A Prospective, Multicenter, Single Arm, Post-Approval Study of the Lutonix® Drug Coated Balloon for Treatment of Femoropopliteal Arteries in United States Females (CONFIRM Trial)

Investigational Plan

CL0025-01
Version 3.0
December 1, 2017

Sponsor:

[redacted]

Study Device: Lutonix® 035 Drug Coated Balloon PTA Catheter (Lutonix® Catheter)

NCT Number: 02813577 (Number added post approval as per CT.gov requirement)

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

PROTOCOL SIGNATURE PAGE

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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. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to ICH Good Clinical Practice (GCP), Declaration of Helsinki, 21 CFR 812 and parts 50, 54, 56 and any local regulations.

_____

Clinical Site Name

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

SUB-INVESTIGATOR PROTOCOL SIGNATURE PAGE

A Prospective, Multicenter, Single Arm, Post-Approval Study of the Lutonix Drug Coated Balloon for Treatment of Femoropopliteal Arteries in United States Females (CONFIRM Trial)

CL0025-01
Version 3.0

I have read this protocol and agree to adhere to the requirements. I agree to conduct the study in accordance with the signed Clinical Study Agreement (CSA), ICH Good Clinical Practice (GCP), applicable privacy laws such as HIPAA, Declaration of Helsinki, 21CFR parts 50, 54, 56 and 812 and any local regulations.

_____

Clinical Site Name

_____	_____	_____
Site Sub-Investigator (Print Name)	Site Sub-Investigator (Signature)	Date

Protocol Synopsis

Title	A Prospective, Multicenter, Single Arm, Post-Approval Study of the Lutonix Drug Coated Balloon for Treatment of Femoropopliteal Arteries in United States Females (CONFIRM Trial)
Test Device	Lutonix® 035 Drug Coated Balloon PTA Catheter (Lutonix® Catheter, PMA P130024)
Study Design	Prospective, Multicenter, Single Arm, Safety and Effectiveness
Overview	The study will enroll US female patients presenting with claudication or ischemic rest pain and an angiographically significant lesion in the superficial femoral or popliteal artery. Subjects are treated per IFU with the Lutonix Catheter. Subjects will have a Duplex Ultrasound and clinical follow-up through two (2) years.
Purpose	To assess the safety and effectiveness of the Lutonix Catheter for treatment of stenosis or occlusion of the femoral and popliteal arteries in the US female population.
Objective	To evaluate the safety and effectiveness of the Lutonix Catheter for treatment of stenosis of the femoropopliteal arteries in the US female population.
Enrollment	Approximately 165 patients will be enrolled at a minimum of 10 US centers and a maximum of 25.
Follow-Up Schedule	*Clinical and DUS*: 1, 6, 12, and 24 Months
Primary Endpoints	Safety: Composite of freedom from all-cause peri-operative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death. Effectiveness: Primary Patency of the target lesion at 12 months: Primary Patency is defined as Freedom from target lesion restenosis (TLR) and from Binary Restenosis. Binary Restenosis is adjudicated by the independent Core Laboratory based on Peak Systolic Velocity Ratio (PSVR) ≥ 2.5 and / or abnormal waveforms, or based on angiographic ≥ 50% diameter stenosis.
Secondary Endpoints	*The following endpoints will be assessed at 1 month:* • Composite of freedom from all-cause perioperative (≤ 30 day) death and freedom from the following: index limb amputation, index limb re-intervention, and index-limb-related death. • Major Vascular Complications (<30 days)

	The following endpoints will be assessed at 1, 6, 12 and 24 months: • All-cause death • Clinically Driven Target Lesion Revascularization (TLR) • Target Vessel Revascularization (TVR) • Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature • Rate of unanticipated and anticipated device related serious adverse events • Amputation (above the ankle)-Free Survival (AFS) • Change of Rutherford classification from baseline • Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization) • Change of resting Ankle Brachial Index (ABI) from baseline
Inclusion Criteria	**Clinical Criteria** 1. Non-pregnant female ≥18 years of age; 2. Rutherford Clinical Category 2-4; 3. Patient is willing to provide informed consent, is geographically stable, comply with the required follow up visits and testing schedule; **Angiographic Criteria** 4. De novo or restenotic lesion(s) in native superficial femoral or popliteal arteries; 5. Lesion ≥70% stenosis by visual estimate; 6. Target reference vessel diameter of 4-7 mm; 7. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography. (Treatment of target lesion acceptable after successful treatment of inflow artery lesions. Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication.) 8. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography after successful vessel preparation; 9. Successful antegrade wire crossing and vessel preparation (may include pre-dilatation) of the target lesion. Successful vessel preparation is defined by residual stenosis ≤30% without any major vascular complications. 10. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment except for remote common femoral patch angioplasty separated by at least 2 cm from the lesion(s).
Exclusion Criteria	1. Life expectancy of <2 years;

	2. Subject is currently participating in an investigational drug or device study, or previously enrolled in this study. Enrollment in another investigational drug or device study during the follow up period is not allowed. 3. History of stroke within 3 months; 4. History of myocardial infarction (MI), thrombolysis or angina within 2 weeks of index procedure; 5. Renal failure or chronic kidney disease with serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis; 6. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel.
National Principal Investigator	Chris Metzger, MD [redacted]
Sponsor Contact:	[redacted]
Angiographic Core Lab	[redacted]
DUS Core Lab	[redacted]

TABLE OF CONTENTS

Tables

1 INTRODUCTION

The Lutonix® 035 Drug Coated Balloon PTA Catheter (LUTONIX® Catheter) has been approved by the Food and Drug Administration (P130024) for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions up to 300 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm. The purpose of this post-approval study is to assess the safety and effectiveness of the LUTONIX® Catheter in the US female population.

1.1 CLINICAL BACKGROUND

Peripheral arterial disease (PAD) is highly prevalent in the general population in the US with an estimated 20% of those over the age of 70 having clinically significant vessel involvement [1]. It may present with intermittent claudication, resulting in reduced quality of life due to pain in the legs on exercise, or with more severe symptoms of critical limb ischemia, such as rest pain or ischemic wounds. The restriction in blood flow that causes these symptoms may be related to disease at a variety of different sites in the legs, including the aortoiliac segments, the femoropopliteal segments, or the smaller infrapopliteal arteries. The femoropopliteal artery, including the superficial femoral artery (SFA) and popliteal artery, is the most commonly involved vessel in the peripheral circulation and the most common site for lower limb interventions [2].

Indications for surgical or endovascular intervention in PAD include claudication, rest pain, and ischemic skin ulceration or gangrene which may progress to ischemic limb loss. Since 1997, a significant change in practice has occurred, with endovascular interventions replacing surgical bypass as the dominant revascularization therapy. The most common intervention is percutaneous transluminal angioplasty (PTA), in which the stenotic artery is dilated with a balloon tipped catheter inserted under fluoroscopic guidance.

A drug coated balloon (DCB) is a standard angioplasty balloon coated with an antiproliferative agent on the balloon surface. Many DCBs have been approved for use in Europe since 2008, and since 2014 LUTONIX® Catheter is also available in the US. Compared with drug eluting stents (DES) and other existing therapeutic approaches, DCB offers local delivery of an antiproliferative agent to the vasculature without implantation of a stent. DCBs have the potential to benefit patients with femoropopliteal artery disease by providing more durable patency than PTA without requiring a permanent implant. This allows a broader population to be treated and preserves flexibility of future therapeutic treatment options for patients with peripheral vascular disease and multiple co-morbidities.

1.2 LUTONIX PRECLINICAL TESTING

A thorough panel of biocompatibility, bench, and animal testing was performed based on international standards and Food and Drug Administration (FDA) guidance. Results from these combined studies demonstrated functionality and provided reasonable assurance of device safety. Animal studies in porcine model included six-month histopathology studies examining local,

regional, and systemic effects of Lutonix DCB at 1x and 4x doses, and to evaluate pharmacokinetics. Results demonstrated complete endothelialization, vascular healing, no safety problems, and no systemic effects related to the paclitaxel coating [3]. In addition, paclitaxel levels in porcine arterial tissue at 30 days were sufficient to reduce smooth muscle cell proliferation [4]. Additionally, coating adhesion integrity was assessed during development to assure that the drug is applied uniformly on the balloon during the manufacturing process and does not flake off the balloon during handling in clinical environment. Finally, each batch of finished Lutonix DCB devices undergoes release testing for appearance, identity, potency, content uniformity, impurities, in vitro release, particulate matter and endotoxins to help assure consistent safety and effectiveness for all devices.

The Lutonix DCB received CE Mark approval in 2010 and PMA approval from FDA in 2014. It is currently commercialized in over 20 countries.

1.3 CLINICAL STUDY BACKGROUND

1.3.1 THE LEVANT 2 PIVOTAL IDE TRIAL

The pivotal Levant 2 IDE study (NCT01412541) was designed in collaboration with physicians and FDA to demonstrate safety and efficacy of the Lutonix Catheter for treatment of femoropopliteal lesions in a larger population and to obtain US FDA approval. Levant 2 is a prospective, multicenter, single blind, 2:1 randomized, controlled trial, comparing outcomes after treatment of symptomatic femoropopliteal artery lesions with Lutonix Catheter vs. uncoated PTA.

The trial pre-specified two primary endpoints that must both be met for trial success. The primary effectiveness endpoint is primary patency of the target lesion at 1 year. Primary patency is defined as the absence of target lesion restenosis and freedom from target lesion revascularization (TLR). The primary safety endpoint is freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb reintervention, and index-limb-related death. The tested hypothesis was that DCB would demonstrate superior effectiveness and non-inferior safety compared to PTA.

The trial enrolled patients with symptomatic claudication or ischemic rest pain (Rutherford category 2-4) and an angiographically significant atherosclerotic lesion (>70% diameter stenosis, ≤15 cm length) in the superficial femoral and/or popliteal arteries of diameter 4 to 6 mm with a patent outflow artery to the foot.

Enrollment began in July 2011, and randomization of 476 patients (n = 316 DCB vs. N = 160 PTA) at 55 centers was completed in July 2012. One year follow-up and primary endpoint analysis has been completed, and clinical follow-up was completed in October 2017.

Baseline demographics, comorbidities, and lesion characteristics were well matched between groups; 43% of patients were diabetic, 35% were current smokers, and 8% had critical limb ischemia (CLI). The mean lesion length was 62.8 mm and the treated length was 108 mm.

Levant 2 met both pre-specified primary endpoints. Primary patency for Lutonix Catheter (65.2%) was superior to control PTA (52.6%, p= 0.015) at 12 months, demonstrating superior efficacy. The primary safety endpoint success rate for Lutonix DCB (83.9%) was non-inferior to control PTA (79.0%, p = 0.005). Freedom from TLR was 87.7% for DCB compared to 83.2% for control PTA.

Several secondary endpoints were also analysed but not hypothesis tested. Procedural success (< 30% residual stenosis without SAE) was similar for Lutonix Catheter and control PTA (88.9% vs. 86.8%), demonstrating effectiveness at acute restoration of patency. The Rutherford scores, walking impairment (WIQ) scores, ABI, six minute walk test, and quality of life questionnaires each showed improvements from before treatment through 12 months in both treatment groups. At 12 months, 88.2% of Lutonix DCB patients and 82.4% of control PTA patients had improved Rutherford Class compared to baseline. Mean improvement in the WIQ total score was 23.9 ± 27.6% for Lutonix DCB compared to 19.2 ± 26.5% for control PTA, and improvement in WIQ walking distance was 31.5 ± 37.0% vs. 22.2 ± 35.4%, respectively. Improvements in ABI, six minute walk test, EQ-5D, and SF-36v2 through 12 months were similar for both groups.

Secondary safety endpoints were generally similar for Lutonix Catheter and control PTA. These included respectively, all-cause death (2.4% vs. 2.8%), amputation (0.3% vs. 0.0%), amputation-free survival (97.6% vs. 97.2%), thrombosis (0.4% vs. 0.7%), target vessel revascularization (TVR, 13.3% vs. 18.2%), cardiovascular hospitalization (9.1% vs. 7.1%), and major vascular complications (6.3% vs. 4.9%; defined as hematoma >5 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, transfusion). Adverse events were similar for both treatment groups and consistent with historic data for the enrolled population with symptomatic PAD.

Levant 2 successfully demonstrated superior efficacy and non-inferior safety of Lutonix Catheter compared to control PTA.

1.3.2 THE LEVANT 2 REGISTRY (CONTINUED ACCESS & SAFETY REGISTRIES)

Levant 2 Continued Access (NCT01628159) and Safety (NCT01790243) registries were initiated for collection of additional safety data after completion of Levant 2 enrollment. These studies followed the same Levant 2 clinical protocol for the test arm in every aspect of inclusion/exclusion criteria, follow-up schedule, and treatment procedure, but were not randomized. They were conducted using the same data collection practices, independent core labs, and CEC adjudication process for SAE's. Sites that had enrolled in the randomized Levant 2 trial enrolled in Continued Access, and new sites enrolled in the Safety Registry. Results were pre-specified to be reported side-by-side and pooled with the roll-in and randomized DCB-treated cohorts of the Levant 2 randomized trial in order to provide a DCB-treated cohort of sufficient size to detect and describe the rate of unexpected rare (1-2%) drug- or device- related adverse events, the primary endpoint, with precision. Secondary endpoints include the primary endpoints and most of the secondary endpoints of the Levant 2 randomized trial.

Enrolment was completed on September 27, 2013. A total of 657 subjects were enrolled at 63 sites across the United States (US) and Europe (EU). Baseline characteristics and treated lesions were comparable to the randomized cohort. As of the August 4, 2014 database export, the 30-day follow-up window has been completed (98.8% compliance), and 95.1% and 75.6% of registry subjects have completed 6-month and 12 month follow-up, respectively; mean follow-up is 325 days. Clinical follow-up, monitoring, and CEC adjudications are ongoing.

Together with the randomized study, n = 1029 patients have been treated with Lutonix DCB and followed for a mean duration of 438 days. There are no unanticipated device- or drug-related adverse events, the primary endpoint, as of this reporting date. For an observed incidence rate of 0%, the upper bound of the one-sided 95% CI = 0.3% at 30 days, 0.3% at 6 months, and 0.4% at 12 months.

Overall device and procedural success rates for all DCB were 99.9% and 87.8%, respectively, and similar for roll-in, randomized, and registry cohorts. For all DCB-treated patients, the proportion of subjects meeting the composite safety endpoint (freedom from all-cause perioperative death and index limb-related death, amputation, and reintervention) was 99.4% (1003/1009) at 1 month, 96.0% (906/944) at 6 months and 90.5% (708/782) at 12 months. The 12 month rate of all cause death (1.4%), amputation (0.1%), AFS (98.6%), TVR (8.3%), thrombosis (0.1%), cardiovascular hospitalizations (10.2%), and major vascular complications (3.6%) are comparable across cohorts and consistent with safety. No additional safety risks have been identified to date.

Overall freedom from TLR for the all DCB-treated patients was 97.0% (914/942) at 6 months and 92.5% (719/777) at 12 months. Rutherford Class was significantly improved at all time points compared to baseline; through 12 months, 87% of patients had an improvement in Rutherford Class, 72% by 2 or more grades. Sustained improvement in Rutherford Class without TVR was observed in 79% of patients. These clinical endpoints compare favorably to historic results and provide further support for the clinical benefit of Lutonix DCB.

Taken as a whole, the Levant 2 randomized and registry studies demonstrate that treatment of native femoropopliteal lesions with Lutonix DCB provides more durable patency than standard PTA through 12 months with comparable safety and provides a reasonable assurance of safety and effectiveness.

1.4 LUTONIX POST APPROVAL STUDY RATIONALE

The Levant 2 trial provided the pivotal clinical evidence supporting the safety and effectiveness of Lutonix Catheter. Both primary endpoints (superior effectiveness and non-inferior safety) were met in the intent-to-treat (ITT) population by direct comparison to conventional balloon angioplasty. Levant 2 demonstrated that treatment of native femoropopliteal lesions with Lutonix Catheter provides more durable patency and safety comparable to standard PTA. FDA therefore approved Lutonix Catheter (P130024) for treatment of the entire population enrolled in the pivotal trial.

As in most clinical trials, Levant 2 was not powered to statistically examine differences in results between subgroups. Although the overall treatment effect was generally consistent across

subgroups, unexpected results were observed in a few subsets. Given the multiplicity of subgroups and their limited sample sizes, chance is the most likely explanation for differences in subgroup results that are commonly observed in clinical trials [5].

Although the pivotal study was not powered for subgroup analyses, the primary effectiveness data suggested a reduced treatment effect in women, as compared with observed outcomes in men. Primary patency for females was 56.4% for DCB compared to 61.4% for PTA (difference -4.9%), while for males patency was 70.6% for DCB compared to 48.4% for PTA (difference 22.2%). In contrast, primary safety data suggested an enhanced treatment effect in women, as compared with observed outcomes in men. Primary safety for females was 80.4% for DCB compared to 67.4% for PTA (difference 13.0%), while for males primary safety was 86.2% vs. 84.5% (difference 1.7%).

Possible drivers of this unexpected inverse endpoint correlation by gender, were investigated in depth, including potential differences in baseline covariates and effect modifiers. A series of exploratory statistical models consistently demonstrated smoking to be a better statistical predictor of effectiveness than gender. In addition, although randomization was successful at balancing baseline characteristics for the entire Levant 2 ITT population, within the US female subset there were significant differences between lesions allocated to DCB compared to PTA that would be expected to favour primary patency outcomes for lesions treated in the control PTA group. These observations support – but do not prove – the conclusion that the observed outcome differences by gender are due to chance.

The observed results by gender therefore warrant further investigation. The aim of this post approval study is to provide additional clinical evidence of effectiveness and safety of the Lutonix Catheter in the US female population.

2 STUDY PURPOSE AND OBJECTIVE

2.1.1 PURPOSE

The purpose of the study is to assess the safety and effectiveness of the Lutonix Catheter for treatment of stenosis or occlusion of the femoral and popliteal arteries in the US female population.

2.2 OBJECTIVE

The objective of the study is to evaluate the safety and effectiveness of the Lutonix Catheter for treatment of stenosis of the femoropopliteal arteries in the US female population.

3 ENDPOINTS

3.1 PRIMARY ENDPOINTS

3.1.1 SAFETY

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

3.1.2 EFFECTIVENESS

The primary effectiveness endpoint is primary patency of the target lesion at 12 months. Primary Patency is defined as Freedom from TLR and from Binary Restenosis. Binary Restenosis is adjudicated by the independent Core Laboratory based on PSVR ≥ 2.5 and / or abnormal waveforms or based on angiographic ≥ 50% diameter stenosis.

3.2 SECONDARY ENDPOINTS

The following endpoints will be assessed at 1 month:

- Composite of freedom from all-cause perioperative (≤ 30 day) death and freedom from the following: index limb amputation, index limb re-intervention, and index-limb-related death.
- Major Vascular Complications (<30 days)

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

- All-cause death
- Clinically Driven Target Lesion Revascularization (TLR)
- Target Vessel Revascularization (TVR)
- Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature
- Rate of unanticipated and anticipated device related serious adverse events
- Amputation (above the ankle)-Free Survival (AFS)
- Change of Rutherford classification from baseline
- Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization)
- Change of resting Ankle Brachial Index (ABI) from baseline

4 DEVICE DESCRIPTION

4.1 CATHETER DESCRIPTION

The LUTONIX® 035 Drug Coated Balloon PTA Catheter (LUTONIX® Catheter) consists of an over the wire catheter with a drug coated balloon fixed at the distal tip. The balloon is coated with a specialized formulation that includes the drug paclitaxel. The LUTONIX® Catheter is 0.035" guidewire compatible, with a low profile, semi-compliant balloon formed to a low profile tapered

tip to facilitate advancement of the catheter to and through the stenotic region of the vessel. Two radiopaque marker bands delineate the working length of the balloon and are located under the proximal and distal ends of the balloon to facilitate fluoroscopic visualization of the balloon during delivery and placement. The proximal portion of the catheter includes an inflation female Luer Lock hub and a guidewire female Luer Lock hub. Each product is packaged with a balloon protector that has been positioned over the balloon and a disposable wire lumen stylet, both of which are to be removed prior to use. Any commercially available balloon lengths may be used in this trial.

4.2 INDICATIONS FOR USE

Always refer to the electronic instructions for use (IFU) available online for the current indications for use. As of the date of this protocol revision, the indication for use is as follows: The Lutonix® 035 Drug Coated Balloon PTA Catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions up to 300 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.

4.3 CONTRAINDICATIONS

The LUTONIX® Catheter is contraindicated for use in:

- Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

4.4 DEVICE INSTRUCTIONS

Please refer to the most current IFU available online for complete details.

5 RISK-BENEFIT ANALYSIS

5.1 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.

5.1.1 RISKS FOR PERIPHERAL CATHETERIZATION PROCEDURE

Due to the high similarity of the LUTONIX® Catheter to other marketed balloon catheters, procedural use is not expected to significantly change or increase risks during the index procedure. Complications and AEs associated with use of the LUTONIX® Catheter are listed in the IFU.

Potential adverse events which may be associated with a peripheral balloon dilatation procedure include:

- Additional intervention
- Allergic reaction to drugs, excipients or contrast medium
- Amputation/loss of limb
- Aneurysm or pseudoaneurysm
- Arrhythmias
- Embolization
- Hematoma
- Hemorrhage, including bleeding at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness
- Pneumothorax or hemothorax
- Sepsis/infection
- Shock
- Stroke
- Thrombosis
- Vessel dissection, perforation, rupture, or spasm

5.1.2 ASSOCIATED RISKS FROM THE DRUG COATING

The balloon coating on LUTONIX® Catheter includes the API paclitaxel and excipients sorbitol and polysorbate. The Levant 2 randomized and registry trials (section 1.3.1 and 1.3.2 above) demonstrate safety comparable to conventional uncoated angioplasty catheters, and no unexpected additional risks attributable to the drug coating have been observed to date. Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

Potential adverse events which 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

- Myelosuppression
- Peripheral neuropathy

5.2 RISK MANAGEMENT PROCEDURES

The investigational plan is specifically designed to manage and minimize risks through careful subject selection, thorough training of investigators, adherence to the pre-determined time points to assess subject clinical status and regular clinical monitoring visits by Sponsor appointed monitoring personnel.

Follow-up exams including duplex ultrasound will be performed to assess the target vessel patency and assess overall subject status.

5.3 POTENTIAL BENEFITS

There are no guaranteed benefits from participation in this study. LUTONIX® Catheter is a currently available treatment option. Although the superior effectiveness of LUTONIX® Catheter over PTA was demonstrated for the general population, participation in this study will determine whether or not that is true for the subpopulation of US women. Information gained from the conduct of this study will therefore be of significant benefit to others with the same medical condition.

5.4 EARLY TERMINATION

The Sponsor 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:

- Evidence of an Investigator's failure to maintain adequate clinical standards
- Evidence of an Investigator or staff's failure to comply with the signed Clinical Trial
- Agreement with Sponsor, protocol, regulations, or any conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA (21 CFR 812.46(a))
- Inaccuracy or late submission of data forms and core lab images
- Evidence of safety concerns
- Change of staff at site that adversely impacts trial conduct
- Failure to secure subject informed consent or HIPAA forms
- Falsification of data, or any other breech of ethics or scientific principles

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

In the event of study suspension or termination, the Sponsor will send a report outlining the circumstances to the IRB and all Investigators and FDA as required by regulation. A suspended or

terminated study may not be reinitiated without approval of the reviewing IRB and FDA, as required by regulation.

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

6 CLINICAL STUDY DESIGN

The study is a prospective, multicenter, single-arm study. The study will enroll approximately 165 patients presenting with claudication or ischemic rest pain and an angiographically significant lesion in the superficial femoral or popliteal artery and a patent outflow artery to the foot. Subjects will be treated with the LUTONIX® Catheter and followed with ultrasound and clinical visits through 2 years. Patients will be enrolled at a minimum of 10 US sites and a maximum of 25.

6.1 SCREENING AND INFORMED CONSENT

All female 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 Investigator or authorized delegate will discuss the study and ask the patient to participate. Prior to enrollment, the patient must be fully informed of the nature of the study, details of study procedures, anticipated benefits, and potential risks of participation as required by applicable law. Provide the patient with a copy of the Informed Consent Form (ICF) and HIPAA authorization approved for use by the IRB and review its content, allowing adequate time for questions. An ICF template is provided in **Appendix B**. All information pertinent to the clinical study shall be provided in writing and in native, non-technical language that is understandable to the patient. Patients will be assured that they may withdraw from the study at any time and for any reason and this decision will not influence her relationship with the Investigator and/or study staff.

The patient must be allowed sufficient time to decide whether to participate. Once the patient has read and understands the ICF, she will indicate her willingness to participate in the study by signing and dating the ICF. The ICF must also be signed and dated by the person obtaining informed consent. The investigator or authorized delegate must document in the subject's medical records that the patient was consented and the date of which informed consent was obtained. The original signed ICF will be retained in the subject's clinical study record. A copy of the signed and dated ICF will be provided to the subject and a copy placed in the subject's medical record.

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 and for baseline data collection:

- Physical examination including:
    - Heart rate, brachial blood pressure, and weight
    - Rutherford Classification

- Resting Ankle-Brachial Index (ABI) (within 90 days)
- Relevant medical history
- Pregnancy test (blood or urine; if female of child bearing potential)
- Serum creatinine level (within 30 days)

6.2 PATIENT SELECTION FOR ENROLLMENT

Patients 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.

6.3 INCLUSION AND EXCLUSION CRITERIA

6.3.1 INCLUSION CRITERIA

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

Clinical Criteria

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

Angiographic Criteria

4. De novo or restenotic lesion(s) in native superficial femoral or popliteal arteries;
5. Lesion ≥70% stenosis by visual estimate;
6. Target reference vessel diameter of 4-7 mm;
7. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography. (Treatment of target lesion acceptable after successful treatment of inflow artery lesions. Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication.)
8. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography after successful vessel preparation;
9. Successful antegrade wire crossing and vessel preparation (may include pre-dilation) of the target lesion. Successful vessel preparation defined by residual stenosis ≤30% without any major vascular complications.

10. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment except for remote common femoral patch angioplasty separated by at least 2 cm from the lesion(s).

6.3.2 EXCLUSION CRITERIA

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

1. Life expectancy of <2 years;
2. Subject is currently participating in an investigational drug or device study or previously enrolled in this study. Enrollment in another investigational drug or device study during the follow up period is not allowed
3. History of stroke within 3 months;
4. History of MI, thrombolysis or angina within 2 weeks of index procedure;
5. Renal failure or chronic kidney disease with serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis;
6. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;

7 STUDY PARTICIPATION

7.1 ENROLLMENT

After signing the informed consent document, a patient will be considered enrolled in the study after baseline angiographic results and after successful vessel preparation confirm that the target lesion meets all appropriate inclusion/exclusion criteria and the subject is treated with the LUTONIX® Catheter.

Subjects that meet baseline angiographic criteria but do not meet post vessel preparation angiographic criteria will not be treated with the LUTONIX® Catheter or enrolled in the study. Subjects who are not treated with the LUTONIX® Catheter will be treated per standard of care and will not be enrolled in the study.

7.2 BASELINE ANGIOGRAM

Digital Subtraction Angiography (DSA) should be obtained per Angiographic Core Lab Guidelines. Standard off-line Quantitative Vascular Angiography (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 DICOM format that are suited for QVA analysis. For purposes of ensuring protocol compliance, all angiograms must be submitted to the Core Laboratory as soon after the case as possible. Please refer to the Angiographic Core Lab Guidelines for specific procedural imaging and submission instructions.

7.3 IN-FLOW LESION TREATMENT

A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography is required. Treatment of inflow artery lesions may be performed. Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication.

7.4 PRE-DILATATION / VESSEL PREPARATION

Successful vessel preparation of the target lesion must be confirmed prior to treatment with the LUTONIX® Catheter. Successful vessel preparation is defined by residual stenosis ≤30% without any major vascular complications. Always limit the longitudinal length of the pre-dilatation balloon, or other appropriate vessel preparation modality, to avoid creating a region of vessel injury that is outside the boundaries of the area to be treated by the LUTONIX® Catheter.

7.5 TREATMENT WITH LUTONIX CATHETER

Always follow the current IFU for procedural information and use of the LUTONIX® Catheter. The Investigator should determine the appropriate size of the balloon to be used by online QVA (if possible) or by visual estimate. A balloon compliance chart is included on each device product label. 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 Failures/Malfunctions/Defects Case Report Form must be completed.

All Device Deficiencies occurring during the conduct of this study will be recorded in the eCRF system, and reported by the Investigator to the Sponsor in a timely manner.

Deficient devices shall be returned to the Sponsor. The further management of device deficiencies by the Investigator and the Sponsor/manufacturer will adhere to the appropriate national laws and regulations.

8 TREATMENT OF SUBJECT

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

8.1 STANDARD TESTS, PROCEDURES, AND FOLLOW-UP

Table 1 displays the required schedule for treatment and evaluation. This schedule is consistent with most standard clinical care pre- and post-interventional procedures. The times for each test are broad enough to fit into most routine testing procedures.

All subjects treated with the LUTONIX® Catheter will return for follow-up at 1, 6, 12, and 24 months post procedure.

TABLE 1. FOLLOW-UP SCHEDULE AND TESTING REQUIREMENTS

Event	Pre- Procedure	Procedure	1 Month	6 Month	12 Month	24 Month	Unplanned Angio/Revasc
Visit Window	30 days		±7 days	±30 days	±60 days	±60 days	
Inclusion/Exclusion Criteria	√	√					
Informed Consent	√						
Medical History	√						
Physical Exam (HR , BP, and weight)	√		√	√	√	√	√
Resting ABI	√[1]		√	√	√	√	√
Rutherford Classification	√		√	√	√	√	√
Pregnancy Test [2]	√						
Angiogram		√					√
Adverse Event Monitoring		√	√	√	√	√	
Duplex Ultrasound (after clinical assessment)			√	√	√	√	√

[1]*Resting ABI is required within 90 days of index procedure*
[2]*Females of childbearing potential only*

8.1.1 TESTING

8.1.1.1 PREGNANCY TESTING

For women of childbearing potential, a pre-procedure pregnancy test must be done (blood or urine). Pre-procedure samples may be taken up to 30 days prior to the index procedure.

8.1.1.2 PHYSICAL EXAM

Physical exam includes the items noted below and must be performed pre-procedure and at 1, 6, 12, and 24 months. The physical exam should also be completed prior to any repeat angiogram or revascularization, if possible.

- Heart Rate, Brachial Blood Pressure, and weight
- Rutherford Classification

Rutherford classification is required pre-procedure, 1 month, 6 months, 12 months, and 24 months. It should also be collected at any repeat angiogram or revascularization. It can be measured with or without treadmill, but must be performed consistently among subjects over the lifespan of the study.

8.1.1.3 ANKLE-BRACHIAL INDEX (ABI)

A resting ABI must be performed at each visit per local standard practice, and consistently among subjects over the lifespan of the study for the index limb. The baseline ABI may be obtained within 90 days prior to the index procedure. Post procedure resting ABI must be collected at 1 month, 6 months, 12 months, and 24 months and any revascularization.

8.1.1.4 DUPLEX ULTRASOUND

Duplex Ultrasound (DUS) must be performed after the index procedure at 1, 6, 12 and 24 months and any revascularization. Since the DUS is critical to assessing study endpoints, the quality of this test is extremely important. The core lab will be closely monitoring the quality of all incoming images for compliance. Sites should ensure that only DUS operators who are trained on the trial specific DUS guidelines are performing these tests. Refer to the Duplex Ultrasound Core Lab Guidelines.

The primary responsibility of the core lab is to provide consistent interpretation of imaging data across all study sites. Data obtained from the core lab readings will be used for study purposes only and not for clinical treatment of the subject. It is the responsibility of each site to perform the local interpretation of the imaging for clinical assessment, and to maintain a copy of the DUS and angiography studies and report in the medical record. The core lab will not be responsible to notify the site of any abnormal findings that are identified in the studies.

Lutonix will use only the measurements from the core lab for analysis. If the core lab determines the study is unreadable, the subject may be asked to return for another DUS.

8.1.2 FOLLOW-UP PROCEDURES

All subjects will return for follow-up at 1, 6, 12 and 24 months post procedure for required testing at each follow-up visit time point. All subjects are required to complete all assigned follow-up visits and procedures. See **Table 1** above for required testing at each follow-up visit time point.

8.2 UNSCHEDULED ANGIOGRAPHY/REVASCULARIZATION

A duplex ultrasound (DUS) is required prior to an angiography of the index limb, and the image should be submitted to the DUS core lab. In the event that a subject undergoes repeat angiography or reintervention of the target limb after the index procedure is complete, the angiogram 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.

Following submission of the angiographic images from the first target lesion reintervention after the index procedure, no subsequent angiographic images are required to be submitted to the core lab for evaluation unless requested by the sponsor.

8.2.1 DISCONTINUATION

Subjects can withdraw from the study at any time for any reason. The reason for withdrawal will be documented. There will be no further follow-up (per this study protocol) on the subject who has withdrawn.

If a subject is potentially lost to follow-up, a minimum of three (3) attempts to contact the subject will be recorded in source documentation, including date and name of site personnel trying to make contact. One of the three (3) attempts to contact the subject must be via a certified letter.

9 ADVERSE EVENTS

The Principal Investigator or designee is responsible for the detection, documentation and reporting to the Sponsor of events meeting the criteria and definitions of an Adverse Event (AE), as provided in this protocol.

For purposes of this study, the following events are <u>not</u> considered adverse events because they are expected to occur in conjunction with endovascular procedures / post-procedure timeframe, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-operative pain (within 24 hours post-index procedure) at the access site and/or related to position on procedure table
- Minor, localized tenderness, swelling, induration, bruising, oozing, hematoma <5 cm at vascular access site
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-index procedure)
- Chest pain without associated ECG changes
- Hematocrit decrease from baseline not associated with hemodynamic changes, remaining above 30% and not requiring transfusion
- Electrolyte imbalance without clinical sequelae following PTA, even if requiring correction
- Low grade fever (≤38°C/≤101.4°F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Dissection (Grade A and B) which occur during the index procedure

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

Only the following types of endpoint related adverse events need to be reported:

- Events leading to death
- Target limb reintervention
- Target limb amputation
- Any event deemed to be device- or procedure-related

- Major vascular complication within 30 days of the index procedure
- Any event involving the target limb that requires treatment

AEs involving the target limb that are observational (do not require treatment) do not require reporting. The Investigator at the site should utilize his/her own clinical judgment in evaluating adverse events, and may decide to report events not noted on the list above.

Adverse Event Severity

The Investigator will use the following definitions to rate the severity or intensity 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 and procedure

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

Not Related	The event is definitely not associated with the study procedure/device. The adverse event is due to an underlying or concurrent illness, concomitant medication or the effect of another procedure.
Possibly Related	The temporal sequence between the study procedure/device and the event is such that the relationship cannot be ruled out completely and the event cannot be attributed to the subject's condition, concomitant therapy or the effect of another procedure.
Definitely Related	The temporal sequence between the study procedure/device and the event is such that the relationship is obvious, certain, or there is little doubt regarding the relationship.

9.1 ADVERSE EVENT REPORTING

Adverse Events should be documented in the medical records and in the eCRF. AEs experienced by the subject which require reporting per this protocol will be collected from the time point of

enrollment (i.e. after successful vessel preparation is confirmed and the subject is treated with the LUTONIX® Catheter) until the subject's end of study participation. Redacted source documentation for adjudication purposes will be submitted to Lutonix per request. Refer to **Table 3.** Investigator Reports for reporting requirements.

Event review and adjudications will be specified in the Safety Management Plan.

10 DATA COLLECTION AND MONITORING

10.1 DATA COLLECTION

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

All subject information collected during the course of this study will be kept confidential according to applicable state and federal laws and regulations.

10.1.1 ELECTRONIC CASE REPORT FORMS (ECRF)

The Investigator is responsible for ensuring the accuracy and completeness of all study documentation.

All required clinical data for this trial will be collected in web-based standardized electronic case report forms (eCRF). FDA 21 CFR 11 will be followed as well as other applicable legislation on the handling of electronic data. Subject personal information will be pseudonymized. Site numbers and subject numbers 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 the Sponsor and/or the appropriate regulatory body.

10.2 MONITORING

Monitoring is necessary to ensure adequate protection of the rights and safety of human subjects and the quality and integrity of the data obtained during the study. It is the responsibility of Lutonix as the sponsor of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met.

Sites will be monitored according to the Investigational Plan, Clinical Trial Agreement, ICH GCP guidelines, FDA regulations and guidance relevant to this clinical study, and the approved monitoring plan. The Investigator will make subject and study records available to the clinical monitor for periodic inspection. Monitoring personnel will monitor for accuracy and timely submission of CRFs and core lab images, compliance with the investigational plan, meeting enrollment commitments, applicable regulations, the signed Investigator Agreement and any conditions of approval imposed by the reviewing IRB and/or regulatory agencies.

The clinical monitors will maintain personal contact with the Investigator and staff throughout the study by phone, email, and on-site visits. The monitors will compile and submit to Lutonix a

monitoring report after each visit that will include any findings, conclusions, and actions taken to correct deficiencies.

At the close of the study at an investigational site, appropriately trained personnel appointed by Lutonix will make a final on-site or remote 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 account 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.

11 DEVICE ACCOUNTABILITY

Commercially available LUTONIX® 035 Drug Coated Balloon PTA Catheters will be utilized for this study. In the case where there is a device malfunction or deficiency, the Investigator must make every possible effort to return the device to Lutonix.

12 STUDY MANAGEMENT

12.1 INDEPENDENT EVENT REVIEW

Select events will be reviewed and adjudicated as specified in the Safety Management Plan.

13 REGULATORY RESPONSIBILITIES

13.1 ETHICS OVERSIGHT

13.1.1 INSTITUTIONAL REVIEW BOARD (IRB) RESPONSIBILITIES

All IRBs must comply with applicable IRB regulations (21 CFR 50) in reviewing and approving device investigations. An IRB shall safeguard the rights, safety, and well-being of all study subjects. The IRB shall be composed of members meeting the minimum requirements set forth in 21 CFR 56.107.

13.1.2 INITIAL APPROVAL

Investigators must submit the study protocol to their IRB and obtain written approval before Lutonix will approve the site to conduct and participate in the study. The Investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular safety reporting and study timelines.

Part of the IRB approval must include approval of an Informed Consent Form (ICF) that is specific to the study. The ICF may be modified to suit the requirements of the individual site; however, all required elements as required by FDA regulations (21 CFR 50.25) must remain. Lutonix or designee must pre-approve each ICF prior to initial submission to the IRB.

The Investigator will provide Lutonix or designee with copies of approval letters, reports, and approved ICF documents.

13.1.3 ANNUAL RENEWAL

An IRB shall conduct continuing review of the clinical study at intervals appropriate to the degree of risk posed by the device, but not less than once per year (21 CFR 56.109). A copy of the IRB renewal and other applicable documents are required to be sent to Lutonix.

Continuation of research after expiration of IRB approval is a violation of the regulations.

13.2 INVESTIGATIONAL PLAN AMENDMENTS

Investigational Plan amendments may occur during the course of the study and will be reviewed prior to implementation to determine if the changes affect the: validity of the data; risk-to-benefit ratio; scientific soundness of the Investigational Plan; or the rights, safety, or welfare of the human subjects involved in the clinical study.

Investigational Plan amendments that affect any of the above criteria will require FDA approval prior to implementation. Amendments that do not meet the criteria above will be reported to the FDA according to 21 CFR 812.35. Any amendments to the protocol, as well as possible associated information and ICF changes, will be submitted to the IRB and written approval obtained prior to implementation.

14 SELECTION OF CLINICAL SITES AND INVESTIGATORS

The Sponsor will select Investigators who are qualified and experienced to participate in this post approval study. Sites will be selected based upon a review of a recent site assessment and the qualifications of the site. Any site that becomes deactivated prior to initial enrollment, either by the Sponsor or by the individual site itself, may be replaced. The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training, and federal databases will be searched to ensure that the Investigator is not prohibited from engaging in federally sponsored clinical research.

14.1 INVESTIGATOR'S RESPONSIBILITIES

Each Investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the Clinical Investigational Plan (CIP) and applicable laws and regulations. The site Principal Investigator may select qualified Sub-Investigators at their site and will maintain responsibility for oversight of all procedures and data collection. All Sub-Investigators must be trained on all aspects of the protocol prior to enrolling or performing CIP required procedures. All physicians performing the index procedure must be trained as Sub-Investigators in the study.

The Investigator may not enroll until the Sponsor or designee receives and approves (when necessary) the following minimum documents:

- Complete Signed Investigator Agreement
- Financial Disclosure Forms for Investigator and all participating sub-Investigators
- IRB Roster or General Assurance number

- IRB Protocol and Informed Consent Approvals
- Current curricula vitae (CV) for Investigators and sub-Investigators
- Site Delegation of Authority Log
- Protocol Training of PI, sub-investigators who perform the index procedure, and primary 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.

14.1.1 INVESTIGATOR AGREEMENT

Each Principal Investigator must sign the Clinical Study Agreement prior to their participation in the study. In addition, each Sub-Investigator must sign the Sub-Investigator Protocol Signature page prior to conducting study activities. The Investigator's signature signifies his/her agreement to follow the Investigational Plan and all regulations and reporting requirements.

14.1.2 FINANCIAL DISCLOSURE

Investigators will also be required to sign a Financial Disclosure prior to study participation, which documents the Investigator's and his/her immediate family's financial interest in the Sponsor and study outcomes. Investigators must inform Lutonix of any changes to the information within the Financial Disclosure throughout the course of the study and for a period of one year following the completion of the study.

14.2 RECORDS

14.2.1 SPONSOR RECORDS

The Sponsor will maintain without limitation the following records:

- The Investigational Plan and all amendments
- Revision controlled CRF templates, ICF templates, and research authorization templates
- CRFs with audit trails completed by sites and applicable DCFs
- Signed Clinical Trial Agreements and any amendments
- Investigator Financial Disclosure information
- IRB approval letters, including a copy of the approved ICF and research authorization form
- IRB roster or Assurance number
- All correspondences relating to the conduct of the study between Lutonix and the FDA, sites, IRBs, CEC, and core laboratories

- CVs for all Investigators
- Investigational Plan related training records for all applicable study personnel
- Any other FDA required records

14.2.2 INVESTIGATOR RECORDS

Records to be maintained by the Investigator in a designated site file include without limitation:

- Sponsor and IRB approved Investigational Plan and all amendments
- Signed Study Agreement and all amendments thereto
- IRB approval letters, including a copy of the approved informed consent forms and research authorization form template, progress reports, AE reports
- IRB roster or Assurance number
- All correspondence relating to the conduct of this clinical study between the site and Lutonix, IRBs, and other Investigators
- CVs and copies of professional licenses for all Investigators, if applicable
- Study personnel signatures and documentation of the Principal Investigator's delegation of responsibilities
- Sponsor Site Visit Log
- Documentation of Lutonix and IRB approval of changes made to the informed consent and research authorization forms
- Investigational Plan related training records for all applicable study personnel
- Financial Disclosure documentation for the Principal Investigator and sub-Investigators
- Any other FDA required records

The following records must be maintained and be readily available for each subject enrolled:

- Signed and dated informed consent and research authorization forms
- Completed eCRFs and queries
- Records pertaining to adverse events and subject's death occurring during the study
- Complete medical records including procedure reports, imaging reports, and all additional records required to verify entries on the eCRFs

14.2.2.1 RETENTION

Records are subject to FDA inspection. Subject study records, correspondence files, all supporting study documentation, and reports as described above must remain on file at the site for a minimum of two years after the latter of the following dates (21 CFR 812.140(d)):

- The date on which the study is terminated or completed
- The date the records are no longer required for purposes of supporting an application to the FDA to market the device

Lutonix must be contacted if the Principal Investigator plans to leave the site to ensure that arrangements for a new Principal Investigator or records transfer are made prior to the Investigator's departure. The FDA will be notified of this transfer no later than 10 working days after the transfer occurs (812.140 (e)).

All Investigators must contact Lutonix prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

14.2.3 IRB RECORDS

Each reviewing IRB must maintain the following records (21 CFR 56.115):

- All pertinent correspondence relating to the study
- All records of membership and affiliations
- Meeting minutes

14.3 REPORTS

14.3.1 SPONSOR REPORTS

Sponsors are responsible for preparing and submitting the following complete, accurate, and timely reports (CFR 812.150(b)). Refer to **Table 2** for the types of reports to be submitted.

TABLE 2. SPONSOR REPORTS

Report	Submit To	Timeframe
Unanticipated Adverse Device Effects	FDA, IRBs, and Investigators	Ten (10) working days after receiving notice of the event
Withdrawal of IRB Approval	FDA, IRBs, and Investigators	Five (5) working days
Withdrawal of FDA approval	IRBs and Investigators	Five (5) working days
Current Investigator List	FDA	Six (6) month intervals
Progress reports	FDA and IRBs	Annually
Final Reports	FDA, IRBs, and Investigators	Six (6) months after completion or termination

Report	Submit To	Timeframe
Recall and device disposition (Request for Investigator to return, repair, or dispose of any device)	FDA and IRBs	Thirty (30) working days
Failure to obtain informed consent	FDA	Five (5) working days

In addition, Lutonix will provide accurate, complete, and current information about any aspect of the study upon request of the FDA or a reviewing IRB.

14.3.2 INVESTIGATOR REPORTS

Investigators are required to prepare and submit to Lutonix complete, accurate, and timely reports on this clinical study as required by regulations (CFR 812.150(a)). Refer to **Table 3** for the types of reports to be submitted.

TABLE 3. INVESTIGATOR REPORTS

Report	Submit To	Timeframe
Unanticipated Adverse Device Effects	IRB and Lutonix	As soon as possible but no later than ten (10) working days
Subject death	IRB and Lutonix	Lutonix: within 24 hours of knowledge IRB: per local requirements
SAE/SADE	IRB and Lutonix	Lutonix: Five (5) working days of knowledge IRB: per local requirements
Failure to obtain informed consent	IRB and Lutonix	Five (5) working days
Subject withdrawal	Lutonix	Five (5) working days
Continuing IRB approval	IRB	Prior to continuing review date
Withdrawal of IRB Approval	Lutonix	Five (5) working days
Progress reports	IRB and Lutonix	Annually, at a minimum or as required by IRB
Final Reports	IRB and Lutonix	Three (3) months after termination or completion of a study or the Investigator's part in a study

In addition, Investigators must provide accurate, complete, and current information about any aspect of the clinical study upon request of the Sponsor, IRB or FDA.

15 PUBLICATIONS

The trial will be registered in the ClinicalTrials.gov website upon approval by a human subject review board 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 will be submitted to a reputable scientific journal. All public reporting of the results of the study will eliminate identifiable references to the subjects. Following the publication of the main manuscript, secondary analyses proposals will be considered for publication from individual Investigators. No submissions may be made without the written approval from Lutonix.

16 STATISTICAL ANALYSIS PLAN

16.1 OVERVIEW OF STUDY DESIGN

This is a single-arm study design that will enroll approximately 165 US female 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. Subjects will be followed for 24 months. Primary and secondary endpoints will be summarized descriptively as appropriate..

16.2 ANALYSIS CONVENTIONS

General reporting will include descriptive summaries of baseline information, subject medical history, characteristics of the treated lesion, procedure information, effectiveness measures as outlined below, the composite safety information, target lesion revascularization information, and study accountability information. Variables reported at multiple visits will also be summarized by visit if applicable. Descriptive statistics of frequency data will be the count and percents calculated based on available data. Numeric descriptive measures include the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum statistics. Kaplan-Meier estimates of event rates or event-free survival will be provided for some endpoints. Results at 24 months will only include descriptive summaries. If confidence intervals are provided in support of specific analyses they will be two-sided 95% intervals. No inferential testing is planned for the study and any testing performed will be identified as post-hoc.

16.3 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) Population will be based on all subjects enrolled in the study. The primary effectiveness will be based on evaluable ITT subjects receiving treatment with a known outcome through 12 months. A Safety Population will be used for all safety endpoints and only include subjects who are treated with the Lutonix DCB and have some evidence of follow-up as indicated by any reported adverse event, any post-procedure follow-up assessments, or a recorded discharge

date. If the ITT and Safety Population are the same, then only the ITT population will be used in discussion of the study results.

A Per-Protocol (PP) Population may be used to summarize the primary endpoints and selected secondary endpoints. The PP population would include treated subjects without major protocol violations and the identification of major protocol violations would be completed before closure of the database.

16.4 HANDLING MISSING DATA

This protocol provides descriptive statistics only, hence no sensitivity analyses are planned to assess the impact of missing data on hypothesis testing. The number of non-missing observations will be reported for all endpoint summaries to indicate the completeness of the data set. Further, Kaplan-Meier estimates of the success rate will also be provided for time dependent measures. These estimates incorporate the censoring of events and will be unbiased if the reasons subjects are missing do not relate to their outcome at the point they are censored.

16.5 ASSESSMENT OF POOLABILITY OF SITES

The results for the primary endpoints will be summarized by study sites descriptively in order to allow a review of the homogeneity of results by study site. Primary Endpoints

16.5.1 EFFECTIVENESS ENDPOINT AND SAMPLE SIZE CALCULATION

The primary effectiveness endpoint is primary patency at 12 months and it will be analysed on a per-lesion basis.

A sample size of 165 subjects was selected for this study in order to allow for 140 subjects with 12 month outcomes assuming a 15% drop-out rate. This sample size was selected based on precision (width of the confidence interval) for the primary endpoint. Assuming a response rate of 65%, the primary patency success rate observed in the LEVANT 2 pivotal study for DCB subjects, the expected two-sided exact confidence interval is (56.5%, 72.9%) which provides less than +/- 10% around the estimate (91/140 = 65%). Further, the lower expected bound is adequate as it will differentiate from the control PTA response in the LEVANT 2 study.

16.5.2 SAFETY ENDPOINT AND SAMPLE SIZE CALCULATIONS

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

The sample size was considered adequate based on the expected 95% confidence interval for the primary safety endpoint success rate being less than plus or minus 10%. Assuming a response rate of 84.3% (118/140) and 140 completer subjects, the two-sided 95% exact confidence interval is (77.2%, 89.9%).

16.6 SECONDARY ENDPOINTS

The following effectiveness and safety endpoints will be summarized descriptively as appropriate. For selected endpoints 95% confidences for event or success rates will be calculated using exact binomial intervals or using Kaplan-Meier methodology. Additional endpoints include:

The following endpoints will be assessed at 1 month:

- Composite of freedom from all-cause perioperative (≤ 30 day) death and freedom from the following: index limb amputation, index limb re-intervention, and index-limb-related death.
- Major Vascular Complications (<30 days)

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

- All-cause death
- Clinically Driven Target Lesion Revascularization (TLR)
- Target Vessel Revascularization (TVR)
- Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature
- Rate of unanticipated and anticipated device related serious adverse events
- Amputation (above the ankle)-Free Survival (AFS)
- Change of Rutherford classification from baseline
- Sustained Clinical Benefit (improvement in Rutherford Class compared to baseline AND freedom from target vessel revascularization)
- Change of resting Ankle Brachial Index (ABI) from baseline

17 REFERENCES

1. Newman AB, Shemanski L, Manolio TA et al. *Ankle–arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study Group*. Arterioscler Thromb Vasc Biol 1999; 19: 538–45.
2. Levy, P.J., *Epidemiology and pathophysiology of peripheral arterial disease.* Clin Cornerstone, 2002. **4**(5): p. 1-15.
3. Yazdani, S.K., et al., *Vascular, downstream, and pharmacokinetic responses to treatment with a low dose drug-coated balloon in a swine femoral artery model.* Catheter Cardiovasc Interv, 2013.
4. Axel, D.I., et al., *Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery.* Circulation, 1997. **96**(2): p. 636-45.
5. Pocock, S., et al., *International differences in treatment effect: do they really exist and why?* Eur Heart J, 2013. **34**(24): p. 1846-52.

APPENDIX A: DEFINITIONS

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

Adverse Device Effect (ADE)
An AE related to the use of the study device.

Adverse Event (AE)
Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

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 and Minor Amputations.

- **Major Amputation -** Amputation of the lower limb above the ankle
- **Minor Amputation -** Amputation of a foot, or of a part thereof

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.

Anticipated Adverse Event

Any AE whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the CIP, predefined in the CIP and/or IFU.

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).

Device Deficiency
Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance and may include malfunctions, use errors, and inadequate labeling.

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

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. Type A and B dissections are not considered adverse events for reporting.

Enrollment
A patient is considered enrolled in the study after baseline angiographic results and after successful vessel preparation confirm that the target lesion meets all appropriate inclusion/exclusion criteria and is treated with the **LUTONIX® Catheter**.

Index Limb Related Death
Any death adjudicated during event review as "related" to a complication of the index limb.

Major Vascular Complications (<30 days)
Hemorrhagic vascular complications included the following:

- Haematoma at access site >5 cm
- False aneurysm
- AV fistula
- Retroperitoneal bleed

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

Patent Run-off
At least one patent native outflow artery from the popliteal to the ankle, free from significant (≥50%) stenosis as confirmed by angiography or ultrasound.

Per-Protocol (PP)
All as-treated subjects characterized by appropriate exposure to treatment (procedurally correct as pre-specified) and the absence of major protocol violations (including violations of entry criteria) that if not met for a given subject may obscure the evaluation of effectiveness in that subject.

Primary Patency
Primary Patency is defined as Freedom from TLR and from Binary Restenosis. Binary Restenosis is adjudicated by the independent Core Laboratory based on PSVR ≥ 2.5 and / or abnormal waveforms or based on angiographic ≥ 50% diameter stenosis .

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

PSVR
Peak Systolic Velocity Ratio

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

Restenosis
Either ≥50% restenosis of the diameter of the reference-vessel segment by QVA or peak systolic velocity ratio of ≥2.5 or as adjudicated by the DUS Core Lab.

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

Rutherford Categories
Categorical description of the symptoms associated with the obstruction of the lumen of the peripheral arteries (NCI C78533).

0	Asymptomatic: documented peripheral arterial disease, without symptoms of claudication or ischemic pain
1	Mild claudication: ischemic limb muscle pain that does not limit walking, or limits walking only after >2 blocks (>600 feet, or 2 football fields)
2	Moderate claudication: ischemic limb muscle pain that limits walking to 1-2 blocks (300-600 feet, or 1-2 football fields)
3	Severe claudication: ischemic limb muscle pain that limits walking to <1 block (<300 feet, or 1 football field)
4	Ischemic rest pain: pain in the distal foot at rest felt to be due to limited arterial perfusion
5	Minor tissue loss: nonhealing ischemic ulcer(s) on distal leg, or focal gangrene with diffuse pedal ischemia
6	Major tissue loss: ischemic gangrene extending above TM level, functional foot no longer salvageable without extensive revascularization efforts

Adapted from VQI PVI registry, Rutherford J Vasc Surg 1997;26:517-38, ACC/AHA PAD Data Standards Circulation 2012;125:395-467, and PARC J Am Coll Cardiol 2015.

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.

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Required intervention to prevent permanent impairment or damage, or
- Caused a congenital anomaly/birth defect

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.

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

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.

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 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

Unanticipated Adverse Device Effect (UADE)
A UADE is an ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

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 compared to baseline.

APPENDIX B: INFORMED CONSENT FORM

Provided separately.

APPENDIX C: DATA POINTS COLLECTED

Provided separately.