *(p=0.001)*	0.4 ±1.2	1.7 ±1.8
Binary Restenosis (6 month)	17%	44%
TLR (6 month)	4%	37%
TLR (24 month)	15%	52%
FemPac		
Endpoint	DCB (n=41)	PTA (n=48)
Late Lumen Loss (6 month), n±SD - Primary Endpoint *(p=0.031)*	0.5 ±1.1	1.0 ±1.1
Binary Restenosis (6 month)	19%	47%
TLR (6 month)	7%	33%
TLR (24 month)	13%	50%

The results of these two early pilot studies suggest that local delivery of paclitaxel by a DCB directly to tissues of the diseased vessel wall is safe and effective as a treatment for femoropopliteal stenosis.

1.1.1 THE LEVANT I FIRST-IN-MAN TRIAL SUMMARY

The LEVANT I trial (NCT00930813) is a trial which compared femoropopliteal treatment with the Moxy Drug Coated Balloon to a standard PTA catheter (with and without stenting) with a primary endpoint of late lumen loss. One hundred-one randomized subjects have been enrolled at 9 European centers. After a defined pre-dilatation, subjects were stratified to the balloon strata or stent strata and then randomized to treatment with the Moxy Drug Coated Balloon or a standard PTA catheter (control group). Subject inclusion and exclusion criteria were similar to previous

[12] Tepe G. et, al. Local Delivery of Paclitaxel to Inhibit Restenosis during Angioplasty of the Leg. *NEJM*. 2008, 358;7. 689-699.

[13] Werk M et. al. Inhibition of Restenosis in Femoropopliteal Arteries. *Circulation.* 2008;118(13):1358-65.

femoropopliteal studies, with lesion length of 4-15 cm and vessel diameter 4-6 mm. Subject demographics, baseline lesion characteristics, Rutherford Category, device, and procedural success were similar between arms. The Moxy Drug Coated Balloon showed safety at 30 days compared to control with no unanticipated adverse device effects, similar adverse event rates and no reports of thrombus in the DCB arm.

At 6 months, clinical follow up compliance was 91%, and 74% and subjects underwent protocol defined repeat angiography. Major 6-month angiographic and clinical endpoint results are listed in Table 2 for the intent-to-treat (ITT) population (n=101) and in Table 3 by stratification group.

TABLE 2: LEVANT I TRIAL PRIMARY ANALYSIS AT 6 MONTHS, ITT

Angiographic	**Moxy Drug Coated Balloon**	**PTA**
Primary Endpoint, n ±SD *- Late Lumen Loss (p = 0.016)*	*0.46 ±1.13*	*1.09 ±1.07*
Binary Restenosis, n/N (%)	11/39 (28)	18/35 (50)
Clinical	**Moxy Drug Coated Balloon**	**PTA**
TLR, n/N (%)	6/47 (12.8)	10/45 (22.2)
TVR, n/N (%)	6/47 (12.8)	15/46 (32.6)
Thrombosis, n/N (%)	0/49 (0)	2/52 (4)
Amputation , n/N (%)	1/49 (2)*	0/52 (0)
Death, n/N (%)	1/49 (2)*	3/52 (6)

**Amputation and Death in same subject. Formally adjudicated as not device or procedurally related.*

TABLE 3: LEVANT I RESULTS BY STRATIFICATION GROUPS AT 6 MONTHS

Angiographic	**Balloon-Only Strata**		**Stent Strata**	
	Moxy	PTA	Moxy	PTA
Late Lumen Loss, n ±SD	0.45 ±1.18	1.19 ±1.15	0.49 ±1.01	0.90 ±0.91
Binary Restenosis, n/N (%)	9/31 (29)	14/24 (58)	2/8 (25)	4/11 (36)
Clinical	Moxy	PTA	Moxy	PTA
TLR, n/N (%)	5/36 (13.9)	7/33 (21.2)	1/11 (9.1)	3/13 (23.1)
TVR, n/N (%)	5/36 (13.9)	9/33 (27.3)	1/11 (9.1)	6/13 (46.2)

In the ITT population, the primary endpoint of mean late lumen loss at 6 months was significantly lower in the Moxy Drug Coated Balloon arm (0.46±1.13) compared to the PTA arm (1.09±1.07), with a p value of 0.016, consistent with efficacy of Moxy Drug Coated Balloon for this indication. The difference in mean late loss between arms was also significant in the balloon-only stratification group (0.45±1.18 vs. 1.19±1.15, p=0.024).

The Moxy Drug Coated Balloon demonstrated safety comparable to conventional PTA in the LEVANT I Trial, with similar AE and SAE rates through 6 months. There were no unanticipated

adverse device effects in the drug-coated balloon arm, and overall adverse event rates were similar to conventional uncoated balloon angioplasty. Secondary clinical endpoints trended in favor of the Moxy Drug Coated Balloon arm, particularly TLR (12.8% vs. 22.2% in PTA arm) and target vessel revascularization (TVR) (12.8% vs. 32.6%).

As part of a pharmacokinetics sub-study, serum paclitaxel levels were collected and analyzed in 7 Moxy Drug Coated Balloon subjects. All subjects had detectable serum paclitaxel immediately after the index procedure, with a mean maximum concentration C_{max} = 58.4±83.2 ng/mL. Mean total exposure AUC_{all} = 73.2±45.3 ng*h/mL. The mean residence time (from index procedure to the last measurable concentration) of paclitaxel in serum MRT_{last} = 5.64±4.56 hours.

In summary, 6-month results demonstrated the feasibility, safety, and efficacy of the use of the Moxy Drug Coated Balloon for treatment of femoropopliteal lesions, with a significantly improved late lumen loss and similar adverse events rates as compared to PTA through 6-months.

1.2 DEVICE AND STUDY RATIONALE

The Moxy Drug Coated Balloon is indicated for percutaneous transluminal angioplasty of obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries ≤15 cm in length and ≥4.0 to ≤6.0 mm in diameter.

The drug coating on the Moxy Drug Coated Balloon contains paclitaxel and excipients (drug carrier) with a history of human safety for intravenous use. Each component has been safely used in other products. PTA catheters have been in commercial use for over 25 years, and the Moxy Drug Coated Balloon meets international standards (e.g. ISO 10555) developed over time to validate the mechanical safety of dilation catheters. The anti-proliferative drug paclitaxel is a well understood active pharmaceutical ingredient (API) with an extensive history of human use in oncology[14] and drug-eluting stents (DES)[15]. The maximum total dose of 3.8 mg on the largest peripheral Moxy Drug Coated Balloon is less than 2% of the dose of approximately 300mg infused during a single course of cancer therapy. In addition, GLP animal Safety and Safety Margin studies have been performed to confirm the safety of the Moxy Drug Coated Balloon.

2 STUDY OBJECTIVES AND ENDPOINTS

Data from all subjects will be analyzed on an ITT basis regardless of final treatment disposition, device success or procedural success.

[14] Pacific Yew: Draft Environmental Impact Statement. Appendices. U.S. Departments of Agriculture, Interior, and Health and Human Services. January 1993.

[15] Lasala J, et.al. An Overview of the TAXUS® Express®, Paclitaxel-Eluting Stent Clinical Trial Program. Journal of Interventional Cardiology. 2006, Vol 19: 5 pp431-442

2.1 PRIMARY OBJECTIVE

The primary objective of the LEVANT 2 Clinical Study is to demonstrate superior efficacy and non-inferior safety at one year of the Moxy Drug Coated Balloon by direct comparison to a standard PTA catheter for treatment of stenosis or occlusion of the femoropopliteal arteries.

2.2 PRIMARY ENDPOINTS

2.2.1 SAFETY

The primary safety endpoint is the composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death.

2.2.2 EFFICACY

The primary efficacy endpoint is primary patency of the target lesion at 1 year. Primary patency is defined as the absence of target lesion restenosis (defined by Duplex Ultrasound Peak Systolic Velocity Ratio (DUS PSVR) ≥2.5) and freedom from TLR.

2.3 SECONDARY ENDPOINTS

The following endpoints will be reported using descriptive statistics in the final Study Report.

Efficacy

- Acute Device, Technical and Procedural success

The following endpoints will be assessed at 6, 12 and 24 Months:

- Primary and Secondary Patency (DUS PSVR <2.5)
- Alternative Primary and Secondary Patency based on alternative definitions of DUS PSVR <2.0 and <3.0
- DUS Clinical Patency (DUS PSVR <2.5 without prior Clinically Driven TLR)
- Target Lesion Revascularization (TLR)
    - Clinically-driven
    - Total *(clinical and DUS/angiography-driven)*
- Change of Rutherford classification from baseline
- Change of resting ABI from baseline
- Change in Walking Impairment Questionnaire from baseline
- Change in Six Minute Walk Test from baseline in a subset of patients
- Change in quality of life from baseline, as measured by EQ-5D and SF36-v2 surveys

Safety

- Freedom at 30 days from all-cause death, index limb amputation above the ankle and TVR (VIVA Safety Endpoint)

- Composite of freedom from all-cause perioperative (≤30 day) death and freedom from the following at 1, 6, 24, 36, 48, and 60 months: index limb amputation, index limb re-intervention, and index-limb-related death.

The following endpoints will be assessed at 1, 6, 12, 24, 36, 48 and 60 months:

- All-cause death
- Amputation (above the ankle)-Free Survival (AFS)
- Target Vessel Revascularization (TVR)
- Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature
- Major vascular complications
- Readmission for cardiovascular events

Other

- Target limb related hospital days at 1 and 2 years

The primary analysis is ITT, including all randomized subjects. Secondary as-treated and per-protocol analyses will also be performed.

3 DEVICE DESCRIPTION

The Moxy Drug Coated Balloon is a standard PTA catheter with a drug coating on the balloon portion of the catheter. The Moxy Drug Coated Balloon is an over-the-wire type design with working lengths of 100 and 130 cm and is compatible with 0.035" guidewires. Marker bands are located at the proximal and distal ends of the balloons to assist in delivery and placement. The balloon surface between the marker bands is coated with a specialized immediate release non-polymer based coating formulation that includes the anti-proliferative drug – paclitaxel - at a surface concentration of 2µg/mm^2.

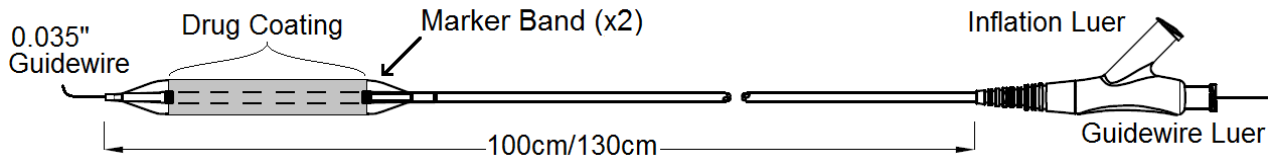

FIGURE 1: MOXY DRUG COATED BALLOON

All devices are provided sterile and for single-use only and are clearly labeled for investigational use only. No more than two devices may be deployed in a single target lesion during a single procedure.

3.1 INTENDED USE / INDICATIONS FOR USE

The Moxy Drug Coated Balloon is indicated for percutaneous transluminal angioplasty of obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries ≤15cm in length and ≥4.0 to ≤6.0mm in diameter.

3.2 ACTIVE PHARMACEUTICAL INGREDIENT (API): PACLITAXEL

Paclitaxel, discovered in 1967 and commercially developed by Bristol-Myers Squibb, is a well known mitotic inhibitor indicated for use in the treatment of patients with lung, ovarian, breast, head and neck cancers and advanced forms of Kaposi's sarcoma. Paclitaxel is also approved for the prevention of restenosis. Various dosages are used depending on target treatment and range from multiple 300 mg IV infusions for oncology therapy to a single maximal nominal dose of 282 µg for devices that treat restenosis, such as coronary stents. Please refer to Figure 2 and the Investigator's Brochure for a more detailed review of paclitaxel.

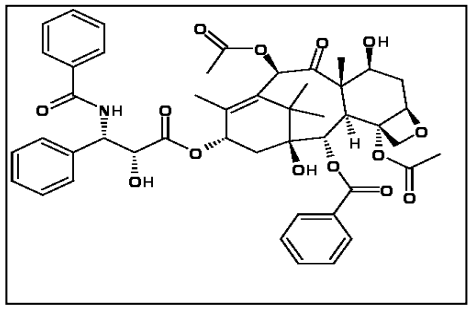

FIGURE 2 : CHEMICAL STRUCTURE OF PACLITAXEL

3.3 EXCIPIENT (DRUG CARRIER)

The balloon coating includes small amounts of well known excipients (drug carrier) that are approved by the Food and Drug Administration (FDA) as inactive ingredients in drug products for intravenous (IV) drug delivery.

3.4 DEVICE INSTRUCTIONS

A comprehensive set of Instructions for Use (IFU), including warnings and precautions, has been created. Please refer to the most current IFU packaged with the device for complete details on preparation and procedural use of the device. A sample IFU can be found in Appendix G.

3.5 SUPPLY & SUPPORT OF INVESTIGATIONAL DEVICE

An investigational device supply of the Moxy Drug Coated Balloon will be made available to all activated study sites. The investigational device matrix that is currently available for this study is listed in Table 4. Always confirm current site inventory supply prior to enrolling subjects into the study.

TABLE 4: DEVICE MATRIX, MOXY DRUG COATED BALLOON

Balloon Diameters	Balloon Lengths		
	40mm	60 mm	100 mm
4 mm	√	√	√
5 mm	√	√	√
6 mm	√	√	√

Prior to start of study enrollment, Lutonix or their designee will perform formal device training for study site personnel and support staff. Each study site will receive a supply of the Moxy Drug Coated Balloons upon completion of the protocol requirements for study initiation. Additional training and support will be provided as needed on an ongoing basis. Any unused devices must be returned to the sponsor at the time site enrollment stops or upon sponsor request. After use, this product may be a potential biohazard. Handle and dispose of in accordance with acceptable medical practices and applicable local, state and federal laws and regulations. For quality control purposes, devices may be requested to be returned to the sponsor before or after use, in which case the site should return devices by following the Return Material Authorization (RMA) instructions located in the study binder.

4 RISK-BENEFIT ANALYSIS

4.1 POTENTIAL RISKS

The potential risks and benefits of participation in this study are clearly identified in the subject Informed Consent Form (ICF) and are to be explained to the subject and/or their legal representative prior to participating in the study. The Moxy Drug Coated Balloon and standard uncoated percutaneous angioplasty catheters are intended to be the only devices used for treatment of the target lesion.

Due to the high similarity of the Moxy Drug Coated Balloon to other marketed balloon catheters, procedural use is not expected to significantly change or increase risks during the initial procedure. However, it shares the risks of conventional balloon angioplasty treatment of patients with femoropopliteal disease. There may also be risks associated with the drug coating on the Moxy Drug Coated Balloon that are unknown at this time. Please refer to the Investigator's Brochure for more details on the development of the Moxy Drug Coated Balloon.

4.1.1 RISKS FOR PERIPHERAL CATHETERIZATION PROCEDURE

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

- abnormal heart rhythms
- abrupt vessel closure
- allergic reaction
- aneurysm or rupture of the artery

- AV fistula
- bleeding
- death
- dissection
- embolization
- femoral nerve compression with associated neuropathy
- groin area bruising and discomfort
- hematoma
- infection
- kidney failure
- low blood pressure
- perforation
- pseudoaneurysm
- respiratory failure
- stroke
- total occlusion or thrombosis
- vessel trauma that may require re-intervention or surgical repair

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

Even if the balloon catheter procedure is deemed successful, it is associated with a meaningful risk of vessel narrowing within 12 months (depending on risk factors). Additional therapy may be required within 12 months such as re-intervention using angioplasty or surgery.

Patients undergoing an interventional procedure are often treated with courses of thienopyridines such as clopidogrel or prasugrel, which may cause thrombocytopenic purpura and/or bleeding complications. In rare cases, these drugs may cause a significant reduction in white blood cell count, which may in turn result in serious infections. Aspirin is also a common drug used before and after such procedures. Aspirin is known to contribute occasionally to causing gastrointestinal ulcers (bleeding or non-bleeding). Aspirin may also affect platelet function to the extent of causing bleeding complications (which may be minor, major, or life threatening). If such conditions occur, the patient may require surgery, blood transfusion, or platelet transfusion.

Any of the above could cause prolonged illness, permanent impairment of daily function or, in rare cases, death. Possible treatments could include, but are not limited to emergency PTA and vascular surgery. It is expected that the fluoroscopy time of the interventional procedure will be similar to the time required for conventional percutaneous lower extremity interventional procedures and not pose additional risks to the subject or lab personnel.

4.1.2 ASSOCIATED RISKS FROM THE DRUG COATING

The balloon coating includes the API paclitaxel and small amounts of well known excipients (drug carrier) that are approved by the Food and Drug Administration (FDA) as inactive ingredients in drug products for intravenous (IV) drug delivery. Additional adverse events that may be unique to the paclitaxel drug coating include:

- allergic/immunologic reaction
- alopecia
- anemia
- blood product transfusion
- gastrointestinal symptoms
- hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- hepatic enzyme changes
- histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- myalgia/arthralgia
- peripheral neuropathy

There may be other risks associated with the drug coating that are unknown at this time.

There are no adequate and well-controlled studies published in pregnant women or men intending to father children who have received paclitaxel in either the test or control device. Studies performed in rats and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 3 and 16 times the dose provided by the largest Moxy Drug Coated Balloon-coated with 3.8 mg of paclitaxel adjusted for body surface area). The drug resulted in increased resorptions and increased fetal deaths. No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (a daily dose of approximately 3 times the dose of the largest Moxy Drug Coated Balloon, adjusted for body surface area). Use of the test or control devices in women who are of childbearing potential or in men intending to father children should therefore take reproductive risk into careful consideration.

4.2 RISK MANAGEMENT PROCEDURES

Eligibility criteria have been selected that exclude patients who are at a higher risk for experiencing an anticipated adverse event in order to reduce the risks to subjects who participate in this study. In addition, subjects enrolled in this study will receive a defined anti-platelet regimen and are required to follow the pre-specified clinical follow-up schedule described in Section 7. In addition, follow-up duplex ultrasound will be performed to assess the target vessel patency, and all adverse events are formally monitored and independently adjudicated.

Extensive reliability engineering testing has been performed on the Moxy Drug Coated Balloon to help mitigate any risks to the subjects due to product failure. Additionally, animal studies using

the Moxy Drug Coated Balloon have been conducted to ensure that the device performs as intended without introducing more risks during the interventional procedure.

Investigational device training will be conducted at each initiated study center and appropriate training records will be maintained.

4.3 POTENTIAL BENEFITS

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the Moxy Drug Coated Balloon may reduce the potential for restenosis of the lesion, thereby reducing the need for repeat hospitalization and/or procedure(s).

Additionally, information gained from the conduct of this study may be of benefit to others with the same medical condition. As with all investigational medical devices, the long-term results of using the Moxy Drug Coated Balloon are not known at the present time. Alternatives to the use of the Moxy Drug Coated Balloon include standard or cutting balloon angioplasty, vascular stenting, atherectomy, cryoplasty, or vascular radiation and surgery (vessel bypass with native or synthetic vessel). Lutonix believes that the risk for significant injury or death due to the Moxy Drug Coated Balloon is extremely low, and the potential benefits of decreased restenosis and decreased need for reintervention is likely, but these potential risks and benefits have yet to be quantified.

4.4 EARLY TERMINATION

Lutonix, Inc. (Sponsor) and the Data Monitoring Committee (DMC) 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.

The Sponsor may terminate Investigator and site participation in the study for issues including but not limited to the following issues:

- Evidence of an Investigator's failure to maintain adequate clinical standards
- Evidence of an Investigator or staff's failure to comply with the protocol
- Inaccuracy or late submission of data forms and core lab images
- Inability to meet enrollment targets (1.5 subjects/month)
- Conditions of approval imposed by the reviewing IRB/EC and/or regulatory agencies
- Evidence of safety concerns or protocol non-compliance
- Change of staff at site that adversely impacts trial conduct

Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw from the study and their site may be replaced

Notification of suspension or termination will occur no later than five (5) working days after the Sponsor makes the determination. In the event of study suspension or termination, the Sponsor

will send a report outlining the circumstances to the Institutional Review Board (IRB)/Ethics Committee (EC), and all Investigators and Regulatory Authorities as required by regulation. A suspended or terminated study may not be reinitiated without approval of the reviewing IRB/EC and Regulatory Authorities, as required by regulation.

The Investigator must notify the IRB/EC in writing as soon as possible but no later than within 10 days if the premature termination is related to safety or compliance issues.

5 CLINICAL STUDY DESIGN

The study will enroll subjects presenting with claudication or ischemic rest pain and an angiographically significant lesion in the superficial femoral or popliteal artery and a patent outflow artery to the foot. After successful protocol-defined pre-dilatation, subjects that are unlikely to require a stent based on strict angiographic criteria (absence of major flow-limiting dissection from the lumen and ≤70% residual stenosis or the lesion is not appropriate for stenting due to proximity to the knee joint) are randomized 2:1 to treatment with either the Moxy Drug Coated Balloon (test arm) or standard PTA catheter (control arm).

Subjects that do not meet post-predilatation criteria are excluded (and treated per standard practice) and followed for safety only (via telephone or clinical follow up) for 30 days. Randomized subjects will have ultrasound and clinical follow-up through 2 years and telephone follow-up through 5 years. There is no pre-set limit to site enrollment, however site enrollment will be tracked and managed to ensure approximately 50% of the overall randomized enrollment occurs at US sites.

Figure 3 contains an overview of the study.

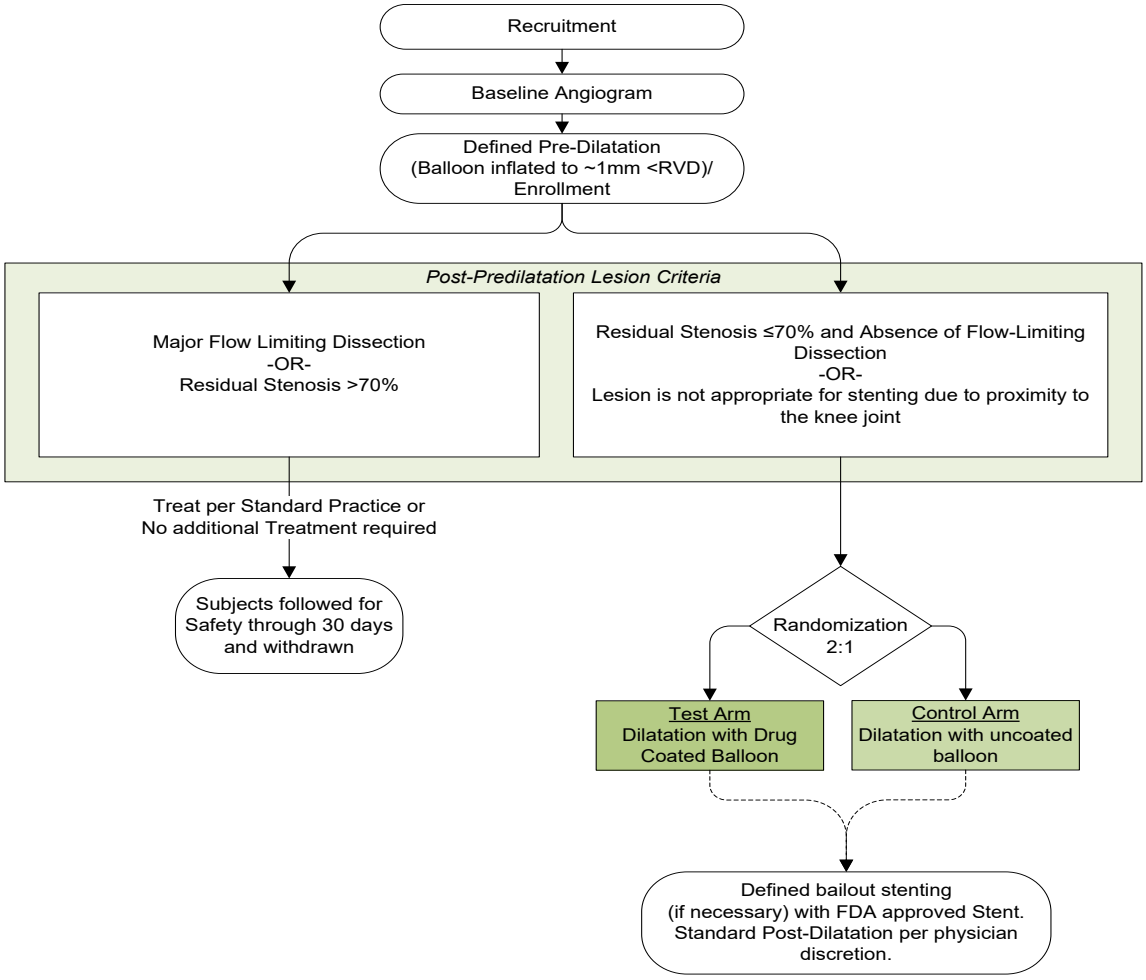

Figure 3: Study Flowchart

5.1 SCREENING PROCEDURES

All patients admitted for a percutaneous revascularization of a femoropopliteal artery should be screened for study eligibility. If inclusion criteria are met and no exclusion criteria are present at the time of screening, the patient should be entered into a study Screening Log. Once the patient's eligibility has been determined, the Investigator will discuss the study and ask the patient to participate. Prior to enrollment, the patient must sign the informed consent form approved for use by the IRB/EC or other appropriate committee. A copy of the signed and dated Informed Consent will be provided to the subject. Subjects will be assured that they may withdraw from the study at any time and for any reason. The background and purpose of the study, participation requirements, as well as the potential benefits and risks of the procedure(s) must be explained to the subject.

The status of all patients screened, whether enrolled, withdrawn, etc., should be captured on the study Screening Log for tracking and reporting purposes.

If not already performed as standard practice, the following assessments and tests must be performed after obtaining informed consent and prior to the index procedure (within 30 days unless otherwise noted) to verify and complete eligibility:

- Physical examination (including blood pressure, heart rate, and temperature) performed by either an MD, Physician's Assistant, or Nurse Practitioner
- Relevant medical history
- Rutherford Classification
- Blood analysis
    - CBC with differential (hemoglobin, hematocrit, platelets and leukocytes) (differential: neutrophils, lymphocytes, monocytes and basophils)
    - CMP
        - Glucose
        - Calcium
        - Protein (albumin, TP)
        - Electrolytes (bicarbonate, chloride, sodium, potassium)
        - Kidney (BUN, creatinine)
        - Liver (ALP, ALT, AST, bilirubin)
    - Pregnancy Test (blood or urine; if female of child bearing potential)
- Resting Ankle-Brachial Index (ABI) (within 90 days)
- Walking Impairment Questionnaire
- EQ5D and SF-36-v2 Questionnaires
- Six Minute Walk Test

5.2 PATIENT SELECTION FOR ENROLLMENT

Subjects must meet all the clinical eligibility criteria, agree to participate and comply with study protocol requirements and follow-up schedule, and provide informed consent.

All subjects are expected to remain available (geographically stable) for the duration of the study follow-up period. If any subject moves away, every effort must be made to maintain the follow-up schedule including having an appropriate physician follow the subject. The Investigator is responsible for ensuring that each follow-up visit occurs at the specified time and that all applicable data is reviewed and entered into the electronic case report form system (eCRF) in a timely fashion.

5.2.1 ROLL-IN SUBJECTS AND CASE PROCTORING REQUIREMENTS

After site initiation, each site must perform a proctored Moxy Drug Coated Balloon procedure prior to enrolling subjects in the randomized portion of the trial. This is intended to train site

personnel in proper procedure and data collection. All roll-in subjects must meet all protocol requirements (including enrollment criteria and follow-up) and the sponsor (or designee) must be in attendance for training purposes. A subject(s) who was proactively designated as a roll-in, but subsequently treated per the standard practice arm (i.e. not treated with the Moxy Drug Coated Balloon) is not considered a roll-in. The roll-in subjects will be analyzed separately from the randomized cohort. Based on a total of 55 sites, a maximum of 55 of roll-in subjects is expected. Some centers may have more than one investigator performing the study procedure; each investigator enrolling in the study must undergo formal Moxy procedure proctoring with a sponsor representative (or designee) during their initial study case(s). The sponsor reserves the right to limit the number of investigators performing the study procedure at a site and can expand case proctoring requirements as necessary to ensure compliance.

5.3 SUBJECT INCLUSION AND EXCLUSION CRITERIA

5.3.1 INCLUSION CRITERIA

Subjects must meet all inclusion criteria to be enrolled in the study.

Clinical Criteria

1. Male or non-pregnant female ≥18 years of age;
2. Rutherford Clinical Category 2-4;
3. Patient is willing to provide informed consent, is geographically stable and comply with the required follow up visits, testing schedule and medication regimen;

Angiographic Criteria

Lesion Criteria

4. Length ≤15 cm;
5. Up to two focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. two discrete segments, separated by several cm, but both falling within a composite length of ≤15 cm);
6. ≥70% stenosis by visual estimate;
7. Lesion location starts ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the TP trunk;

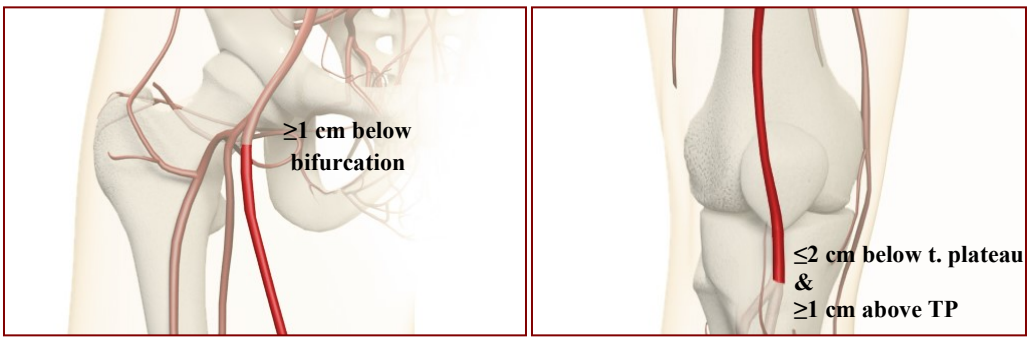

FIGURE 4: ALLOWED LESION LOCATION

8. *de novo* lesion(s) or non-stented restenotic lesion(s) >90 days from prior angioplasty procedure;
9. Lesion is located at least 3 cm from any stent, if target vessel was previously stented;
10. Target vessel diameter between ≥4 and ≤6 mm and able to be treated with available device size matrix;
11. Successful, uncomplicated (without use of a crossing device) antegrade wire crossing of lesion;
12. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions);

    NOTE: Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication.

13. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure);
14. Contralateral limb lesion(s) cannot be treated within 2 weeks before and/or planned 30 days after the protocol treatment in order to avoid confounding complications;
15. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment.

5.3.2 EXCLUSION CRITERIA

Patients will be excluded if ANY of the following conditions apply:

1. Pregnant or planning on becoming pregnant or men intending to father children;
2. Life expectancy of <5 years;
3. Patient is currently participating in an investigational drug or other device study or previously enrolled in this study;
   NOTE: Enrollment in another clinical trial during the follow up period is not allowed.
4. History of hemorrhagic stroke within 3 months;
5. Previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the index procedure;
6. History of MI, thrombolysis or angina within 2 weeks of enrollment;
7. Rutherford Class 0, 1, 5 or 6;
8. Renal failure or chronic kidney disease with MDRD GFR ≤30 ml/min per 1.73 m^2 (or serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis);
9. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion;
10. Inability to take required study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication;

11. Anticipated use of IIb/IIIa inhibitor prior to randomization;
12. Ipsilateral retrograde access;
13. Composite lesion length is >15 cm or there is no normal proximal arterial segment in which duplex flow velocity can be measured;
14. Significant inflow disease. Successful treatment of inflow disease allowed prior to target lesion treatment;
15. Known inadequate distal outflow (>50% stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion;
16. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;
17. Severe calcification that renders the lesion undilatable;
18. Use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).

6 STUDY/TREATMENT PROCEDURES

6.1 ENROLLMENT

A subject is considered enrolled in the study after both of the following steps have occurred:

- Baseline angiographic confirmation that the target lesion meets all appropriate inclusion/exclusion criteria.
- Defined pre-dilatation balloon inflation has begun.

All subjects enrolled and randomized in the trial will be followed for the entire duration of the study and included in the ITT analysis. Subjects that do not meet post-predilation criteria are enrolled, but not randomized, and treated per standard practice and followed for safety for 30 days via telephone or clinical visit. Subjects with target lesions that, after baseline angiography, do not meet all inclusion/exclusion criteria and are not pre-dilated per protocol are considered screen failures and will not be enrolled or randomized in the study.

6.2 MOXY DRUG COATED BALLOON INSTRUCTIONS FOR USE (IFU)

Always follow the current IFU packaged with the device for procedural information, preparation and use of the Moxy Drug Coated Balloon. Any devices found to be defective or that do not perform as expected should be returned immediately to the Sponsor for evaluation and a Device Malfunction Form must be completed.

A balloon compliance chart is included on each device product label.

If more than one Moxy Drug Coated Balloon will be needed to treat the entire pre-dilated segment(s)/lesion(s), the combination of lengths available should be carefully considered beforehand to ensure complete coverage of the target lesions (within the maximum length of

15cm) and, at the same time, reduce unnecessary vessel dilatation. The IFU also contains detailed information on lesion coverage and minimal inflation times.

6.3 BASELINE ANGIOGRAM

DSA- or Cine- angiograms should be obtained per core lab guideline. Standard off-line QVA acquisition procedures will be followed for analysis at the independent Imaging Core Laboratory. All angiography procedures (both index and non-scheduled) must be recorded in such a way that they are suited for off-line QVA. For purposes of ensuring protocol compliance, all angiograms must be submitted to the core laboratory as soon after the case as possible.

6.4 IN-FLOW LESION TREATMENT

Absence of inflow disease (≥50% stenosis) as confirmed by angiography is required for enrollment in the study. Enrollment is allowed following complete successful treatment per standard practice of inflow artery lesions, with successful treatment defined as attainment of a residual diameter stenosis ≤30% without death or major vascular complication.

6.5 PRE-DILATATION

Always refer to the current IFU packaged with the Moxy Drug Coated Balloon for complete pre-dilatation requirements.

Lesion(s) pre-dilatation(s) is required for all (test and control) patients. The predilatation balloon should be a standard PTA balloon inflated to a diameter approximately 1 mm less than the reference vessel diameter (RVD). Always limit the longitudinal length of the pre-dilatation balloon to avoid creating a region of vessel injury that is outside the boundaries of the area to be treated by the Moxy Drug Coated Balloon (i.e. geographical miss). In order to reduce dissections and potential subject allocation to the standard practice arm after pre-dilatation, careful and controlled pre-dilatation(s) inflations should be performed and recorded (on film).

See Table 5 for an overview of lesion assessment. If, after pre-dilatation, the lesion site has a major flow-limiting dissection or residual stenosis >70%, the subject will not be randomized but is instead treated per institutional standard practice. Nonrandomized subjects excluded after pre-dilatation will be followed for 30 days for safety and then withdrawn.

TABLE 5: POST PRE-DILATATION LESION(S) CRITERIA

Angiographic Condition	Treatment
Major Flow Limiting Dissection -OR- Residual Stenosis >70%	Excluded, not randomized, and followed for safety through 30 days
Residual Stenosis ≤70% and Absence of Flow-Limiting Dissection -OR- Lesion is not appropriate for stenting due to proximity to the knee joint	Randomized 2:1 to Test (Moxy Drug Coated Balloon) or Control (standard PTA catheter)

6.6 RANDOMIZATION

If after pre-dilatation(s), patients are determined to meet the criteria for randomization, they will be randomized using a pre-specified site randomization system. Subjects will be randomized in a 2:1 fashion to Test (Moxy Drug Coated Balloon) or Control (standard PTA catheter), see

Figure 3.

6.6.1 TREATMENT WITH STANDARD PTA CATHETER (CONTROL)

For subjects randomized to the control arm, a treatment with an uncoated standard PTA catheter will be performed following the Investigator's standard procedure for such a treatment and utilizing a locally approved, standard off-the-shelf PTA balloon. Use of embolic capture angioplasty balloons or cutting/scoring balloons is not allowed.

The Investigator should determine the appropriate size of the balloon to be used by visual assessment. The Investigator should use an uncoated balloon of similar length and diameter to the Moxy Drug Coated Balloon to ensure similarity of treatment between test and control arms.

6.6.2 TREATMENT WITH MOXY DRUG COATED BALLOON (TEST)

Please refer to the current Moxy Drug Coated Balloon IFU for detailed information on device use.

The Investigator should determine the appropriate size of the balloon to be used by online QVA (if possible) or by visual estimate. The Moxy Drug Coated Balloon should extend at least 5 mm proximally and distally of the pre-dilatation segment. Care should be taken not to extend the entire injury segment unnecessarily.

6.7 POST TREATMENT AND PROVISIONAL (BAILOUT) STENTING PROCEDURES

The rate of provisional (i.e. bailout) stenting in prior SFA clinical trials, including those investigating drug coated balloons, has varied considerably. In particular, a discrepancy has been noted in bailout rates between control and treatment arms. This discrepancy is likely attributable to investigator bias that the control arm is less likely to succeed and thus the threshold for stenting

test-device treated subjects is lower. There is no consensus or established objective criteria that are validated regarding the appropriate threshold for provisional SFA stenting. In the absence of an established threshold, the determination to bailout has previously been based on criteria that are either subjective or largely left to the discretion of the individual operator and his/her judgment.

The current trial design is intended to minimize the need for bailout stenting; imbalance in bailout stenting between treatment arms could influence the outcome of the study. Due to the importance of equal treatment between test and control groups, plus the need within the medical community to establish validated criteria for provisional stenting, this trial will utilize more rigorous criteria for bailout stenting. Specifically, the trial will employ the additional requirement of a pressure gradient measurement to document an unsatisfactory balloon-only outcome (obtained by measuring pressures proximal and distal to the lesion simultaneously). The minimum pressure gradient threshold for bailout stenting (Table 6) has been established by consulting a number of experts who have extensive experience with SFA intervention, some of whom utilize pressure gradients routinely in their practices. Requiring confirmation of a baseline pressure gradient prior to stenting establishes objective criteria that must be met for bailout stenting (and should reduce the rate in this study).

TABLE 6: PROVISIONAL (BAILOUT) CRITERIA

Bailout Prevention
Treatment requirement prior to bailout stenting: • Prolonged (>2 minutes) balloon inflation(s) • Vasodilators and/or thrombolytic agents per investigator discretion
Bailout Criteria
• Residual stenosis of >50% (based on careful in-lab review of angiograms including QVA if available) *or* major flow-limiting dissection (Record angiography in 2 orthogonal views) ***and*** • Documented translesional pressure gradient of >20mmHg (using ≤4F end-hole catheter) or >10mmHg (pressure wire) measured immediately distal to the target lesion

These criteria are set as the minimum baseline pressure gradient requirement for allowing bailout stenting; however, bailout stenting is not required for pressures equal to or exceeding these thresholds (i.e. presence of a gradient at/above these thresholds does not require that the operator place a stent). Rather, these thresholds are seen as minimum requirements for bailout stenting; below these thresholds, bailout stenting is not allowed.

If the criteria for bailout stenting are fulfilled, placement of a bare nitinol stent approved by the FDA for use in the SFA is allowed. The physician should use the shortest stent possible to treat only the clinically significant dissection or residual stenosis and not the entire target lesion. Antiplatelet therapy should be prescribed per the stent manufacturer's IFU.

The angiographic core lab and study steering committee will be monitoring cases of bailout stenting throughout the course of enrollment for compliance to provisional (bailout) criteria listed in this section.

6.8 UNSCHEDULED ANGIOGRAPHY/REVASCULARIZATION

A DUS is required prior to any subsequent angiography of the index limb, and the images must be submitted to the DUS Core Lab. In the event that a subject undergoes repeat angiography after the index procedure is complete, all subsequent angiograms for the index limb or, in the event of an index limb revascularization, all procedural angiograms must be forwarded to the Angiographic Core Lab for review and analysis. Attempts should be made to record the same views and angles as from the index procedure. Treatment of any new non-target lesions is left to the discretion of the Investigator however, use of drug-device combination products (e.g. DES or DCB) is not recommended within 90 days of the index procedure.

7 TREATMENT OF SUBJECT

Lutonix (or its designee) reserves the right to attend index or DUS procedures in order to ensure protocol compliance, proper device handling and adequate image capture.

7.1 BLINDING PLAN

In order to minimize the introduction of bias into the study, a pre-specified blinding plan has been developed. All Duplex Ultrasound operators, core lab evaluators, and members of the Clinical Events Committee (CEC) will be blinded to the subject's treatment assignment. Both the subject as well as the investigator conducting the follow-up visit will be blinded to treatment until the completion of the 12 month visit. Blinding procedures will be reviewed at the time of each site initiation by a sponsor representative. Blinding procedures and instructions are as follows:

Time point	Blinding Procedure
Informed Consent/ Pre-Procedure	During review of the study and the informed consent process with the patient, blinding procedures, timelines and rationale should be discussed with the subject and any care takers.
Randomization	Communication to the Investigator performing the procedure as to the randomized treatment should be done in such a way as to prevent the subject from overhearing which group they have been allocated to. Hand signals, written codes, scripts or headphones can all be employed to ensure the subject remains blinded. Each site must develop a system that best works with lab work flow.
Post-Procedure	It is important that recovery and hospital/clinic staff is educated to the protocol blinding requirements and that the subject and care taker are not inadvertently unblinded during the recovery period. In addition, the medical record should clearly identify the subject as a study participant and the type of treatment should be kept confidential.
Follow-up	The one month (if clinical visit), 6 and 12 month follow-up visits must be performed by a blinded site investigator. If only a single interventional investigator exists at any one site, an additional site sub-investigator qualified to conduct follow up assessments for this population (physician, nurse practitioner, physician assistant, etc.) should be appointed to conduct the blinded study related follow-up visits prior to any standard follow up, if applicable, with the interventional investigator. The clinical status of the subject (for assessment of clinical and primary safety endpoints) should be established prior to performing the required DUS (for assessment of the primary efficacy endpoint).
Unblinding	A subject may not become unblinded prior to the completion of the 12 month follow up unless it should become medically necessary as determined by the investigator.

7.2 MEDICATIONS

Table 7 displays the required medication regimen for this study. All medications administered will be recorded in the subject's medical record. These medication and schedules are consistent with

standard hospital practice. Details of each requirement can be found in the sections below. In subjects ≥75 years of age and/or <60kg, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (diabetes or history of prior MI) where its effect appears to be greater and its use may be considered. Always refer to the current package insert.

TABLE 7: MEDICATION SCHEDULE

Drug	Pre-Procedure	Procedure	Post-Procedure*
Aspirin	75-325 mg/day	NA	75-100 mg/day indefinitely
Clopidogrel	75 mg or 300 mg loading dose	NA	75 mg daily for at least 1 month.
OR **Prasugrel*** **	10 mg/day or loading dose of 60 mg	NA	for at least 1 month (discontinue with active bleeding) >60 kg - 10 mg/day <60 kg - 5 mg/day**
Anticoagulation	Per Hospital Standard Practice		

**For cases of provisional (bailout) stenting, refer to the Stent IFU for dosing instructions*

***The effectiveness and safety of this dose has not been prospectively studied*

****Ticlodipine use per label is an acceptable alternative only if neither Clopidogrel nor Prasugel are appropriate*

7.2.1 PRE-PROCEDURE

Subjects that are already taking daily chronic aspirin therapy should receive a dose of 75-325 mg aspirin within 24 hours prior to the index procedure. Those subjects not already taking daily chronic aspirin therapy should be given at least 300 mg aspirin at least 2 hours and preferably 24 hours before the procedure is performed.

If the subject is known to be receiving a stent for a non-target lesion (i.e. inflow lesion), it is suggested that 3 days before the intervention clopidogrel (75 mg per day) or prasugrel (10 mg per day) be prescribed. The initial loading dose of clopidogrel or prasugrel should attempt to be started prior to the index procedure, but must occur no later than 2 hours after the completion of the index procedure.

7.2.2 INTRA-PROCEDURE

All subjects must receive adequate anticoagulation according to hospital standard practice.

7.2.3 POST-PROCEDURE

Approved vascular closure devices are allowed. Clopidogrel (75 mg/daily) or prasugrel (5-10 mg/daily) must be prescribed for at least 1 month, unless a stent is placed, in which case antiplatelet therapy should be prescribed per the stent manufacturer's IFU. Updated guidelines will be implemented via note-to-file if changes in the recommended doses occur.

7.3 STANDARD TESTS, PROCEDURES, AND FOLLOW-UP

Table 8 displays the required schedule for randomized subject treatment and evaluation. This schedule is consistent with standard clinical care pre- and post-interventional procedures. The times for each test are broad enough to fit into most hospital routine testing procedures.

Subjects enrolled, but not randomized, and treated per standard practice will be followed for safety through 30 days. The 30 day follow-up visit can be performed as a telephone or clinical visit. Duplex ultrasound imaging is not a protocol requirement for this group. Details of each testing requirement can be found in the sections below.

Table 8: Follow-Up Schedule and Testing Requirements for Randomized Subjects

Event	Screening (pre-consent)	Pre-Procedure	Procedure	Post- Procedure	1 Month[1]	6 Month	12 Month	24 Month	36 Month[1]	48 Month[1]	60 Month[1]
Visit Window	30 days	30 days			±2 weeks	±1 month	±1 month	±2 month	±2 month	±2 month	±2 month
Inclusion/Exclusion Criteria	√	√	√								
Informed Consent		√									
Medical History	√										
Physical Exam[2]		√		√	√[3]	√	√	√			
Medication Compliance		√			√	√	√	√	√	√	√
Resting ABI		√[4]		√[4]	√[4]	√	√	√			
Rutherford Classification		√				√	√	√			
Blood Analysis (CBC with differential; CMP, pregnancy[6])		√[5]		√	√[3]	√	√				
Six minute Walk Test[7]		√				√	√	√			
WIQ, EQ5D and SF36-v2 Questionnaires		√				√	√	√			
Angiogram			√								
Adverse Event Monitoring			√	√	√	√	√	√	√	√	√
Duplex Ultrasound (after clinical assessment)				√[8]		√	√	√			
PK Study[9]		√		√	√						

[1] *Follow-up can be by telephone or clinical visit, depending on timing of duplex ultrasound (if required)*

[2] *Physical Exam must be performed by and MD, PA, or NP*

[3] *Required if clinical visit occurs*

[4] *Resting ABI is required within 90 days of index procedure. Resting ABI is not required post procedure or at 1-month, but investigator encouraged to capture if possible*

[5] *Pre-procedure blood analysis must be performed within 30 days of the procedure*

[6] *Pre-procedure and females of childbearing potential only*

[7]Unless physical condition precludes from testing
[8]Baseline duplex is only required once (anytime post-procedure through the 1-month visit)
[9]A subset of approximately 30 subjects at select USA sites

At 6, 12, and 24 month follow-up visits, the clinical status of the subject (for assessment of clinical and safety endpoints) should be established prior to performing the required DUS (for assessment of patency).

7.3.1 TESTING

7.3.1.1 LABORATORY TESTING

Laboratory samples must be drawn pre-procedure, post-procedure, and at the 6 and 12-month clinical visits. All laboratory values must be recorded on the appropriate study eCRFs. Pre-procedure samples may be taken up to 30 days prior to the index procedure.

Laboratory test reporting requirements include:

- CBC with differential (hemoglobin, hematocrit, platelets and leukocytes) (differential: neutrophils, lymphocytes, monocytes and basophils)
- CMP
    - Glucose
    - Calcium
    - Protein (HSA, TP)
    - Electrolytes (bicarbonate, chloride, sodium, potassium)
    - Kidney (BUN, creatinine)
    - Liver (ALP, ALT, AST, bilirubin)
- Pregnancy Test (blood or urine; if female of child bearing potential)

7.3.1.2 PHARMACOKINETIC TESTING

In a subset of approximately 30 subjects treated with the Moxy Drug Coated Balloon at selected sites in the USA, small amounts of blood (2 vials per sample) will be collected for pharmacokinetic (PK) testing (blood paclitaxel level analysis) during the index hospitalization and at the study required 1 month follow-up visit. Blood collection will occur at the time points shown in Table 9. Efforts should be made to include only those subjects who will be available to provide all scheduled samples. Detailed PK collection instructions and materials will be provided to select sites by the PK core laboratory. These subjects may have a 4F venous sheath inserted at the time of procedure and left in situ until all blood tests are completed to provide for additional subject comfort. Any subjects receiving a drug-eluting/coated stent within 12 months prior or during the index procedure cannot be included in the PK testing. All Moxy Drug Coated Balloons used to treat patients undergoing PK testing will be returned to Lutonix after the procedure for analysis.

TABLE 9: SCHEDULE OF PK SAMPLING

PK Sample	Time Point
1	Pre-Procedure (baseline)
2	Immediately Post Procedure
3	1 Hour Post Procedure
4	3 Hours Post Procedure
5	Before Discharge
6	1 Month Clinical Follow-up Visit

In order to maintain subject blinding and avoid unnecessary needle sticks, subjects will not be informed that blood drug levels are only being completed in the test arm population. Instead, they will be instructed that sampling is random. Subjects that are participating in the PK study must have their 1 month visit conducted as a clinical visit in order to obtain the final PK sample.

7.3.1.3 ANKLE-BRACHIAL INDEX (ABI)

A resting ABI must be performed per local hospital standard, and consistently among subjects over the lifespan of the study.

7.3.1.4 RUTHERFORD SCALE

Rutherford classification can be measured with or without treadmill, but must be performed consistently among subjects over the lifespan of the study.

7.3.1.5 SIX MINUTE WALK TEST

For subjects with no confounding health issues that would complicate the test (e.g. respiratory, cardiac, orthopedic impairments), a six minute walk test will be performed.

See Appendix C for detailed Walk Test information.

7.3.1.6 WALKING IMPAIRMENT QUESTIONNAIRE

The WIQ form will be completed at pre-procedure and at 6, 12 and 24 months.

See Appendix D for the questionnaire form.

7.3.1.7 QUALITY OF LIFE QUESTIONNAIRES

The EQ5D and SF36-v2 surveys will be completed at pre-procedure and at 6, 12 and 24 months.

See Appendices E and F for the questionnaire forms.

7.3.1.8 DUPLEX ULTRASOUND AND ANGIOGRAPHY GUIDELINES

The initial baseline DUS must be performed after the index procedure (up to 1 month ±2 weeks post-procedure), and again at 6, 12 and 24 months. Since DUS is critical to assessing study endpoints, the quality of this test is extremely important. The Core Labs will be closely monitoring the quality of all incoming images for compliance. Sites should ensure that only DUS operators who are trained on the protocol and DUS guidelines are performing these tests. Refer to the Duplex Ultrasound and Angiography Guidelines Manual of Operations for the most current

version of the documentation requirements. See Appendix I and Appendix J for detailed core lab guidelines.

7.3.2 FOLLOW-UP PROCEDURES

The Investigator or Research Coordinator will contact randomized subjects via phone (or via clinical visit if preferred or as part of a regular follow-up) at approximately 1 month, 36 months, 48 months and 60 months (and possibly longer if required) in order to assess for any adverse events and medication compliance.

All randomized subjects will return for follow-up at 1 (if required for duplex ultrasound), 6, 12 and 24 months post procedure. See Table 8 for required testing at each follow-up visit time point. Refer to Section 7.1 Blinding Plan for specifics on maintaining the blind during the follow-up visits.

Following randomization, all subjects are required to complete all assigned follow-up visits and procedures. During the duration of the study, all events need to be reported in the web-based eCRF. Subjects will be instructed to report adverse events to their study physician between evaluation visits.

Relevant medications will be recorded on the eCRF. Anti-platelet therapy compliance including dose, periods of interruption (and reason for interruption), and invasive procedures deterred due to the need to take anti-platelet therapy will also be recorded on the eCRF.

8 ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation. See Appendix A for detailed AE definitions.

8.1 ADVERSE EVENT REPORTING

All adverse events occurring since the start of the study procedure must be recorded in the eCRF. All serious adverse events will be reviewed and adjudicated by the Clinical Events Committee to determine whether it is related to the device or procedure. All adverse events occurring in this study will be classified in accordance with the adverse event signs or symptoms. Any Serious Adverse Event must be reported to Lutonix or designee within 24 hours of knowledge. All adverse events will be reported to the IRB/EC per local requirements.

9 SUBJECT WITHDRAWAL CRITERIA

Subjects can withdraw from the study at any time for any reason; the reason for withdrawal will be documented. All data available at the time of withdrawal (if any) will be used for analysis. There will be no further follow-up (per this study protocol) on the subject who has withdrawn. Subjects who withdraw from the study will not be replaced, however loss-to-follow-up has been considered for sample size statistics.

If a visit is missed, the site is required to document a minimum of three (3) attempts to contact the subject within the follow-up window. If the subject only misses one protocol required visit, the site should repeat the three (3) attempts to contact the subject followed by a certified letter. When a subject misses two (2) consecutive follow-up visits with failure of all contact attempts, the subject may then be considered lost to follow up and exited from the study.

10 DATA COLLECTION AND MONITORING

10.1 DATA COLLECTION

The Investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews. These documents will be completed in an expedited fashion.

10.1.1 ELECTRONIC CASE REPORT FORMS (ECRF)

All required clinical data for this trial will be collected in web-based standardized e- CRFs. Clinical trial data will be collected in accordance with the Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials. Subject personal information should be blinded. Site numbers, subject numbers and initials will be used to track subject information throughout the study.

The eCRF is designed to accommodate the specific features of the study design. Modification of the eCRF will only be made if deemed necessary by Lutonix and/or the appropriate regulatory body.

10.1.2 ANGIOGRAMS AND DUPLEX ULTRASOUNDS

All core lab raw data will be sent to the independent Core Lab listed in the study summary. All Core Lab evaluators will be blinded to the randomized treatment. A specific algorithm will be used to analyze each core lab result. This information will be documented on a study form and the data transmitted to Data Management for integration into the main study database.

10.2 MONITORING

A formal written Monitoring Plan will be developed in accordance to FDA guidelines 53 CFR 4723 and the study protocol by the CROs appointed for this study and approved by Lutonix. Appropriately trained and qualified monitoring personnel will monitor the progress of this study. Prior to protocol submission to the site, a formal pre-qualification visit will be conducted by a Lutonix employee or designee at sites who have not previously been involved in Lutonix-sponsored trials. Pre-qualification visits are done to confirm the appropriate staff, experience, resources, equipment, and patient population exist for this protocol.

Each site will have an initiation visit performed by a Study Monitor and a member of the Lutonix clinical staff. This visit will ensure that the investigator understands his/her responsibility for conducting this study at his/her center. This includes, but is not limited to, device accountability,

protocol compliance, informed consent process, enrolling appropriate subjects, and IRB/EC submissions, approvals, and continuing reviews.

Monitoring will be performed on 100% of original medical records of all enrolled subjects for all case report form data fields. Sites will be monitored according to the approved monitoring plan. Monitoring personnel will monitor for accuracy and timely submission of data forms and core lab images, and compliance with the study protocol, meeting enrollment commitments, applicable regulations, the signed Investigator Agreement and any conditions of approval imposed by the reviewing IRB/EC and/or regulatory agencies. Monitoring personnel will also confirm documentation of the informed consent process, missing visits or examinations, and the reason for any subject failing to complete the study.

Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the clinical site will be asked to stop enrollment and complete outstanding follow-up visits for subjects already enrolled at their site.

Monitoring visits will be scheduled based on the enrollment rate at each site, duration of the study, compliance, and any suspected inconsistency in data that requires investigation.

The Study Monitors will maintain personal contact with the Investigator and staff throughout the study by phone, mail, and on-site visits. The Study Monitors will compile and submit to Lutonix a monitoring report after each visit which will include any findings, conclusions, and actions taken to correct deficiencies. Specifically, the Study Monitors will review:

- Screening Procedures
- Subject Randomization
- Discontinuation of Treatment
- Source Data
- Adverse Event/Serious Adverse Event Recording and Reporting
- Investigational Device Reconciliation
- Study Data and Core Lab Data Submission
- Protocol Deviations

At the close of the study at an investigational site, appropriately trained personnel appointed by Lutonix will make a final on-site visit. The purpose of this visit is to collect all outstanding study data documents, ensure that the Investigator's files are accurate and complete, review record retention requirements with the Investigator, make a final accounting of all study supplies shipped to the Investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented and communicated to the Investigator.

10.3 SOURCE DOCUMENTATION

Auditors, monitors, medical IRB/ECs, the study Sponsor and regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled subject. (No source documentation will be recorded directly on a CRF). At a minimum, the following must be included in each subject's file:

- Sufficient medical history and current physical condition, including any medication(s) the subject is taking at the time of the procedure to assess the subject's eligibility;
- The medical file should reveal the subject's participation in this study, including start and expected follow-up time;
- Dated report of the investigational procedure including medication, material usage, and complications, if applicable;
- Dated reports of the discharge and follow-up assessments;
- Dated results of required laboratory tests;
- Any adverse event(s), the resultant action or treatment, and outcome, if applicable; and
- In the case of withdrawal of subject consent, reason and subject status at time of withdrawal.

The Investigator will permit study–related monitoring, audits, IRB/EC review and authority inspections by allowing direct access to the source data.

In case of electronic source data, access will be allowed or dated print-outs will be available prior to the monitoring visits. Print-outs should not be limited to the vascular data only, but should include all available data related to the identified subject(s).

10.4 RECORD RETENTION

The Sponsor and Investigator will maintain the following accurate, complete, and current records relating to the conduct of the investigation according to national requirements. The data for some of these records may be available in computerized form from the CRO, but the final responsibility for maintaining study records remains with the Investigator. These include:

- All correspondence with another Investigator, an IRB/EC, a Core Laboratory, Lutonix, a monitor, or regulatory agency, including required reports;
- Records of receipt, use, or disposition of the investigational device, including receipt dates, serial and/or lot numbers, names of all persons who received or used the device, why and how many devices were returned to or otherwise

disposed of. Device reconciliation logs should be kept current and available to Lutonix and monitor upon request;

- Records of each subject's case history, source documents, evidence of informed consent, all relevant observations of adverse study device effects, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, and the date of each study treatment;
- Screening log, enrollment log, study personnel visit log;
- Any other records that the regulations require to be maintained.

10.5 STUDY PROCESSING

10.5.1 COMMUNICATION

During the course of the study, regular teleconference calls between Lutonix, the CRO, the Study Monitor(s) and each clinical site (if necessary) will be conducted to resolve any problems concerning the protocol and data collection. Every effort will be made to ensure compliance with the protocol.

10.5.2 TRAINING

The training of appropriate clinical site personnel and support staff will be the responsibility of Lutonix or their designee. To ensure proper device usage, uniform data collection and protocol compliance, Lutonix or their designee will present a formal documented training session(s) to study site personnel which will include, but may not be limited to, the following:

- Techniques for the identification of eligible subjects
- Investigational Plan
- Device Training
- Core lab Instructions
- Instructions on study and adverse event data collection
- Schedules for follow-up with the study site coordinators
- Regulatory requirements

Detailed feedback regarding completion of forms will be provided by Lutonix or designee, through regular site monitoring.

11 DEVICE ACCOUNTABILITY

All investigational Moxy Drug Coated Balloon must be stored in a locked storage facility to which only the Investigator and/or designated study staff will have access. The Investigator is responsible for device accountability at the trial site. The Investigator may assign the responsibility for the device accountability to an appropriate study staff member, but remains the final responsible person. The Investigator must ensure that the device is used only in accordance with the protocol

and current IFU. The Investigator must maintain records that document device delivery to the trial site, the inventory at the site and administration to each subject. These records must include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial subjects. The Investigator must maintain records that adequately document which device the subject received according to the protocol and the assigned randomization. In the case where a device has failed, the Investigator must make every possible effort to return the device to Lutonix; instructions for this procedure will be provided in the Manual of Operating Procedures.

11.1 SUPPLY AND SUPPORT OF INVESTIGATIONAL DEVICE

An investigational device supply will be made available to all study sites. The device matrix will include various diameter and lengths to accommodate the anatomy of the target population. Prior to the start of study enrollment, Lutonix or their designee will perform formal device training of study site personnel and support staff. Each study site will receive a supply of the Moxy Drug Coated Balloons upon completion of the protocol requirements for study initiation. Additional training and support will be provided on an ongoing basis.

For resupply of Moxy Drug Coated Balloons, the site is to contact the Sponsor or its designee.

12 STUDY MANAGEMENT

The Principal Investigators for this study are Kenneth Rosenfield, MD, Boston, MA, USA and Dierk Scheinert, MD, Leipzig, Germany.

12.1 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. This committee will meet as needed by conference or teleconference to monitor enrollment, clinical site progress, and protocol compliance. The SC will make decisions by majority vote. The specific tasks of the Steering Committee are to:

- Act upon recommendations of the Data Monitoring Committee
- Resolve problems in cooperation with the Clinical Trial Manager
- Sole discretion for stopping or otherwise modifying the study based on clinical data collected
- Provide publication policy
- Approve study reports and papers for publications (including abstracts) and presentations of clinical data of any Investigator

The Steering Committee will be comprised of representatives from Lutonix, the Principal Investigators, core lab directors and non-Investigator physicians representing Interventional Cardiology, Vascular Surgery and Interventional Radiology specialties.

Members of the Steering Committee, in conjunction with the CRO and imaging core laboratories, will oversee protocol compliance and implement steps of corrections, actions or warnings letters as necessary. Any site found to have major or repeated compliance issues will be contacted by a Steering Committee member, or designee, for necessary discussion and/or retraining. The Steering Committee may stop enrollment at any site based on compliance or safety issues.

12.2 DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) is responsible for the oversight and safety monitoring of the study. The DMC advises the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DMC members are leading experts in peripheral vascular disease, cardiovascular medicine and biostatistics who are not participating in the trial and have no affiliation with Lutonix.

During the enrollment phase of the trial, the DMC will review accumulating safety data to monitor for incidence of serious vascular events that would warrant modification or termination of the trial.

Any DMC recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Steering Committee for consideration and final decision. However, if the DMC at any time determines that a potential serious risk exists to subjects in this trial, the DMC chairman will immediately notify the Steering Committee.

The DMC will meet at regular intervals to review the safety data. DMC responsibilities, membership, meeting frequencies, and procedures will be outlined in the DMC charter.

12.3 CLINICAL EVENTS COMMITTEE

The Clinical Events Committee (CEC) is made up of a minimum of three clinicians with expertise in vascular intervention and who are not participants in the study or members of the SC. The members of the CEC will be blinded to the subject's treatment. 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 in order to classify a clinical event. All members of the CEC will be blinded to the primary results of the trial. The CEC will meet regularly to review and adjudicate all clinical events. The committee will also review and rule on all deaths that occur throughout the trial.

13 REGULATORY RESPONSIBILITIES

13.1 IRB/EC APPROVAL

Investigators must submit the study protocol to their IRB/EC and obtain written approval before being allowed to conduct and participate in the study. Annual re-approval must also be obtained.

The Investigator is also responsible for fulfilling any conditions of approval imposed by the IRB/EC, such as regular safety reporting, study timing, etc. The Investigator will provide Lutonix or designee with copies of such approvals and reports.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the IRB/EC and written approval obtained prior to implementation.

13.2 REGULATORY APPROVAL

In the USA an IDE application must be submitted to the FDA. IDE approval must be received prior to the inclusion of the first US subject.

In the EU, the study must be submitted to the Competent Authorities in each country that the study is being conducted, according to the national requirements. Approval or a confirmation from the authority that the study can start must be received prior to the inclusion of the first EU subject.

13.3 INFORMED CONSENT

Part of the IRB/EC approval must include approval of an Informed Consent Form (ICF) that is specific to the study and approved by the FDA and any other relevant regulatory bodies. The Investigator must administer this approved ICF to each prospective study subject, and obtain the subject's signature on the ICF prior to enrollment in the study. The ICF may be modified to suit the requirements of the individual site. The Investigator will provide Lutonix or designee with a copy of the approved ICF for his/her site. Lutonix or designee must pre-approve each ICF prior to initial submission to the IRB/EC; major changes must be approved by the FDA.

The study must be explained in a language that is understandable to the subject and he/she must be allowed sufficient time to decide whether to participate. All subjects will be assured that they have the right to withdraw from the study at any time during the course of the protocol and this decision will not influence his/her relationship with the Investigator (treating physician) and/or study staff.

13.4 SELECTION OF CLINICAL SITES AND INVESTIGATORS

The Sponsor will select Investigators who are qualified and experienced to participate in the investigation of the study devices. Sites will be selected based upon a review of a recent site assessment and the qualifications of the (primary) Investigator(s) at the site. Investigators may be selected to participate in the study after submitting a current curriculum vitae (CV).

All Investigators must be approved by the Sponsor prior to participation in the study.

Any site that becomes deactivated prior to initial enrollment, either by the sponsor or by the individual site itself, will be replaced.

Due to the potential for an imbalance in the randomization ratio from low enrolling sites, any site not able to enroll a subject within 2 months (60 days) of formal initiation will be replaced. The sponsor will proactively be tracking site based enrollment throughout the study and may implement enrollment restrictions to assist in balanced enrollment across sites.

13.5 INVESTIGATOR'S RESPONSIBILITIES

Each Investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the Investigational Plan and applicable laws and regulations. The site Principal Investigator will select qualified co-investigators at each site and will maintain responsibility for oversight of all procedures and data collection. All co-investigators must be trained on all aspects of the protocol prior to enrolling and performing procedures. All interventionalists performing procedures must be trained as co-investigators in the study.

The Investigator may not begin enrollment or receive the initial shipment of the investigational devices until Lutonix or designee receives and approves (when necessary) the following minimum documents:

- Complete Signed Investigator Agreement
- Financial Disclosure Forms for all participating Investigators
- IRB/EC Roster
- IRB/EC Protocol and Informed Consent Approvals
- Investigators' and Co-Investigators' current curricula vitae (CV)
- Laboratory Normal Values and Lab Certification
- Site Signature and Responsibility Form

The most recent list of Investigator names and addresses can be found in Appendix L, and will be updated by the Sponsor during the study as needed.

13.5.1 STUDY COORDINATOR

To ensure proper execution of the Investigational Plan, each Investigator must identify a Study Coordinator for the site. Working with and under the authority of the Investigator, the Study Coordinator helps ensure that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration. The Investigator has the ultimate responsibility of all study requirements.

13.5.2 REPORTS

Table 10 below displays a list of the reports that are the Investigator's responsibility to generate. The table also shows to whom the report is to be sent, and with what frequency or time constraints. While some of these reports will be developed by or with the assistance of the CRO or Lutonix, the final responsibility for them rests with the Investigator.

TABLE 10: REPORTS REQUIRED FROM CLINICAL INVESTIGATORS

Report Type	Prepared For:	Time Constraints of Notification
Subject death during investigation	Lutonix/CRO/IRB/EC	To Lutonix/CRO: Verbal within 24 hours and written report within 48 hours. To IRB/EC: Written documentation of the event within 10 working days
SAE/UADE	Lutonix/CRO/IRB/EC	If serious or life-threatening, within 24 hours by email, fax, CRF or phone to Lutonix/CRO, followed by a written documentation of the event within: • 10 working days to Lutonix/CRO and IRB/EC
Report of subject enrollment	CRO	By Enrollment fax within 24 hours
Subject withdrawal	Lutonix/CRO	Within 5 working days
Withdrawal of IRB/EC approval	Lutonix/CRO	Immediately by telephone followed by a copy of the notification within 5 working days
Continuing IRB/EC re-approval	IRB/EC	Prior to continuing review date.
Progress report	Lutonix/CRO/IRB/EC	Submitted at regular intervals or annually
Significant deviations from Investigational Plan	Lutonix/CRO/IRB/EC	Within 5 working days
Failure to obtain ICF	Lutonix/CRO	Within 5 working days
Final summary report	Lutonix/CRO	Within 3 months

13.6 LUTONIX RESPONSIBILITIES

An Investigator Meeting and site initiation visit will occur with each study site in order to orient the Investigator and staff to information such as: the investigational device, the Investigational Plan, applicable regulations and requirements, and expectations of the study, including the numbers and time frame for subject enrollment, subject selection, informed consent, required clinical data, and record keeping.

Lutonix or designee (CRO) will maintain the following records:

- All correspondence which pertains to the investigation
- Signed Investigator Agreements/Compensation Agreements, and Curriculum Vitaes
- Adverse effects and complaints
- All Case Report Forms (signed by the Investigator)
- Investigational Plan
- Pre-Study Visit Form
- Monitoring Reports

14 PUBLICATIONS

The trial will be registered in the ClinicalTrials.gov website upon approval by a human subject review board of the appropriate national health authorities in order to meet the criteria of the International Committee of Medical Journal Editors. All publications will follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org, October 2008).

After the conclusion and final analysis of the trial results, a formal abstract presentation may be made at a major cardiovascular conference and the study results, approved by the Principal Investigator and the Steering Committee, will be submitted to a reputable scientific journal.

Following the publication of the main manuscript, secondary analyses proposals will be considered for publication from either the Steering Committee members or individual Investigators. Before publishing or presenting data from the study, the Research Institution, Principal Investigator, and Co-Investigator(s) agree to submit copies of any and all proposed manuscripts or abstracts to Lutonix at least 30 days in advance of submitting to a publisher or other third party. No submissions may be made without the written approval from Lutonix.

15 STATISTICAL ANALYSIS PLAN

15.1 OVERVIEW OF STUDY DESIGN

The LEVANT 2 pivotal trial is a global, multi-center, randomized clinical trial comparing the Moxy Drug Coated Balloon to standard PTA for the treatment of stenosis of the femoropopliteal arteries. Approximately 750 subjects will be enrolled in order to include a total of 476 randomized subjects at up to 55 global centers. Enrollment will be stopped once 476 subjects are randomized. Subject randomization will be allocated 2:1 Moxy Drug Coated Balloon (test arm) to standard PTA catheter (control arm) after successful pre-dilatation.

Subjects are considered enrolled in the study after being consented and the defined pre-dilatation balloon inflation has begun. Based on angiographic results after predilatation, some will not meet criteria for randomization, and these nonrandomized patients are followed only for safety and do not contribute to the required evaluable sample size of 476 randomized subjects. However, since the patient underwent a protocol defined predilatation, they are considered to be enrolled even though they are not randomized.

The approximate number 750 of enrolled patients was estimated from the proportion of subjects in LEVANT I that were stratified after predilatation to stenting as well as data from other studies reported in the literature. Approximately 1/3 or more of total number of predilatated subjects will likely not be randomized and will be treated per standard of care. Enrollment will continue only until a randomized sample size of 476 is achieved, since this is the randomized sample size necessary for primary endpoint analysis presuming up to 15% loss-to-follow-up (i.e. 405 evaluable subjects).

Successful pre-dilatation is defined as ≤70% residual stenosis and an absence of flow-limiting dissection based on strict angiographic criteria. Subjects who met these criteria are randomized. Subjects who do not meet post-predilitation lesion success criteria are not randomized and are instead treated per hospital standard practice, followed for safety for 30 days, and then withdrawn. Subjects who are enrolled and randomized will be followed clinically for 24 months to assess the primary endpoints of patency and freedom from serious adverse events with further follow-up extending out to 5 years.

The primary analysis is an ITT analysis using proportion-based testing. For the study to be considered successful, superiority of Moxy Drug Coated Balloon must be demonstrated for the primary efficacy endpoint, and non-inferiority of the Moxy Drug Coated Balloon must be demonstrated for the primary safety endpoint. US and non-US enrollment will be contemporaneously monitored throughout the study to ensure approximately 50% of randomized subjects occur at US sites.

15.2 ASSESSMENT OF COMPARABILITY OF TREATMENT GROUPS AND POOLABILITY OF SITES AND SECONDARY ANALYSES

To demonstrate the comparability of the Control to Test subjects, the samples will be compared using t-tests or Wilcoxon nonparametric tests for means and X^2-tests for proportions: age, gender, smoking, obesity, hypercholesterolemia, diabetes mellitus, total target lesion length and maximum percent stenosis of the target lesion (via core lab analysis), previous target lesion intervention, ABI of the target limb, and Rutherford grade.

All primary endpoints will also be presented by site, and the sites will be tested for differences in the endpoints. Sites with 3 or fewer randomized subjects will be combined for this purpose.

An analysis will be performed to examine the potential for interaction of site and treatment group. A mixed effects logistic regression model will be fit that includes a fixed effect for treatment group, and random effects for site and the interaction of treatment group and site. If the p-value for the interaction term variance component is <0.15, it will be considered evidence of a statistically significant interaction effect, and additional analyses will be performed to explore the differences between sites to assess their potential causes and whether or not they are clinically meaningful.

All primary endpoints will also be presented by geography (US versus OUS). An analysis will be performed to examine the potential for interaction of geography and treatment group. A logistic regression model will be fit that includes fixed effects for treatment group, geography, and the interaction of treatment group and geography. If the p-value for the interaction term is <0.15, it will be considered evidence of a statistically significant interaction effect, and additional analyses will be performed to explore the differences between geographies to assess their potential causes and whether or not they are clinically meaningful.

In addition, a descriptive analysis that examines the impact of important covariates on study results will be performed. Baseline covariates are age, gender, smoking, obesity, hypercholesterolemia, diabetes mellitus, total target lesion length, and maximum percent stenosis of the target lesion (via core lab analysis), previous target lesion intervention, ABI of the target limb, and Rutherford grade. These covariates will be included along with treatment group in a logistic regression model in order to understand their potential impact on study results and to account for chance imbalances between the randomized groups in these covariates.

To assess the consistency of results under different analyses, secondary as-treated (AT) and per-protocol (PP) analyses will be performed for the primary and secondary endpoints. The AT dataset will include only those subjects treated with either an investigational or control device, and the comparison will be based on the actual device used, not randomized assignment. The PP dataset will include all subjects in the full analysis dataset that are characterized by appropriate exposure to treatment (procedurally correct as pre-specified), availability of measurements, and the absence of major protocol violations including violations of entry criteria. An additional supportive analysis of patients with and without bailout stenting will also be performed based on descriptive statistics, and data will further be presented for PP analysis of subjects with and without bailout stenting.

A descriptive analysis will also be reported for the subset of subjects with treated lesions ≥4 cm, comparable to the inclusion criteria of ongoing VIVA OPC[16] stent registry studies (e.g., SUPERB NCT00933270, OSPREY NCT01118117, and DURABILITY II NCT00530712).

15.3 HANDLING OF MISSING DATA

Endpoints may be missing because subjects have died, have uninterpretable imaging data or have withdrawn from the study prior to the time the endpoint is measured. The primary safety and effectiveness endpoints will be analyzed using survival analysis techniques. In survival analyses, unobserved endpoints are a standard part of the analysis; they are known as "censored observations". As long as the censoring is unrelated to the treatment, this method of handling missing endpoints produces unbiased estimates of the freedom-from-event rates.

The *reason* for the censoring of all subjects with missing endpoints will be reported; if there is any indication that the censoring is related to the Moxy Drug Coated Balloon or to the standard PTA catheter, a worst-case analysis will be performed for each primary endpoint, in addition to the standard analysis. In a worst-case analysis, an event will be assumed to have occurred at the time the subject discontinued participation in the study for all such subjects in the Test group. In the Control group, all subjects with missing data will be assumed *not* to have had an event. In

[16]Rocha-Singh, KJ, et. al. Performance Goals and Endpoint Assesssments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients with Symptomatic Peripheral Arterial Disease. *Cath and Cardio Inter* 69 (2007): 910.

addition, a tipping-point analysis will also be performed, in which assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis. These analyses will constitute sensitivity analyses of the effect of missing data on the study results.

15.4 PRIMARY ENDPOINTS

Primary Safety Endpoint

The primary safety endpoint is a composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above and below the ankle) index limb re-intervention, and index-limb-related death. These events are called "safety events" in the following text.

Primary Efficacy Endpoint

The primary efficacy endpoint is Primary Patency of the target lesion at 1 year. Primary Patency is defined as the absence of target lesion restenosis (defined by DUS PSVR ≥2.5) and freedom from target lesion revascularization (TLR). These events are called "efficacy events" in the following text.

The clinical status of the subject (for assessment of clinical and primary safety endpoints) is established prior to performing the required DUS (for assessment of the primary efficacy endpoint). A patent target lesion (by core lab DUS analysis) at the 12 month visit without a prior TLR is considered an Efficacy Success.

15.4.1 PRIMARY SAFETY ENDPOINT: BACKGROUND CONSIDERATIONS & OUTCOME EXPECTATIONS

The Primary Safety Endpoint includes assessment of clinically significant systemic and downstream vascular complications at 1 year by assessing freedom from all-cause index limb re-intervention (e.g. PTA or surgical bypass) for any reason (e.g. embolism, thrombosis, or restenosis), all index limb amputations (including both major and minor amputations below-the ankle), index-limb-related death, and all-cause perioperative (≤30 day) death.

Primary Endpoint expectations are estimated from an analysis of data from three randomized trials:

- The THUNDER trial[12], a prospective randomized European clinical trials of another manufacturer's drug-coated balloon (DCB) to a standard uncoated balloon to treat femoropopliteal stenosis
- The FemPac trial[13], a prospective randomized European clinical trial of another manufacturer's DCB to a standard uncoated balloon to treat femoropopliteal stenosis
- The LEVANT I study of the Moxy Drug Coated Balloon, which uses the same API as the THUNDER and FemPac DCB, but a different excipient (drug carrier). Like the other studies, the control in the LEVANT I study was a standard PTA balloon.

Although the primary composite safety endpoint as defined in the present study is not specifically reported in THUNDER and FemPac, the rate is estimated as the rate of freedom from all clinical events including death, amputation, any TLR (clinically-indicated or not), embolism or thrombosis in THUNDER at 12 months and in FemPac at clinical follow-up between 18 and 24 months (since 12 month data was not reported). Clinical outcomes reported for these Control studies and LEVANT I are summarized in Table 11: Historic Data for Primary Safety Endpoint Estimation below.

TABLE 11: HISTORIC DATA FOR PRIMARY SAFETY ENDPOINT ESTIMATION

Study	Arm	N	Events (N)					Percent of Subjects	Time (m)	Approx FF @ Time	Hazard Rate[+]	Predicted FF @ 12m[++]
			TLR	Amp	TE	Death	Total					
Thunder[12]	DCB	48	5	2	2	2	11	22.9%	12	77.1%	0.022	77.1%
	Control	54	26	0	3	1	30	55.6%	12	44.4%	0.068	44.4%
FemPac[13]	DCB	45	6	0	1	6	13	28.9%	18	71.1%	0.019	79.7%
	Control	42	21	1	0	3	25	59.5%	18	40.5%	0.050	47.9%
LEVANT I	DCB	49	6	1	0	1	8	16.3%	6	83.7%	0.030	70.1%
	Control	52	10	1	2	3	16	30.8%	6	69.2%	0.061	47.9%

[+] The hazard rate equals -LN(FF @ time)/time.

[++] The predicted FF-event rate at 12 months equals EXP(-hazard*time).

This analysis is complicated by the fact that there is likely to have been some overlap between the adverse events reported in the THUNDER and FemPac studies; however Lutonix does not have access to the raw data, and therefore are not able to assess to what extent this affects the hazard rates. In addition, subjects that based on unacceptable angiographic results after predilatation are likely to require stenting are excluded from the present study, so there may be some inherent positive selection bias that was absent in THUNDER and FemPac. Nevertheless, these factors that might increase the primary endpoint rate are at least partially counterbalanced by the fact that the above studies did not report many adverse index limb events (such as minor below-the-ankle amputations and non-target lesion vascular interventions) that count as safety endpoint failures in the present study.

The most conservative estimates come from the LEVANT I study; the hazard rates in the Test and Control groups are more similar in LEVANT I than in THUNDER or FemPac. The safety endpoint success rate of the Moxy Drug Coated Balloon is therefore assumed to be 70% at 12 months, and of the standard PTA catheter to be 48% at 12 months.

15.4.2 PRIMARY SAFETY ENDPOINT: HYPOTHESES AND SAMPLE SIZE CALCULATION

Objective: To assess whether the proportion of subjects with at least one safety event* in the Test group is inferior or not inferior to that of Control group through 12-months post-index procedure.

H_0: The proportion of subjects with safety events in the Test group through 12-months post-index procedure is clinically inferior to that of the Control group.

H_1: The proportion of subjects with safety events in the Test group through 12-months post-index procedure is clinically non-inferior to that of the Control group.

$$\mathbf{H_0: P_{TEST} - P_{CONTROL} \geq \delta \quad vs. \quad H_1: P_{TEST} - P_{CONTROL} < \delta}^{**}$$

*All-cause perioperative (≤30 day) death, index limb amputation (above and below the ankle), index limb re-intervention, and index-limb-related death are 'safety events'. **$\boldsymbol{\delta}$ is the range of differences that is considered not clinically important (it also known as the "range of indifference" or the "margin of noninferiority").

The statistical analysis will be a Farrington & Manning test for non-inferiority of proportions; the test will be a one-sided test at α=0.025. The response variable in each subject will be the presence or absence of at least one safety event from the time following the index procedure through 12 months. The primary analysis will be ITT. In addition to the primary ITT analysis, secondary as-treated analyses and per-protocol analyses will also be reported but may not be the basis of labeling claims.

The proportions at 12-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported.

Sample Size Estimate: We estimated the sample size under the following conditions:

- The true 12-month proportion in the Test group is 100% - 70% = 30%. The true 12-month proportion in the Control group is 100% - 48% = 52%.
- A 2:1 randomization ratio.
- Farrington & Manning test for non-inferiority of proportions.
- The Type 1 error, α = 0.025 (one-sided).
- The Type 2 error, β = 0.10 (Power = 1 - β = 90%).
- The non-inferiority margin, δ= .05.
- Subjects who are censored without having an event will be omitted from the analysis.

According to PASS 2008 (using the Farrington and Manning test for non-inferiority of proportions), the evaluable sample size required for 90% power is 150 (50 Control plus 100 Test). This endpoint is not the sample-size driver of the study. Randomization of 476 subjects is expected to provide at least 405 evaluable subjects, after adjustment for up to 15% censoring) and approximately 99% power.

15.4.3 PRIMARY EFFICACY ENDPOINT: BACKGROUND CONSIDERATIONS & OUTCOME EXPECTATIONS

The Primary Efficacy Endpoint is Primary Patency of the target lesion at 1 year. Primary Patency is defined as the absence of binary restenosis based on DUS peak systolic velocity ratio (PSVR) ≥2.5 and freedom from TLR.

In order to facilitate comparison with other ongoing studies and in deference to the threshold used in defining the VIVA Physician Group endpoint[17], secondary endpoint alternative patency will also be reported for PSVR binary restenosis thresholds ≥2.0 and ≥3.0. Compared to threshold PSVR ≥2.0, the threshold ≥2.5 more accurately reflects clinically significant stenosis and is more consistent with angiographic results.[18] The primary composite efficacy endpoint as defined in the present study is not specifically reported in THUNDER or FemPac, neither of which included Doppler ultrasound assessment at 1 year.

The efficacy endpoint success rate is instead estimated solely from the observed rate of freedom from TLR (whether clinically-indicated or not) at 18 to 24 months in these studies. It is noteworthy that only after 2 years do TLR rates exceed 6 month angiographic binary restenosis rates. Efficacy events reported for these studies and for the pilot study LEVANT I are summarized in Table 12 below. Efficacy endpoints success rate is estimated in Table 12 from LEVANT I data according to both angiographic and DUS criteria for restenosis, even though DUS will be used in the LEVANT 2 study.

TABLE 12: HISTORIC DATA FOR PRIMARY EFFICACY ENDPOINT ESTIMATION

Study	Arm	N	Events (N)	Percent of Subjects	Time (m)	Approx FF @ Time	Hazard Rate+	Predicted FF @ 12m++
	DCB	48	7	14.6%	18	85.4%	0.009	89.7%
Thunder[12]	Control	54	28	51.9%	18	48.1%	0.041	61.3%
	DCB	45	6	13.3%	18	86.7%	0.008	91.1%
FemPac[13]	Control	42	21	50.0%	18	50.0%	0.039	63.0%
	DCB	49	11	22.4%	6	77.6%	0.044	59.3%
LEVANT I*	Control	52	18	34.6%	6	65.4%	0.072	42.2%
LEVANTI**	DCB	39	11	28.2%	6	71.8%	0.055	51.6%
	Control	35	18	51.4%	6	48.6%	0.120	23.6%

* Numbers of events are estimated from the approximate freedom-from-TLR/DUS>2.5 at 6 months.

** Numbers of events are estimated from the approximate freedom-from-TLR/angiographic patency (<50% stenosis) at 6 months.

+ The hazard rate equals -LN(FF @ time)/time.

[17] Rocha-Singh, K. J. (2007). Performance Goals and Endpoint Assessments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients with Symptomatic Peripheral Arterial Disease. Cath and Cardio Inter , 69, 910.

[18] Schlager, O. (2007). Duplex Sonography Versus Angiography for Assessment of Femoropopliteal Arterial Disease in a "Real-World" Setting. *14*, 452-459.

[++] The predicted FF-event rate at 12 months equals EXP(-hazard*time).

Note that the hazard rates in the Control and Test groups based on the LEVANT I DUS data are more similar than in the THUNDER and FemPac studies or using LEVANT I angiographic data, which means that using the LEVANT I DUS data produces the most conservative (i.e. largest) study sizes. So in spite of its limitations, we used LEVANT I DUS data to estimate study sizes for the current study. The efficacy endpoint success rate of the Moxy Drug Coated Balloon is therefore assumed to be 59% at 12 months, and of the standard PTA catheter to be 42% at 12 months.

15.4.4 PRIMARY EFFICACY ENDPOINT: HYPOTHESIS AND SAMPLE SIZE CALCULATION

Objective: To assess whether the proportion of subjects with at least one efficacy event* in the Test group is equal or not to that of Control group through 12-months post-index procedure.

H_0: The proportion of subjects with efficacy events in the Control group through 12-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with efficacy events in the Control group through 12-months post-index procedure is not equal to that of the Test group.

$$\mathbf{H_0: P_{CONTROL} = P_{TEST} \quad vs. \quad H_1: P_{CONTROL} \neq P_{TEST}}$$

*Target lesion restenosis (defined by DUS PSVR ≥2.5) and target lesion revascularization (TLR) are 'efficacy events'.

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable in each subject will be the presence or absence of at least one efficacy event from the time following the index procedure through 12 months. The primary analysis will be ITT, and a significant rejection of the null hypothesis with results in favor of the Test group will indicate success for this endpoint. In addition to the primary ITT analysis, secondary as-treated analyses and per-protocol analyses will also be reported but may not be the basis of labeling claims.

The proportions at 12-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported.

Sample Size Estimate: The sample size estimate assumed the following:

- The true 12-month proportion in the Test group is 100% - 59% = 41%. The true 12-month rate in the Control group is 100% - 42% = 58%.
- A 2:1 randomization ratio.
- Likelihood ratio chi-square test for inequality of binomial proportions.
- The Type 1 error, α = 0.05 (two-sided).
- The Type 2 error, β = 0.10 (Power = 1 - β = 90%).
- Subjects who are censored without having an event will be omitted from the analysis.

According to PASS 2008, the study evaluable sample size required for 90% power is approximately 405 subjects (135 Control plus 270 Test after eliminating the censored subjects, if any). After adjustment for 15% censoring through 12 months, the study size is 476 (317 in the Test group and 159 in the Control group) randomized subjects. This endpoint is the sample-size driver of the study.

15.5 SECONDARY ENDPOINTS

15.5.1 SECONDARY ENDPOINTS WITH HYPOTHESIS TESTING

The following secondary endpoints will have hypothesis tests. No secondary endpoints will be tested unless *both primary objectives* are passed. All secondary endpoints with hypothesis tests will be included in the product labeling. The primary analysis will be ITT. In addition to the primary ITT analysis, secondary as-treated analyses and per-protocol analyses will also be reported but may not be the basis of labeling claims.

The testing of the secondary objectives will be performed in a hierarchical fashion in the order in which they are listed below. This means that as soon as a null hypothesis is *not rejected*, no further hypotheses will be tested. This hierarchical testing scheme ensures that the study-wide Type 1 error rate is 0.05 when all of the secondary endpoints are tested at α=0.05.

15.5.1.1 SECONDARY ENDPOINT: TOTAL TLR AT 12 MONTHS

Objective: To assess whether the proportion of subjects with a TLR in the Test group is equal or not to that of Control group through 12-months post-index procedure.

H_0: The proportion of subjects with a TLR in the Control group through 12-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with a TLR in the Control group through 12-months post-index procedure is not equal to that of the Test group.

$$\mathbf{H_0: P_{CONTROL} = P_{TEST} \quad vs. \quad H_1: P_{CONTROL} \neq P_{TEST}}$$

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable for each subject will be the presence or absence of a TLR by 12 months.

The proportions at 12-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.2 SECONDARY ENDPOINT: TVR AT 12 MONTHS

Objective: To assess whether the proportion of subjects with a TVR in the Test group is equal or not to that of Control group through 12-months post-index procedure.

H_0: The proportion of subjects with a TVR in the Control group through 12-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with a TVR in the Control group through 12-months post-index procedure is not equal to that of the Test group.

$$\mathbf{H_0: P_{CONTROL} = P_{TEST} \quad vs. \quad H_1: P_{CONTROL} \neq P_{TEST}}$$

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable for each subject will be the presence or absence of a TVR by 12 months.

The proportions at 12-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.3 SECONDARY ENDPOINT: COMPOSITE EVENTS AT 12 MONTHS

Objective: The composite event is: all-cause death at 30 days, and amputation, index-limb reintervention, and index-limb-related death at 12 months. The objective is to assess whether the proportion of subjects with an event in the Test group is equal or not to that of Control group.

H_0: The proportion of subjects with an event in the Control group through 12-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with an event in the Control group through 12-months post-index procedure is not equal to that of the Test group.

$$\mathbf{H_0: P_{CONTROL} = P_{TEST} \quad vs. \quad H_1: P_{CONTROL} \neq P_{TEST}}$$

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable for each subject will be the presence or absence of an event by 12 months.

The proportions at 12-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.4 SECONDARY ENDPOINT: COMPOSITE EVENTS AT 24 MONTHS

Objective: The composite event is: all-cause death at 30 days, and amputation, index-limb reintervention, and index-limb-related death at 24 months. The objective is to assess whether the proportion of subjects with an event in the Test group is non-inferior to that of Control group.

H_0: The proportion of subjects with an event in the Test group through 24-months post-index procedure is clinically inferior that of the Control group.

H_1: The proportion of subjects with an event in the Test group through 24-months post-index procedure is clinically non-inferior to that of the Control group.

$$\mathbf{H_0: P_{TEST} - P_{CONTROL} \geq \delta \quad vs. \quad H_1: P_{TEST} - P_{CONTROL} < \delta^*}$$

*where **δ** = .05 and is the range of differences that is considered not clinically important (it also known as the "range of indifference" or the "margin of noninferiority").

The statistical analysis will be the Farrington and Manning test for non-inferiority of proportions; the test will be a one-sided test at α=0.025. The response variable in each subject will be the presence or absence of at least one event from the time following the index procedure through 12 months.

The proportions at 24-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.5 SECONDARY ENDPOINT: PRIMARY PATENCY AT 24 MONTHS

Objective: To assess whether the proportion of subjects with an efficacy event in the Test group is equal or not to that of Control group through 24-months post-index procedure. For the definition of an efficacy event, please refer to Section 15.4.

H_0: The proportion of subjects with an event in the Control group through 24-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with an event in the Control group through 24-months post-index procedure is not equal to that of the Test group.

$$\mathbf{H_0: P_{CONTROL} = P_{TEST} \quad vs. \quad H_1: P_{CONTROL} \neq P_{TEST}}$$

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable for each subject will be the presence or absence of an efficacy event by 24 months.

The proportions at 24-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.6 SECONDARY ENDPOINT: TOTAL TLR AT 24 MONTHS

Objective: To assess whether the proportion of subjects with a TLR in the Test group is equal or not to that of Control group through 24-months post-index procedure.

H_0: The proportion of subjects with a TLR in the Control group through 24-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with a TLR in the Control group through 24-months post-index procedure is not equal to that of the Test group.

$$\mathbf{H_0: P_{CONTROL} = P_{TEST} \ vs. \quad H_1: P_{CONTROL} \neq P_{TEST}}$$

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable for each subject will be the presence or absence of a TLR by 24 months.

The proportions at 24-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.7 SECONDARY ENDPOINT: TVR AT 24 MONTHS

Objective: To assess whether the proportion of subjects with a TVR in the Test group is equal or not to that of Control group through 24-months post-index procedure.

H_0: The proportion of subjects with a TVR in the Control group through 24-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with a TVR in the Control group through 24-months post-index procedure is not equal to that of the Test group.

$$H_0: P_{CONTROL} = P_{TEST} \quad \text{vs.} \quad H_1: P_{CONTROL} \neq P_{TEST}$$

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable for each subject will be the presence or absence of a TVR by 24 months.

The proportions at 24-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.8 SECONDARY ENDPOINT: COMPOSITE EVENTS AT 24 MONTHS

Objective: The composite event is: all-cause death at 30 days, and amputation, index-limb reintervention, and index-limb-related death at 24 months. The objective is to assess whether the proportion of subjects with an event in the Test group is equal or not to that of Control group.

H_0: The proportion of subjects with an event in the Control group through 24-months post-index procedure is equal to that of the Test group.

H_1: The proportion of subjects with an event in the Control group through 24-months post-index procedure is not equal to that of the Test group.

$$H_0: P_{CONTROL} = P_{TEST} \quad \text{vs.} \quad H_1: P_{CONTROL} \neq P_{TEST}$$

The statistical analysis will be a likelihood ratio chi-square test for inequality of binomial proportions; the test will be a two-sided test at α=0.05. The response variable for each subject will be the presence or absence of an event by 24 months.

The proportions at 24-months post-index procedure, and the confidence intervals of these rates in each group, will also be reported if the null hypothesis is rejected.

15.5.1.9 SECONDARY ENDPOINT: TARGET-LIMB-RELATED HOSPITAL DAYS AT 24 MONTHS

Objective: To assess whether the number of hospital days associated with the treatment of peripheral arterial disease (PAD) in the target limb in the in the Test group is equal or not to that of the Control group through 24-months post-index procedure.

A hospital day is defined as any day the subject spends as a hospital in-subject or any day that the hospital is visited for an emergency-department evaluation or an out-subject procedure. Only those hospital days after the index procedure that are associated with treatment of PAD in the target limb will be included in the analysis. The statistical test will be a based on a Poisson regression analysis in which the regressor is an indicator for the treatment group and there is an offset term for the total days of follow-up for the first 24 months following the index procedure. The test will be a two-sided test of the regression coefficient at α=0.05. The response variable will be the number of hospital days each subject experiences in the 24 months following the index procedure.

$$H_0: \beta_{treatment} = 0$$

$$H_1: \beta_{treatment} \neq 0$$

In the event that the assumptions of the Poisson regression model are not met, a negative binomial model will be employed.

The distribution of hospital days at 24-months post-index procedure in each group, will also be reported.

15.5.2 SECONDARY ENDPOINTS WITH DESCRIPTIVE STATISTICS

The following secondary endpoints will have descriptive statistics estimated. For each endpoint, the estimated mean and standard deviation or proportion and sample size will be calculated and reported for the Control group and for the Test group. (NOTE: Some of these endpoints are also tested endpoints; these were presented above). In addition to the primary ITT analysis, descriptive statistics will also be estimated for the primary endpoints and for each of the following secondary endpoints based on as-treated (AT) and per-protocol (PP) analyses. In addition, descriptive statistics will also be estimated for the subsets of subjects with and without bailout stenting and for patients in the PP dataset with and without bailout stenting.

- Primary safety endpoint in each group as estimated by Kaplan-Meier analysis.
- Primary efficacy endpoint in each group as estimated by Kaplan-Meier analysis.
- Primary and secondary patency at 6, 12 and 24 months:
    - By DUS PSVR <2.0
    - By DUS PSVR <2.5
    - By DUS PSVR <3.0
- TLR at 6 and 24 months:
    - Clinically driven
    - Total (clinical and DUS/angiography-driven)
- DUS Clinical Patency (DUS PSVR <2.5 without prior Clinically Driven TLR)
- Change from baseline at 6, 12 and 24 months:
    - Index-limb Rutherford classification
    - Index-limb resting ABI

  - Walking Impairment Questionnaire score
  - Six-minute Walk Test distance in subjects with no respiratory, cardiac, or orthopedic impairments
  - EQ-5D score
  - SF36 v2 score
- Freedom from death, index-limb amputation above ankle, and TVR at 30 days (VIVA safety endpoint)
- Freedom from the following at 1, 6, 12, 24, 36, 48 and 60 months:
  - All-cause perioperative (≤30-day) death, and from any of the following: index-limb amputation (any level), index-limb re-intervention, and index-limb-related death
  - All-cause death
  - Amputation (above-ankle)
  - TVR
  - Reintervention for treatment of thrombosis or embolism of the target vessel or its distal vasculature
  - Major vascular complication
  - Hospital admissions for cardiovascular events
- Target limb related hospital days at 1 and 2 years.

APPENDIX A: DEFINITIONS

Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Adverse Device Effect

An adverse device effect is any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use for preparation or deployment of the device. It also includes any event that is a result of a user error.

Anticipated Adverse Event

Any undesirable health related experience occurring to a subject whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or Instructions For Use (IFU) that is identified or worsens during a clinical study.

Serious Adverse Event (SAE)

A SAE is an adverse event that:

- led to death or led to a serious deterioration in the health of the subject
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required in-subject hospitalization or prolongation of existing hospitalization or
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

All serious adverse events will be adjudicated by the CEC and reported appropriately.

Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated Adverse Device Effect (UADE)

A UADE is “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not

previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

Adverse Event Severity Stratification

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 sequelae.
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.

Relationship to study device

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study device:

Not Related	The event is definitely not associated with device application. 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 and/or a more likely alternative etiology exists.
Possible	The temporal sequence between device application 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 is relevant or the event abates upon device application completion/removal or the Event cannot be reasonably explained by the subject's condition.
Highly Probable	The temporal sequence is relevant and the event abates upon device application completion/removal, or reappearance of the event on repeat device application (re-challenge).

Relationship to study procedure

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study procedure:

Not Related	The event is definitely not associated with procedure. The adverse event is due to an underlying or concurrent illness or effect of another procedure.
Unlikely	An adverse event has little or no temporal relationship to the procedure and/or a more likely alternative etiology exists.
Possible	The temporal sequence between the 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 is relevant or the event abates upon procedure completion or the Event cannot be reasonably explained by the subject's condition.
Highly Probable	The temporal sequence is relevant and the event abates upon procedure completion, or reappearance of the event on repeat procedure (re-challenge).

Abrupt or Acute Closure

Angiographic documentation of significantly reduced flow due to mechanical dissection, thrombus or severe vessel spasm in the treatment area.

Acute Technical Success

Acute technical success is defined as, a per device basis, the achievement of successful delivery and deployment of the study device(s) as intended at the intended target lesion, without residual dissections, without visible thrombus, without "watermelon seeding" of the balloon, without balloon rupture or inflation/deflation abnormalities and a successful withdrawal of the study system.

All Cause Perioperative Death

All-cause Perioperative Death is defined as death within 30 days of the index procedure.

Amputation of the Index Limb

Amputation includes all amputations including both Major Amputations (above the ankle) and Minor Amputations (including amputations below the ankle).

Ankle Brachial Index Assessment

Ankle systolic pressure/brachial systolic pressure, measured by constructing a ratio from the peak systolic pressure measured during the deflation of the ankle cuffs during Doppler detection to the systolic brachial pressure.

As-Treated
The As-Treated analysis is based only on those subjects treated with either an investigational or control device, and the comparison is based on the actual device used, not randomized assignment.

Binary Restenosis Rate
The presence of a hemodynamically significant restenosis (>50%) as determined by angiography or by duplex ultrasound (defined by systolic velocity ratio≥2.5).

Clinically Driven Target Lesion Revascularization
Revascularization at the target lesion with evidence of target lesion diameter stenosis >50% determined by duplex ultrasound or angiography and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the target limb).

Clinically Driven Target Vessel Revascularization
Revascularization of the target vessel with evidence of diameter stenosis >50% determined by duplex ultrasound or angiography and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the target limb).

DUS Clinical Patency
Defined as patency of the target limb (based on a PSVR threshold < 2.5) without prior Clinically Driven TLR.

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 or marketed.

Device Success
Acute technical success is defined as, a per device basis, the achievement of successful delivery and deployment of the study device(s) as intended at the intended target lesion, without balloon rupture or inflation/deflation abnormalities and a successful withdrawal of the study system. If a device is inserted into the subject but not used due to user error (e.g. inappropriate balloon length or transit time too long), this device will not be included in the device success assessment.

Discharge
The time point at which the subject was released from the admitting hospital or transferred to another facility.

Dissections

National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System:

0: None

A. Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.

B. Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.

C. Extraluminal cap with persistence of contrast after dye clearance from the lumen.

D. Spiral luminal filling defects.

E. New persistent filling defects.

F. Non-A-E types that lead to impaired flow or total occlusion.

Note: Type E and F dissections may represent thrombus.

Enrollment

The point at which the subject has met all the study inclusion and none of the study exclusion criteria, the guidewire has been placed across the study lesion and study pre-dilatation has occurred.

Intent-To-Treat (ITT)

The principle of including outcomes of all subjects in the analysis who are randomized into the study, regardless of the treatment actually received.

Index Limb Related Death

Any death adjudicated by the DMC as "likely related" to a complication of the index limb.

Major Bleeding Complications

Bleeding will be considered major if:

- It leads to death;
- It leads to permanent disability;
- It is clinically suspected or proven to be intracranial (see stroke)
- It produces a fall in hemoglobin of at least 3 mmol/l;
- It leads to transfusion of 2 or more units of whole blood of packed cells;
- Peripheral vascular surgery is necessary.
- All other bleeding will be considered as minor.

Major Vascular Complications

Hemorrhagic vascular complications included the following:

- Haematoma at access site >5 cm
- False aneurysm
- AV fistula
- Retroperitoneal bleed
- Peripheral ischemia/nerve injury

- Any transfusion required will be reported as a vascular complication unless clinical indication clearly other than catheterization complication
- Vascular surgical repair

Patent Run-off
At least one patent native outflow artery from the popliteal to the ankle, free from significant (≥50%) stenosis as confirmed by angiography or ultrasound that has not previously been revascularized.

Per-Protocol (PP)
The PP analysis is based on all subjects that are characterized by appropriate exposure to treatment (procedurally correct as pre-specified), availability of measurements, and the absence of major protocol violations including violations of entry criteria.

Primary Patency
Primary Patency of the target lesion is defined as the absence of binary restenosis based on DUS peak systolic velocity ratio ≥2.5 (or based on angiography if performed), as analyzed by independent core lab, without prior target lesion revascularization. (Alternative Primary Patency is also reported PSVR thresholds ≥2.0 and ≥3.0.)

Procedural success
Attainment of ≤30% residual stenosis in the treatment area by independent core lab analysis without major adverse events during the index procedure.

Popliteal Artery
The vessel located between Hunter's canal and the trifurcation.

PSVR
Peak Systolic Velocity Ratio

Reference Vessel Diameter (RVD)
The interpolated reference vessel diameter is based on a computed estimation of the original diameter of the artery at the level of the obstruction (minimal luminal diameter)

Restenosis

Either ≥50% restenosis of the diameter of the reference-vessel segment by QVA or peak systolic velocity ratio of ≥2.5, determined by blinded ultrasound and independent core lab analysis.

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

Rutherford Categories

Grade	Category	Clinical Description	Objective Criteria
	0	Asymptomatic, no hemodynamically significant occlusive disease	Normal results of treadmill (5 min,2 mph, 12^0 constant grade)
I	1	Mild Claudication	Treadmill exercise complete, post exercise AP is greater than 50 mm Hg but more than 25 mm Hg less than normal
	2	Moderate Claudication	Symptoms between categories 1 and 3
	3	Severe Claudication	Treadmill exercise cannot be completed post exercise AP is less than 50 mm Hg
II	4	Ischemic rest pain	Resting AP of 40 mm Hg or less, flat or barely pulsatile ankle or metatarsal plethysmographic tracing, toe pressure less than 30 mm Hg
III	5	Minor tissue loss, non-healing ulcer, or focal gangrene with diffuse pedal ischemia	Resting AP of 60 mm Hg or less, flat or barely pulsatile ankle metatarsal plethysmographic tracing flat or barely pulsatile, toe pressure less than 40 mm Hg
	6	Major tissue loss, extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

Screen Failures
Subjects screened, but not meeting all study entry criteria and hence are not enrolled, are considered screening failures and will be documented as such on the Screening Logs.

Secondary Patency
Secondary Patency of the target lesion is defined as the absence of binary restenosis based on DUS peak systolic velocity ratio ≥2.5 (or based on angiography if performed) as analyzed by independent core lab, independent of whether or not patency is re-established via an endovascular procedure.

Stroke
Clinical signs/symptoms of focal neurological deficit lasting longer than 24 hours.

Target Lesion
Lesion that is to be treated during the index procedure. For study inclusion, the lesion must be ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the posterior tibial trunk, with the intent of staying above the trifurcation.

Target Lesion Revascularization
A repeat revascularization procedure (percutaneous or surgical) of the original target lesion site.

Target Vessel Revascularization
A repeat revascularization procedure (percutaneous or surgical) of a lesion in the target vessel.

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

Technical Success
Technical Success of the balloon procedure is defined as successful access and deployment of the device and visual estimate of ≤30% diameter residual stenosis during the index procedure without deployment of a bailout stent.

Treatment Area
The entire treated vessel segment in which angioplasty balloons were inflated (the injury segment) including the target lesion.

Thrombosis
A total occlusion documented by duplex ultrasound and/or angiography at the treatment site with or without symptoms Thrombosis may be categorized as acute (<1 day), subacute (1-30 days) and late(>30 days). The presence of thrombus at the target lesion must be noted as an adverse event in the eCRF.

Transient Ischemic Attack (TIA)
Clinical signs/symptoms of focal neurological deficit lasting up to 24 hours

Walking Impairment Questionnaire (WIQ)
A measure of subject-perceived walking performance for subjects with PAD and/or intermittent claudication. This questionnaire estimates walking distance, walking speed and stair climbing capacity.

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

Worsening Rutherford Clinical Category
A deterioration (an increase) in the Rutherford Category by more than 1 category from the earliest post-procedural measurement.