

**A Prospective, Multicenter, Registry of the Lutonix Drug
Coated Balloon for Treatment of
Femoropopliteal Arteries**

LEVANT 2 Safety Registry

Investigational Plan

Version 1.0



Investigational Device: Lutonix Drug Coated Balloon (Formerly
Moxy Drug Coated Balloon)

NCT number: 01790243 (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.

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PROTOCOL SIGNATURE PAGE
The LEVANT 2 Safety Registry Trial Investigational Plan

A Prospective, Multicenter, Registry of the Lutonix Drug Coated Balloon 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:

Date

Initials

The LEVANT 2 Safety Registry Summary

Title	A Prospective, Multicenter, Registry of the Lutonix Drug Coated Balloon for Treatment of Femoropopliteal Arteries (LEVANT 2 Safety Registry)
Investigational Device	Lutonix Drug Coated Balloon (Formerly Moxy Drug Coated Balloon)
Study Design	Prospective, Multicenter, Registry, Safety and Efficacy
Overview	<p>The purpose of the LEVANT 2 Safety Registry is to collect additional safety and efficacy data on the Lutonix Drug Coated Balloon in a large population. The study will enroll a similar patient population and follow the same medication regimen, follow-up schedule, and definitions as the LEVANT 2 Randomized protocol.</p> <p>After successful protocol-defined pre-dilatation, subjects that are determined not to require stenting based on the defined angiographic criteria will be treated with the Lutonix Drug Coated Balloon and followed for 5 years. Subjects that do not meet post-pre-dilatation lesion criteria are excluded (and treated per standard practice) and followed for safety for 30 days.</p>
Purpose	To collect additional safety and efficacy information on the Lutonix Drug Coated Balloon for treatment of stenosis or occlusion of the femoral and popliteal arteries.
Objective	To assess safety and efficacy of use of the Lutonix Drug Coated Balloon for treatment of stenosis of the femoropopliteal arteries in a large population of subjects.
Treatment	All subjects meeting protocol-defined post pre-dilatation criteria will be treated with the Lutonix Drug Coated Balloon.
Enrollment	<p>Enrollment will occur at up to 12 US centers and excludes sites that are participating in the LEVANT 2 Randomized trial and the LEVANT 2 Continued Access Registry study.</p> <p>Up to 975 combined subjects are expected to be enrolled between the LEVANT 2 Safety Registry and the LEVANT 2 Continued Access Registry to ensure approximately 650 subjects treated with the Lutonix Drug Coated Balloon between the two studies.</p>
Subject Follow-Up Schedule	<p><i>Clinical:</i> 6, 12, and 24 Months <i>Duplex Ultrasound (DUS):</i> 0-30 days, 6 months, 12 months, and 24 months <i>Telephone:</i> 1, 36, 48 and 60 Months</p>
Primary Endpoint	Rate of unanticipated device- or drug- related adverse events over time through 60 months
Secondary Endpoints	<p><i>Safety</i></p> <ul style="list-style-type: none"> • Composite of freedom from all-cause perioperative (≤ 30 day) death and freedom from the following at 1, 6, 12, 24, 36, 48, and 60 months: index limb amputation, index limb re-intervention, and

	<p>index-limb-related death.</p> <ul style="list-style-type: none">• Freedom at 30 days from all-cause death, index limb amputation above the ankle and target vessel revascularization (TVR) (VIVA Safety Endpoint) <p>The following endpoints will be assessed at 1, 6, 12, 24, 36, 48 and 60 months:</p> <ul style="list-style-type: none">• Rate of unexpected device- or drug-related adverse events• 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 <p><i>Efficacy</i></p> <ul style="list-style-type: none">• Acute Device, Technical and Procedural success <p>The following endpoints will be assessed at 6, 12 and 24 Months:</p> <ul style="list-style-type: none">• Primary and Secondary Patency.• 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)<ul style="list-style-type: none">○ Clinically-driven○ Total (<i>clinical and DUS/angiography-driven</i>)• Change of Rutherford classification from baseline• Change of resting Ankle Brachial Index (ABI) from baseline
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Inclusion Criteria	<p>Clinical Criteria</p> <ol style="list-style-type: none">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; <p><u>Angiographic Criteria</u></p> <p>Lesion Criteria</p> <ol style="list-style-type: none">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. $\geq 70\%$ 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. <i>de novo</i> 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 ($\geq 50\%$ stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions); <p>NOTE: Successful inflow artery treatment is defined as attainment of residual diameter stenosis $\leq 30\%$ without death or major vascular complication.</p> <ol style="list-style-type: none">13. At least one patent native outflow artery to the ankle, free from significant ($\geq 50\%$) 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.
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<p>Exclusion Criteria</p>	<p>Patients will be excluded if ANY of the following conditions apply:</p> <ol style="list-style-type: none"> 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 m² (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.).
<p>Primary Analytical Subset</p>	<p>All subjects treated with a DCB in the LEVANT 2 Randomized protocol, the LEVANT 2 Continued Access registry and the LEVANT 2 Safety Registry.</p>

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Sponsor/ Contact:	Lutonix, Inc.
CRO	
Electronic Data Capture (EDC)	
Angiographic Core Lab	
DUS Core Lab	

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1 INTRODUCTION

The purpose of the LEVANT 2 Safety Registry is to collect additional safety and efficacy information on the Lutonix Drug Coated Balloon (formerly known as Moxy Drug Coated Balloon) for treatment of stenosis or occlusion of the femoropopliteal arteries in a larger patient population. Enrolled subjects will meet the same protocol requirements and undergo the same follow up and testing schedule as the LEVANT 2 Randomized protocol.

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 years¹ 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 interventions². 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 complications³ and a very high frequency of restenoses after percutaneous intervention⁴. The Lutonix 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 1964⁵, 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-analysis⁶. 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 vasculature⁷. 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,

¹ Zeller, T. Current state of endovascular treatment 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 intermittent 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 Assessments 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.

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 beneficial⁸, although a recent publically presented peripheral study investigating a paclitaxel coated stent has shown benefit over BMS⁹.

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 study¹⁰ 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 disease¹¹.

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 Lutonix Drug Coated Balloon, is one example of a DCB.

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.

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, Hertzler 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.

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 demonstrated preliminary safety and decreased restenosis of the femoropopliteal lesions in the context of standard-of-care stenting. Both the THUNDER¹² and FemPac¹³ 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		
<u>Endpoint</u>	<u>DCB (n=48)</u>	<u>PTA (n=54)</u>
Late Lumen Loss (6 month), n±SD - Primary Endpoint (<i>p</i> =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		
<u>Endpoint</u>	<u>DCB (n=41)</u>	<u>PTA (n=48)</u>
Late Lumen Loss (6 month), n±SD - Primary Endpoint (<i>p</i> =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.

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.

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 Lutonix 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 Lutonix DCB or a standard PTA catheter (control group). Subject inclusion and exclusion criteria were similar to previous 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.

In this randomized, controlled clinical study, the Lutonix DCB demonstrated significantly less late lumen loss at 6 months and similar safety through 24 months by direct comparison to conventional balloon angioplasty. The primary objective was met, and the angiographic and clinical results of the LEVANT I trial demonstrate the feasibility, safety, and efficacy of use of the Lutonix DCB for treatment of femoropopliteal lesions.

In the ITT population, the primary endpoint of mean Late Lumen Loss at 6 months was better in the Lutonix DCB arm (0.46 ± 1.13) compared to the POBA arm (1.09 ± 1.07), with a p value of 0.016, consistent with efficacy of the Lutonix DCB for this indication. The difference in mean late loss between arms was also lower in the balloon-only stratification group (0.45 ± 1.18 vs. 1.19 ± 1.15 , $p=0.024$).

The Lutonix DCB demonstrated safety comparable to conventional angioplasty (POBA) in the LEVANT I Trial, with similar ITT AE and SAE rates through 24 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. The percentage of subjects with any death, amputation, or target lesion thrombosis was 8% for Lutonix DCB compared to 12% for control POBA at study completion.

Secondary clinical endpoints trended in favor of the Lutonix DCB arm on an ITT basis through study completion at 24 months, including TLR (36% vs. 49%, $p = 0.23$), TVR (36% vs. 51%, $p = 0.15$), and primary patency (54% vs. 32% for DUS PSVR < 2.5 without TLR, $p = 0.05$), which are clinically relevant findings consistent with safety of the experimental device and treatment effect over standard PTA. There was no evidence for diminished treatment effect over time; on the contrary, the difference in ITT primary patency between test and control increased after 2 years of follow-up. This was true even in the context of 8 (16%) Lutonix DCB subjects treated with malfunctioning devices that did not fully inflate because twisted balloon folds, and after 2 years all of these had failed primary patency.

In the post hoc subset of subjects treated with normally functioning devices without geographic miss, Lutonix DCB had a lower TLR rate (19% vs. 55%, $p = 0.006$) and higher primary patency

(72% vs. 33% for DUS PSVR < 2.5 without TLR, $p = 0.005$) compared to uncoated PTA balloons. This observation suggests a durable treatment effect and supports the importance of the improved manufacturing processes (to ensure proper balloon folding) and physician training procedures (to minimize geographic miss) that have since been implemented.

Two year clinical follow-up has been completed. Safety of the Lutonix DCB was indistinguishable (and trending superior to) control uncoated balloon angioplasty. The successful primary endpoint of late lumen loss at 6 months and higher primary patency at 2 years demonstrates efficacy.

1.2 DEVICE AND STUDY RATIONALE

The Lutonix 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 Lutonix 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 Lutonix 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 oncology¹⁴ and drug-eluting stents (DES)¹⁵. The maximum total dose of 3.8 mg on the largest peripheral Lutonix 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 Lutonix Drug Coated Balloon.

2 STUDY OBJECTIVES AND ENDPOINTS

Data from all subjects treated with DCB in the LEVANT 2 Randomized protocol (roll-in and randomized to DCB), the LEVANT 2 Continued Access Registry and the LEVANT 2 Safety Registry will be combined and analyzed descriptively. Secondary as-treated, unstented, and per-protocol analyses will also be performed.

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 Safety Registry is to assess safety and efficacy of use of the Lutonix Drug Coated Balloon for treatment of stenosis of the femoropopliteal arteries in a large population of subjects.

2.2 PRIMARY ENDPOINTS

Rate of unanticipated device- or drug- related adverse events over time through 60 months.

2.3 SECONDARY ENDPOINTS

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

Safety

- Composite of freedom from all-cause perioperative (≤ 30 day) death and freedom from the following at 1, 6, 12, 24, 36, 48, and 60 months: index limb amputation, index limb re-intervention, and index-limb-related death.
- Freedom at 30 days from all-cause death, index limb amputation above the ankle and target vessel revascularization (TVR) (VIVA Safety Endpoint)

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

- Rate of unanticipated device- or drug-related adverse events
- 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

Efficacy

- Acute Device, Technical and Procedural success

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

- Primary and Secondary Patency. 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).
- 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 Ankle Brachial Index (ABI) from baseline

3 DEVICE DESCRIPTION

The Lutonix Drug Coated Balloon is a standard PTA catheter with a drug coating on the balloon portion of the catheter. The Lutonix 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 $2\mu\text{g}/\text{mm}^2$.

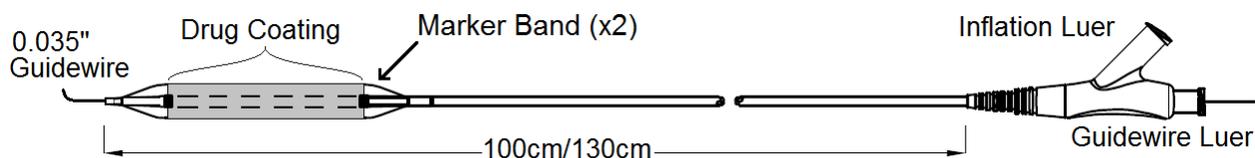


FIGURE 1: LUTONIX DRUG COATED BALLOON

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 Lutonix Drug Coated Balloon is indicated for percutaneous transluminal angioplasty of obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries $\leq 15\text{cm}$ in length and ≥ 4.0 to $\leq 6.0\text{mm}$ 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.

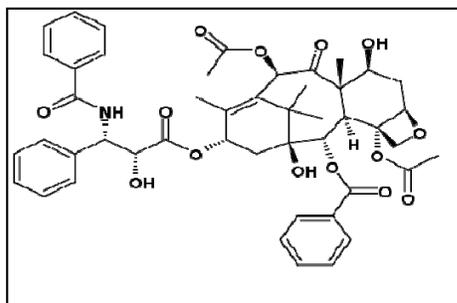


FIGURE 2 : CHEMICAL STRUCTURE OF PACLITAXEL

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 C.

3.5 SUPPLY & SUPPORT OF INVESTIGATIONAL DEVICE

An investigational device supply of the Lutonix 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 2. Always confirm current site inventory supply prior to enrolling subjects into the study.

TABLE 2: DEVICE MATRIX, LUTONIX 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 that have not been previously trained on the use of the Lutonix Drug Coated Balloon. Each study site will receive a supply of the Lutonix 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 Lutonix 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 Lutonix 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 Lutonix Drug Coated Balloon that are unknown at this time. Please refer to the Investigator's Brochure for more details on the development of the Lutonix 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 Lutonix 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 Lutonix 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 Lutonix Drug Coated Balloon to help mitigate any risks to the subjects due to product failure. Additionally, animal studies using the Lutonix 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 Lutonix 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 Lutonix Drug Coated Balloon are not known at the present time. Alternatives to the use of the Lutonix 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 Lutonix 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 Clinical Events Committee (CEC) 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
- 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 $\leq 70\%$ residual stenosis or the lesion is not appropriate for stenting due to proximity to the knee joint) will be treated with the Lutonix Drug Coated Balloon.

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. Treated subjects

will have ultrasound and clinical follow-up through 2 years and telephone follow-up through 5 years.

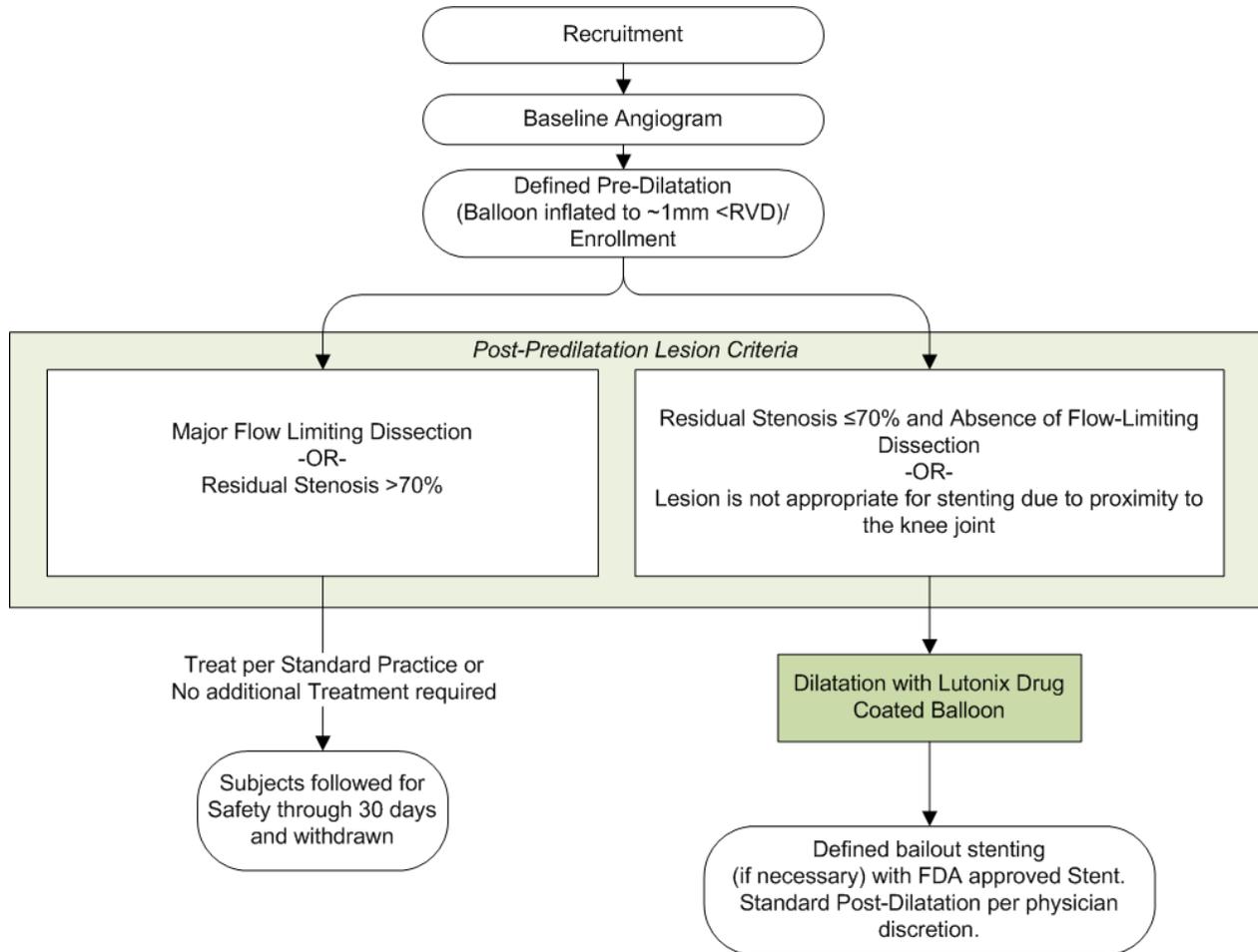


Figure 3 contains an overview of the study.

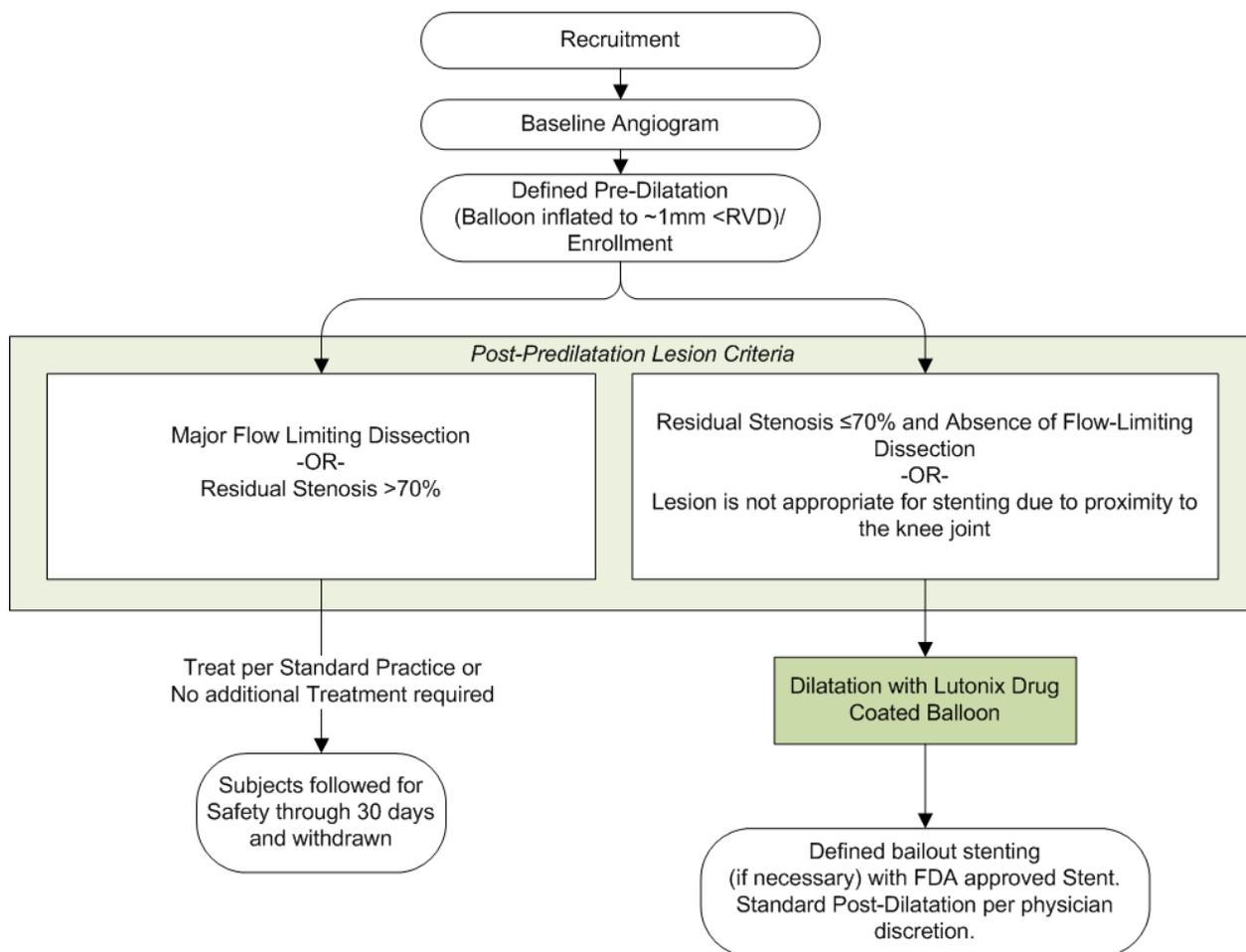


Figure 3: Study Flowchart

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)
 - BMP
 - Glucose
 - Calcium
 - Electrolytes (chloride, sodium, potassium)
 - Kidney (BUN, creatinine)
 - Pregnancy Test (blood or urine; if female of child bearing potential)
- Resting Ankle-Brachial Index (ABI) (within 90 days)

5.2 PATIENT SELECTION FORENROLLMENT

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 CASE PROCTORING REQUIREMENTS

Each investigator enrolling in the study must undergo formal Lutonix Drug Coated Balloon procedure proctoring with a sponsor representative (or designee) during their initial study Lutonix Drug Coated Balloon 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. $\geq 70\%$ 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;

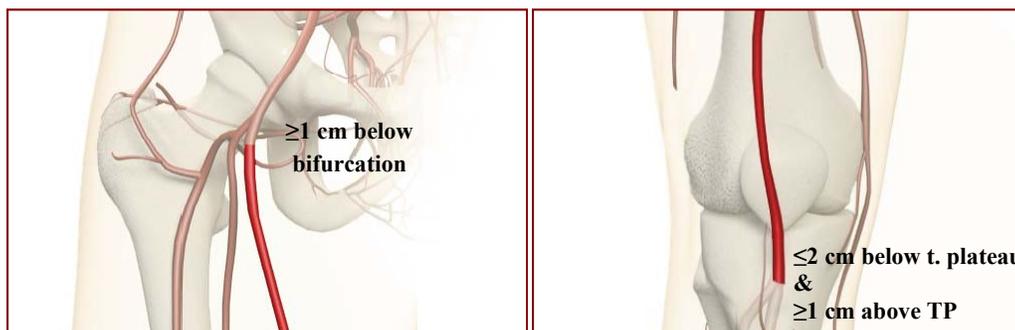


FIGURE 4: ALLOWED LESION LOCATION

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 ($\geq 50\%$ 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 $\leq 30\%$ without death or major vascular complication.

13. At least one patent native outflow artery to the ankle, free from significant ($\geq 50\%$) 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.

Subjects that do not meet post-predilatation criteria are enrolled but 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 treated with the Lutonix Drug Coated Balloon in this study.

6.2 LUTONIX DRUG COATED BALLOON INSTRUCTIONS FOR USE (IFU)

Always follow the current IFU packaged with the device for procedural information, preparation and use of the Lutonix 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 Lutonix 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 ($\geq 50\%$ 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 $\leq 30\%$ without death or major vascular complication.

6.5 PRE-DILATATION

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

Lesion(s) pre-dilatation(s) is required for all 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 Lutonix 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 3 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 treated with the Lutonix Drug Coated Balloon but is instead treated per institutional standard practice. Subjects that are excluded from treatment with the Lutonix Drug Coated Balloon after pre-dilatation will be followed for 30 days for safety and then withdrawn.

TABLE 3: POST PRE-DILATATION LESION(S) CRITERIA

Angiographic Condition	Treatment
Major Flow Limiting Dissection -OR- Residual Stenosis $>70\%$	Excluded, not treated with Moxy Drug Coated Balloon, and followed for safety through 30 days
Residual Stenosis $\leq 70\%$ and Absence of Flow-Limiting Dissection -OR- Lesion is not appropriate for stenting due to proximity to the knee joint	Treatment with the Lutonix Drug Coated Balloon

6.6 TREATMENT

6.6.1 TREATMENT WITH LUTONIX DRUG COATED BALLOON

Please refer to the current Lutonix 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 Lutonix 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 in previous studies. 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. Due to 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 4) 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 4: PROVISIONAL (BAILOUT) CRITERIA

Bailout Prevention
Treatment requirement prior to bailout stenting: <ul style="list-style-type: none"> • Prolonged (>2 minutes) balloon inflation(s) • Vasodilators and/or thrombolytic agents per investigator discretion
Bailout Criteria
<ul style="list-style-type: none"> • Residual stenosis of >50% (based on careful in-lab review of angiograms including QVA if available) <i>or</i> 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/REVASCLARIZATION

A DUS is required prior to any subsequent angiography of the index limb, and the images must be submitted to the DUS Core Lab. ABI and Rutherford Classification are to be assessed prior to any re-intervention of the target limb. 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 MEDICATIONS

Table 5 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 < 60 kg, 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 5: 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**
OR Ticagrelor	90 mg (twice daily) or loading dose of 180 mg	NA	90 mg twice daily for at least 1 month
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

***Ticlopidine use per label is an acceptable alternative only if Clopidogrel, Prasugrel, nor Ticagrelor are appropriate

7.1.1 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) prasugrel (10 mg per day) or ticagrelor (180 mg per day) be prescribed. The initial loading dose of clopidogrel, prasugrel, or ticagrelor 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.

7.1.2 INTRA-PROCEDURE

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

7.1.3 POST-PROCEDURE

Approved vascular closure devices are allowed. Clopidogrel (75 mg/daily) prasugrel (5-10 mg/daily), or ticagrelor (90 mg/twice 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.

7.2 STANDARD TESTS, PROCEDURES, AND FOLLOW-UP

Table 6 displays the required schedule for 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, 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 6: Follow-Up Schedule and Testing Requirements for treated 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
	30 days	30 days			±2 weeks	±1 month	±1 month	±2 month	±2 month	±2 month	±2 month
Visit Window	30 days	30 days									
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; BMP, pregnancy ⁶)		√ ⁵		√	√ ³	√	√				
Angiogram			√								
Adverse Event Monitoring			√	√	√	√	√	√	√	√	√
Duplex Ultrasound (after clinical assessment)				√ ⁷	√	√	√				

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

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

³Required if clinical visit occurs

⁴Resting 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

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

⁶Pre-procedure and females of childbearing potential only

⁷Baseline duplex is only required once (anytime post-procedure through the 1-month visit)

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).

7.2.1 TESTING

7.2.1.1 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)
- BMP
 - Glucose
 - Calcium
 - Electrolytes (chloride, sodium, potassium)
 - Kidney (BUN, creatinine)
- Pregnancy Test (blood or urine; if female of child bearing potential)

7.2.1.2 ANKLE-BRACHIAL INDEX (ABI)

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

7.2.1.3 RUTHERFORD SCALE

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

7.2.1.4 DUPLEX ULTRASOUND AND ANGIOGRAPHY GUIDELINES

The initial baseline DUS must be performed after the index procedure (up to 1 month \pm 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.

7.2.2 FOLLOW-UP PROCEDURES

The Investigator or Research Coordinator will contact treated 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 treated subjects will return for follow-up at 1 (if required for duplex ultrasound), 6, 12 and 24 months post procedure. See Table 6 for required testing at each follow-up visit time point.

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 eCRFs. 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. 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 Bard or 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 original medical records of all enrolled subjects. 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
- Study Treatments
- 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 Lutonix 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 Lutonix 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 Lutonix 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 Clinical Events 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 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 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 APPROVAL

Investigators must submit the study protocol to their IRB 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, 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 and written approval obtained prior to implementation.

13.2 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; 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.

13.3 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.

13.4 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 appropriate IRB approval and any other applicable document (revised investigator agreement, etc.)

- 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

13.4.1 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.

13.4.2 REPORTS

Table 7 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 7: 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: <ul style="list-style-type: none"> • 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

13.5 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 Vitae
- 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 purpose of the LEVANT 2 Safety Registry is to collect additional safety and efficacy information of the Lutonix Drug Coated Balloon for treatment of stenosis or occlusion of the femoral and popliteal arteries in a large population of subjects. The LEVANT 2 Safety Registry is an open-label registry study of the Lutonix Drug Coated Balloon.

Approximately 975 combined subjects will be enrolled into both the LEVANT 2 Safety Registry and the LEVANT 2 Continued Access Registry in order to include a total of 650 subjects treated with the Lutonix Drug Coated Balloon after successful predilatation. 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, up to 1/3 of pre-dilated subjects are not expected to meet criteria for enrollment and will be treated per standard of care. Enrollment will continue only until a sample size of 650 DCB-treated subjects is achieved.

The Primary Endpoint is the rate of unanticipated device- or drug- related adverse events over time through 60 months. Secondary endpoints include the rate at 1, 6, 24, 36, 48, and 60 months and the primary and majority of the secondary endpoints of the LEVANT 2 Randomized Study.

15.2 SAMPLE SIZE JUSTIFICATION

Taken together with the LEVANT 2 Randomized Study, the 650 additional combined DCB subjects enrolled in the LEVANT 2 Safety Registry and the LEVANT 2 Continued Access Registry will provide a safety dataset on 1022 subjects treated with the Lutonix Drug Coated Balloon, since the LEVANT 2 Randomized Protocol includes approximately 55 roll-ins and 317 test subjects randomized to drug coated balloon.

Allowing for up to 15% loss-to-follow-up, an evaluable sample size of 869 test subjects is expected. If the observed rare adverse event rate is 1%, then the upper limit of the 95% Confidence Interval is 1.8% (PASS2008: Exact Clopper-Pearson). Assuming an expected 1% incidence rate, Power is > 95% to observe at least 4 unexpected SAEs (PASS2008: Post-Marketing Surveillance). Similarly, if the observed rate is 2%, then the upper limit of the 95% Confidence Interval is 3.0%. Assuming an expected 2% incidence rate, Power is > 95% to observe at least 11 unexpected SAEs. This study provides the ability to detect and describe the rate of rare unanticipated adverse events with some precision.

15.3 ANALYSIS

Data from all the subjects treated with DCB in the LEVANT 2 Randomized protocol (roll-in and randomized to DCB), LEVANT 2 Safety Registry and the LEVANT 2 Continued Access registry will be combined and analyzed using descriptive statistics. 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. 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. Poolability by geography and by test group (LEVANT 2 Randomized Study roll-ins subjects, randomized subjects in the LEVANT 2 Randomized trial, LEVANT 2 Safety Registry subjects and LEVANT 2 Continued Access Registry subjects) will also be evaluated.

In addition to the primary endpoint, all secondary endpoints will also be analyzed using descriptive statistics.

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 <u>or</u> 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 <u>and</u> 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 <u>or</u> 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 <u>and</u> 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 ($\geq 50\%$) 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 $\leq 30\%$ 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 $\geq 50\%$ 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° 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 $\leq 30\%$ 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.

(APPENDICES B-F PURPOSELY REDACTED)