A Prospective, Multicenter, LEVANT 2 Continuation Registry of the Moxy™ Drug Coated Balloon for Treatment of Femoropopliteal Arteries

LEVANT 2 Continued Access Registry

Version 1.0

Sponsor:

9409 Science Center Drive
New Hope, MN 55428 USA

Investigational Device: Moxy™ Drug Coated Balloon

NCT Number: 01628159 (NCT Number added post-approval per CT.gov requirement)

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

The LEVANT 2 Continued Access Registry Summary

Title	A Prospective, Multicenter, Continuation Registry of the Moxy™ Drug Coated Balloon for Treatment of Femoropopliteal Arteries (LEVANT 2 Continued Access registry)
Investigational Device	Lutonix Moxy™ Drug Coated Balloon
Study Design	Prospective, Multicenter, Continuation Registry, Safety and Efficacy
Overview	The purpose of the LEVANT 2 Continued Access registry is to collect additional safety and efficacy data on the Lutonix Moxy Drug Coated Balloon in a large population. The study will enroll the same patient population and follow the same medication regimen, follow-up schedule, and definitions as the LEVANT 2 randomized protocol. 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 Moxy Drug Coated Balloon and followed for 5 years. Subjects that do not meet post-predilatation lesion criteria are excluded (and treated per standard practice) and followed for safety for 30 days.
Purpose	To collect additional safety and efficacy information on the Moxy 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 Moxy 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 Moxy Drug Coated Balloon.
Enrollment	Enrollment will occur at up to 70 global centers, including up to 55 sites participating in the LEVANT 2 randomized trial and additional sites outside the U.S. For sites participating in the Randomized portion of the trial, enrollment in this registry will not start until the full randomized cohort (476 subjects) has been enrolled. Up to 975 subjects are expected to be enrolled in this continuation study to ensure approximately 650 subjects treated with the Drug Coated Balloon.
Subject Follow-Up Schedule	The follow up schedule will be the same as in the LEVANT 2 randomized protocol, with clinical visits at 6, 12, and 24 months, DUS at 0-30d, 6m, 12m and 24 months and telephone follow-up at 1, 36, 48, and 60 months.
Primary Endpoint	Rate of unanticipated device- or drug- related adverse events over time through 60 months.
Secondary Endpoints	*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 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 *Efficacy* • Acute Device, Technical and Procedural success The following endpoints will be assessed at 6, 12 and 24 Months: • 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) o Clinically-driven o Total *(clinical and DUS/angiography-driven)* • Change of Rutherford classification from baseline Change of resting Ankle Brachial Index (ABI) from baseline
Inclusion Criteria	Inclusion Criteria is the same as in the most recently approved LEVANT 2 randomized protocol (section 5.3.1).
Exclusion Criteria	Exclusion Criteria is the same as in the most recently approved LEVANT 2 randomized protocol (section 5.3.2).
Primary Analytical Subset	All subjects treated with a DCB in the LEVANT 2 Randomized protocol and in the LEVANT 2 Continued Access registry.
Authorized Representative	[redacted]

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1 INTRODUCTION

The purpose of the LEVANT 2 Continued Access registry is to collect additional safety and efficacy information on the Lutonix 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 described in the currently approved LEVANT 2 Randomized protocol.

2 STUDY OBJECTIVES AND ENDPOINTS

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

2.1 CONTINUED ACCESS PRIMARY OBJECTIVE

The Primary Objective is to assess safety and efficacy of use of the Moxy Drug Coated Balloon for treatment of stenosis of the femoropopliteal arteries in a large population of subjects.

2.2 PRIMARY ENDPOINT

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

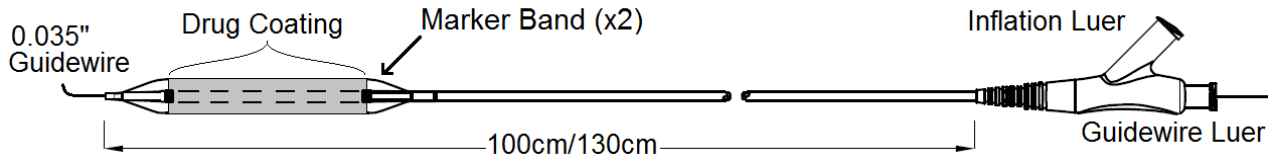

FIGURE 1: MOXY DRUG COATED BALLOON

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

3.1 INTENDED USE / INDICATIONS FOR USE

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

3.2 ACTIVE PHARMACEUTICAL INGREDIENT (API): PACLITAXEL

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

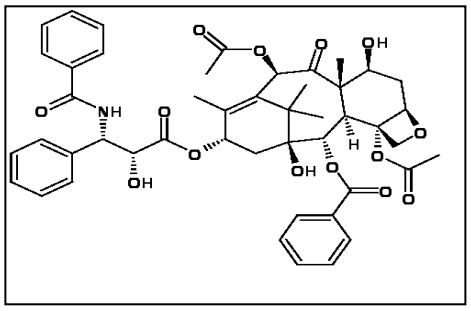

FIGURE 2 : CHEMICAL STRUCTURE OF PACLITAXEL

3.3 EXCIPIENT (DRUG CARRIER)

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

3.4 DEVICE INSTRUCTIONS

A comprehensive set of Instructions for Use (IFU), including warnings and precautions, has been created. Please refer to the most current IFU packaged with the device for complete details on preparation and procedural use of the device. A sample IFU can be found in Appendix G of the LEVANT 2 Randomized protocol.

3.5 SUPPLY & SUPPORT OF INVESTIGATIONAL DEVICE

An investigational device supply of the Moxy Drug Coated Balloon will be made available to all activated study sites. The investigational device matrix that is currently available for this study is listed in Table 1. Always confirm current site inventory supply prior to enrolling subjects into the study.

TABLE 1: DEVICE MATRIX, MOXY DRUG COATED BALLOON

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

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

4 RISK – BENEFIT ANALYSIS

The potential risks and benefits of participation in this study are clearly identified in the subject Informed Consent Form (ICF) and are the same as detailed in the LEVANT 2 Randomized protocol, reference section 4.1 – 4.3 of the LEVANT 2 Randomized protocol for complete risk-benefit analysis.

4.1 EARLY TERMINATION

Lutonix, Inc. (Sponsor) and the Clinical Events Committee will monitor the progression of the continuation access study. If warranted, the study may be suspended or discontinued 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 study 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 design of this continuation study will mirror the LEVANT 2 randomized protocol, except for the randomized component; all subjects that meet the LEVANT 2 criteria for randomization are instead treated with the Moxy Drug Coated Balloon. After successful protocol-defined pre-dilatation, subjects that are unlikely to require a stent based on strict angiographic criteria (absence of major flow-limiting dissection from the lumen and ≤ 70% residual stenosis or the lesion is not appropriate for stenting due to proximity to the knee joint) will be treated with the Moxy 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. Figure 3 contains an overview of the study.

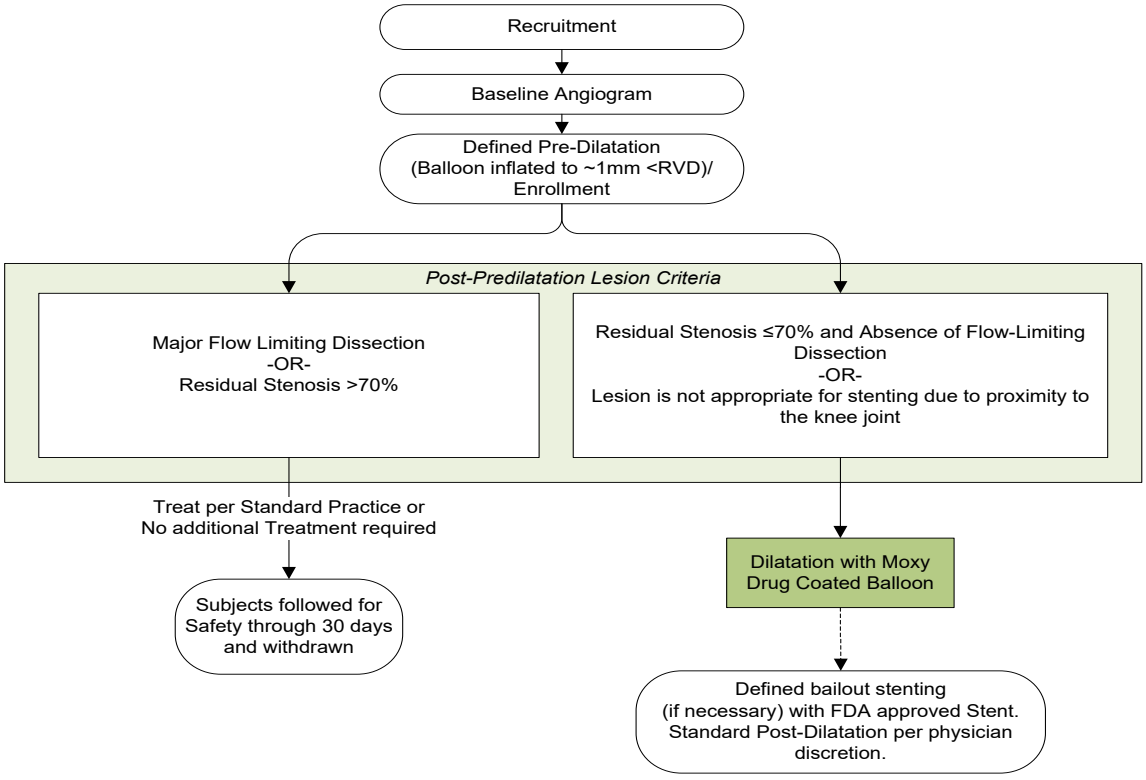

FIGURE 3: STUDY FLOWCHART

5.1 SCREENING PROCEDURES

For sites participating in the Randomized portion of the trial, enrollment in this registry will not start until the full randomized cohort (476 subjects) has been enrolled.
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 LEVANT 2 Continued Access 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.

If not already performed as standard practice, the same assessments and tests must be performed as listed in the most recently approved LEVANT 2 randomized protocol after obtaining informed consent and prior to the index procedure (within 30 days unless otherwise noted) to verify and complete eligibility.

5.2 PATIENT SELECTION FOR ENROLLMENT

Subjects must meet all the clinical eligibility criteria, agree to participate and comply with study protocol requirement 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 Moxy procedure proctoring with a sponsor representative (or designee) during their initial study Moxy case(s) if it was not completed as part of the randomization phase. 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

All Inclusion and Exclusion Criteria will be the same as in the most recently approved LEVANT 2 randomized protocol.

5.3.1 INCLUSION CRITERIA

Reference section 5.3.1 of the LEVANT 2 Randomized protocol.

5.3.2 EXCLUSION CRITERIA

Reference section 5.3.2 of the LEVANT 2 Randomized protocol.

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 Moxy Drug Coated Balloon in this study.

6.2 PRE-DILATATION

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

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

See Table 2 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 Moxy Drug Coated Balloon but is instead treated per institutional standard practice. Subjects excluded from treatment with the Moxy Drug Coated Balloon after pre-dilatation will be followed for 30 days for safety and then withdrawn.

TABLE 2: 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 ≤ 70% and Absence of Flow-Limiting Dissection -OR- Lesion is not appropriate for stenting due to proximity to the knee joint	Treat with Moxy Drug Coated Balloon

6.3 TREATMENT

6.3.1 LUTONIX MOXY DRUG COATED BALLOON

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

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

6.4 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 study 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 study will utilize more rigorous criteria for bailout stenting. Specifically, the study 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 3) 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 3: PROVISIONAL (BAILOUT) CRITERIA

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

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

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

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

6.5 MEDICATIONS

All pre-procedure, Intra-procedure and post-procedure medication requirements will be the same as in the most recently approved LEVANT 2 randomized protocol, reference section 7.2 of the LEVANT 2 Randomized protocol for the complete details of the pre-procedure, intra-procedure, and post-procedure medication regimen.

6.6 STANDARD TESTS, PROCEDURES, AND FOLLOW-UP

All testing, procedures and follow-up requirements will be the same as in the most recently approved LEVANT 2 randomized protocol, (reference section 7.3 of the LEVANT 2 Randomized protocol), with the exception of

- Six Minute Walk Test (7.3.1.5)
- Walking Impairment Questionnaire (7.3.1.6)
- Quality Of Life Questionnaires (7.3.1.7)
- Economic Sub-Study (Appendix K)
- CMP will be replaced with a BMP (without bicarbonate) in order to better correlate with lab capabilities in various geographies.

Pharmacokinetic Testing may be necessary to reach a total of 30 PK sub study subjects if not completed as part of the LEVANT 2 randomized protocol.

TABLE 4: FOLLOW-UP SCHEDULE AND TESTING REQUIREMENTS

Event	Screening (pre-consent)	Pre-Procedure	Procedure	Post- Procedure	1 Month[1]	6 Month	12 Month	24 Month	36 Month[1]	48 Month[1]	60 Month[1]
Visit Window	30 days	30 days			±2 weeks	±1 month	±1 month	±2 month	±2 month	±2 month	±2 month
Inclusion/Exclusion Criteria	√	√	√								
Informed Consent		√									
Medical History	√										
Physical Exam		√		√	√[2]	√	√	√			
Medication Compliance		√			√	√	√	√	√	√	√
Resting ABI[3]		√			√[2]	√	√	√			
Rutherford Classification		√				√	√	√			
Blood Analysis (CBC with differential; BMP, pregnancy[5])		√[4]		√	√[2]	√	√				
Angiogram			√								
Adverse Event Monitoring			√	√	√	√	√	√	√	√	√
Duplex Ultrasound				√		√	√	√			
PK Study[6]		√		√	√						

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

[2] *Required if clinical visit occurs*

[3] *Resting ABI is required within 90 days of index procedure.*

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

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

[6] *PK study in a subset of subjects only*

7 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 of the LEVANT 2 Randomized protocol for details of all the definitions.

7.1 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.

8 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. 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.

9 DATA COLLECTION AND MONITORING

9.1 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.

9.1.1 ELECTRONIC CASE REPORT FORMS (ECRF)

All required clinical data for this trial will be collected in web-based standardized eCRF. The same electronic data capture system and the same DCB treatment eCRF as in the LEVANT 2 randomized protocol will be utilized (minus those data points associated with items excluded in section 6.3). 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.

9.1.2 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.

9.2 MONITORING

A formal written Monitoring Plan will be developed in accordance to FDA guidelines 53 CFR 4723 and the continuation access 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.

Each site will have an initiation visit or call performed by a study team member prior to initiation of enrollment into the continuation access study. This visit or call 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, 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
- 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.

9.3 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).

9.4 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.

9.5 STUDY PROCESSING

9.5.1 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.

9.5.2 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 new study site personnel which will include, but may not be limited to, the following:

- Techniques for the identification of eligible subjects
- Protocol
- 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.

10 DEVICE ACCOUNTABILITY

All investigational Moxy Drug Coated Balloon must be stored in a locked storage facility to which only the Investigator and/or designated study staff will have access. The Investigator is responsible for device accountability at the trial site. The Investigator may assign the responsibility for the device accountability to an appropriate study staff member, but remains the final responsible person. The Investigator must ensure that the device is used only in accordance with the protocol and current IFU. The Investigator must maintain records that document device delivery to the trial site, the inventory at the site and administration to each subject. These records must include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial subjects. The Investigator must maintain records that adequately document which device the subject received according to the protocol and the assigned randomization. In the case where a device has failed, the Investigator must make every possible effort to return the device to Lutonix; instructions for this procedure will be provided in the Manual of Operating Procedures.

11 STUDY MANAGEMENT

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

11.1 SAFETY COMMITTEES

The Steering Committee (SC)and Clinical Events Committee will continue to function in the same manner as in the LEVANT 2 Randomized protocol.

11.2 IRB/EC APPROVAL

Investigators must submit the study protocol to their IRB/EC and obtain written approval before being allowed to conduct and participate in the continued access study. Annual re-approval must also be obtained. The Investigator is also responsible for fulfilling any conditions of approval

imposed by the IRB/EC, such as regular safety reporting, study timing, etc. The Investigator will provide Lutonix or designee with copies of such approvals and reports.

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

11.3 INFORMED CONSENT

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

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

11.4 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 in the continued access study until Lutonix or designee receives appropriate IRB/EC approval and any other applicable document (revised investigator agreement, etc.)

11.4.1 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.

11.4.2 REPORTS

Report requirements will be the same as listed in the most current LEVANT 2 Randomized protocol.

12 PUBLICATIONS

The publication policy will be the same as listed in the most current LEVANT 2 Randomized protocol.

13 STATISTICAL ANALYSIS PLAN

13.1 OVERVIEW OF STUDY DESIGN

The purpose of the LEVANT 2 Continued Access registry is to collect additional safety and efficacy information of the Lutonix Moxy Drug Coated Balloon for treatment of stenosis or occlusion of the femoral and popliteal arteries in a large population of subjects. The LEVANT2 Continued Access Study is an open-label registry study of the Drug Coated Balloon.

Approximately 975 subjects will be enrolled in order to include a total of 650 subjects treated with the Moxy 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 predilated 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.

13.2 SAMPLE SIZE JUSTIFICATION

Taken together with the LEVANT 2 Randomized Study, the 650 additional DCB subjects enrolled in the LEVANT 2 Continued Access registry will provide a safety dataset on 1022 subjects treated with the 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.

US and non-US enrollment will be contemporaneously monitored throughout the study to ensure adequate sampling of both US and non-US subjects.

13.3 ANALYSIS

Data from all the subjects treated with DCB in the LEVANT 2 Randomized protocol (roll-in and randomized to DCB) and in 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 (LEVANT2 roll-ins, randomized subjects, and continued access subjects) will also be evaluated.

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