LUTONIX® 035 Drug Coated Balloon PTA Catheter

Product Features: GEOALIGN® Marker Bands, Peel Away Balloon Protector

INSTRUCTIONS FOR USE

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

Table of Contents

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ENGLISH

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INSTRUCTIONS FOR USE

1 DEVICE DESCRIPTION

1.1 PTA 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 (**Figure 1**). 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. Non-radiopaque GEOALIGN® Marker Bands are designated on the catheter shaft by 1cm increment bands. Each 10cm increment is labeled with the distance from the distal balloon tip (**Figure 2** & **Figure 3**). Thicker bands denote the midway point (5cm) between the labeled distances. GEOALIGN® Marker Bands are designed to be used as a location reference tool. 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. See **Table 1** for additional details.

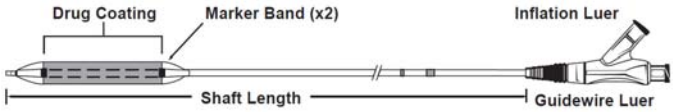


Figure 1. LUTONIX® 035 Drug Coated Balloon PTA Catheter, Model 9004

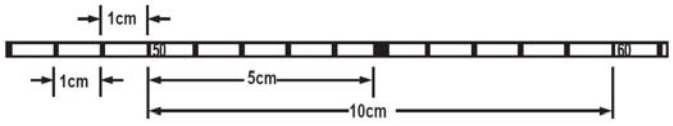


Figure 2. GEOALIGN® Marker Bands are non-radiopaque and designed to be utilized outside the introducer sheath

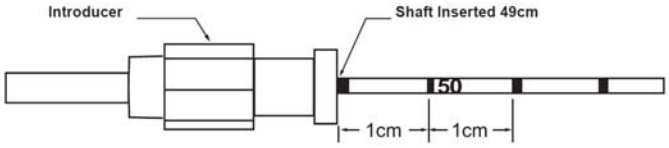


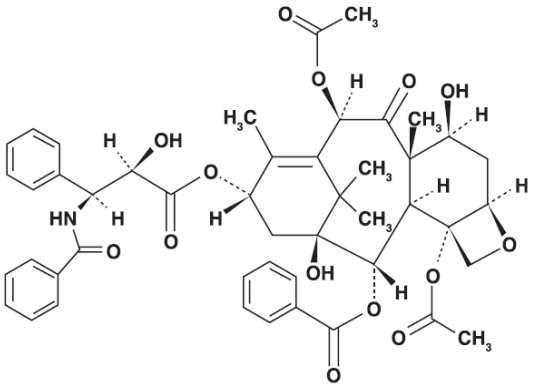
Figure 3. GEOALIGN® Marker Band number in relation to the introducer sheath (example)

Table 1. LUTONIX® 035 Drug Coated Balloon PTA Catheter Product Description (Reference to device specific product label)

Attribute	Peripheral (PTA)
Model Number	9004
Catheter Configuration	Over-the-Wire (OTW)
Available Balloon Diameters	4.0, 5.0, 6.0, 7.0mm
Available Balloon Lengths	40, 60, 80, 100, 120, 150, 220mm
Effective Catheter Length	75, 100, 130cm
Radiopaque Marker Bands	2
Nominal Balloon Pressure	5F Sheath Compatible 6 atm for 4.0 – 5.0mm diameter balloons 7 atm for 6.0mm x 40 – 150mm lengths 6 atm for 6.0mm x 220mm lengths 7 atm for 7.0mm x 40 – 60mm lengths 6 atm for 7.0mm x 80 – 220mm lengths 6F Sheath Compatible 7 atm for 6.0mm x 220mm lengths 7 atm for 7.0mm x 80 – 220mm lengths
Balloon Rated Burst Pressure	5F Sheath Compatible 12 atm for 4.0 – 5.0mm diameter balloons 12 atm for 6.0mm x 40 – 150mm lengths 10 atm for 6.0mm x 220mm lengths 12 atm for 7.0mm x 40 – 60mm lengths 10 atm for 7.0mm x 80 – 220mm lengths 6F Sheath Compatible 12 atm for 6.0mm x 220mm lengths 11 atm for 7.0mm x 80 – 220mm lengths
Maximum Guidewire	0.035"
Minimum Introducer Sheath	5F for 4.0 – 5.0mm diameter balloons 5F for 6.0mm x 40 – 150mm lengths 5F or 6F for 6.0mm x 220mm lengths 5F or 6F for 7.0mm x 80 – 220mm lengths
Crossing Profile	5F Sheath Compatible 4.0mm x all lengths: 5.0F (1.7mm) 5.0mm x 40 – 80 & 220mm lengths: 5.3F (1.8mm) 5.0mm x 100 – 150mm lengths: 5.0F (1.7mm) 6.0mm x 40 – 150mm lengths: 5.3F (1.8mm) 6.0mm x 220mm lengths: 5.2F (1.7mm) 7.0mm x 40 – 60mm lengths: 5.5F (1.8mm) 7.0mm x 80 – 220mm lengths: 5.4F (1.8mm) 6F Sheath Compatible 6.0mm x 220mm lengths: 5.5F (1.8mm) 7.0mm x 80 – 220mm lengths: 5.8F (1.9mm)
Coating Formulation	Active Pharmaceutical Ingredient: Paclitaxel Excipients: polysorbate, sorbitol

1.2 Drug Component Description

The active ingredient on the LUTONIX® 035 Drug Coated Balloon PTA Catheter is paclitaxel. Paclitaxel is a white powder, manufactured by a semi-synthetic process, with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 854. It is highly lipophilic, insoluble in water, and melts at approximately 216-217°C. The chemical name for paclitaxel is 5β,20-Epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate]. Paclitaxel CAS Registry number is 33069-62-4. Paclitaxel has the following chemical structure:



The drug coating is a non-polymer based formulation, consisting of paclitaxel as the active pharmaceutical ingredient and polysorbate and sorbitol, inactive ingredients, which act as the drug carrier.

The paclitaxel coating is evenly distributed across the working length of the balloon at a surface concentration of 2 µg/mm^2 see **Figure 4**. The key functional characteristic of the formulation is to allow for release of paclitaxel to the tissue of the vascular wall during inflation.

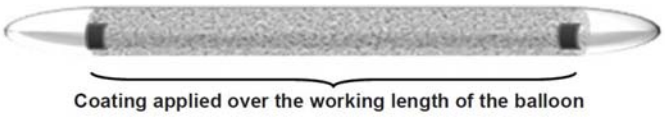


Figure 4. Drug Coating Distribution

Table 2 presents the balloon sizes and the nominal total quantity of paclitaxel on each balloon based on the surface concentration of 2 µg/mm^2.

Table 2. Balloon sizes and Paclitaxel dosage (mg)

Balloon Diameter (mm)	Total Dosage (mg) per Respective Balloon Length						
	40 mm	60 mm	80 mm	100 mm	120 mm	150 mm	220 mm
4.0	1.0	1.5	2.0	2.5	3.0	3.8	5.5
5.0	1.3	1.9	2.5	3.1	3.8	4.7	6.9
6.0	1.5	2.3	3.0	3.8	4.5	5.7	8.3
7.0	1.8	2.6	3.5	4.4	5.3	6.6	9.7

2 INDICATIONS FOR USE

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 300mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm.

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 WARNINGS

- **A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. See Section 10.1 for further information.**
- **Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use.**
- **Do not use if product damage is evident.**
- **The LUTONIX® Catheter is for use in one patient only; do not reuse in another patient, reprocess or resterilize. Risks of reuse in another patient, reprocessing, or resterilization include:**
  - **Compromising the structural integrity of the device and/or device failure which, in turn, may result in patient injury, illness or death.**
  - **Creating a risk of device contamination and/or patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to patient injury, illness or death.**
- **Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended.**
- **Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon.**
- **This product should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds.**
- **The safety and effectiveness of the LUTONIX® Catheter have not been established for treatment in cerebral, carotid, coronary, or renal vasculature.**
- **The safety and effectiveness of using more than four LUTONIX® drug coated balloons or a maximum drug coating quantity of approximately 15.1 mg paclitaxel in a patient has not been clinically evaluated.**

5 PRECAUTIONS

5.1 General Precautions

- The LUTONIX® Catheter should only be used by physicians trained in percutaneous interventional procedures.
- Consideration should be given to the risks and benefits of use in patients with a history of non-controllable allergies to contrast agents.

5.2 Use in Conjunction with Other Procedures

The safety and effectiveness of the LUTONIX® Catheter used in conjunction with other drug eluting stents or drug coated balloons in the same procedure or following treatment failure has not been evaluated.

Note: Use with bare metal stents for bailout if needed in the same procedure following treatment with the LUTONIX® Catheter is permitted.

5.3 Device Handling Precautions

- Do not immerse the LUTONIX® Catheter in a saline bath. Replace any device where the balloon has come into contact with fluids prior to use.
- The coated balloon portion should be handled with dry sterile gloves whenever possible prior to use.
- The balloon protector should stay in place during preparation of the LUTONIX® Catheter and not be removed until just prior to placing over guidewire.

- If difficulty is encountered while removing the balloon protector, a new LUTONIX® Catheter should be utilized. Removing the balloon protector by force can cause a kink in the catheter shaft and lumen constriction may occur, affecting inflation/deflation of the balloon.

5.4 Device Use/Procedure Precautions

- To ensure therapeutic drug delivery:
    - Never inflate the LUTONIX® Catheter prior to reaching the target lesion.
    - The LUTONIX® Catheter should be advanced to the target site as fast as possible (i.e. ~ 30 seconds) and immediately inflated to appropriate pressure to ensure full wall apposition (balloon to artery ratio ≥ 1:1). If the time to deployment of the LUTONIX® Catheter exceeds 3 minutes, the catheter requires replacement with a new unit.
- Maintain balloon inflation for a minimum of 2 minutes (120 seconds). The balloon may remain inflated as long as is required by the standard of care to achieve a good angioplasty outcome.
- Vessel preparation of the target lesion, using the appropriate vessel preparation method as determined by the treating physician, is required prior to the use of the LUTONIX® Catheter.
- Vessel preparation using only pre-dilatation was studied in the LEVANT 2 clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with the LUTONIX® Catheter.
- After insertion, do not over-tighten the hemostatic adaptor (if used) around the LUTONIX® Catheter shaft as lumen constriction may occur, affecting inflation/deflation of the balloon.
- Always advance and retrieve the LUTONIX® Catheter under negative pressure.
- The LUTONIX® Catheter should always be manipulated under fluoroscopic observation when in the body.
- Do not continue to use the LUTONIX® Catheter if the shaft has been bent or kinked.
- Whenever possible, the LUTONIX® Catheter should be the final treatment of the vessel; however, post-dilatation is allowed with another PTA catheter or the previously used LUTONIX® Catheter. Alternatively, placement of a bare metal stent for bailout is allowed, if necessary.

5.5 Pre- and Post-Procedure Antiplatelet Regimen

Dual antiplatelet therapy should be administered according to current medical standards pre-procedure and for a minimum of 4 weeks after the intervention. Prolonged antiplatelet therapy can be given at the discretion of the physician.

6 USE IN SPECIAL POPULATIONS

- Pregnancy – Use in women who are breastfeeding, pregnant or intending to become pregnant or in men intending to father children over the next 2 years is contraindicated.
- Pediatric Use – The safety and effectiveness of the LUTONIX® Catheter in pediatric patients has not been established.
- Geriatric Use – Clinical studies of the LUTONIX® Catheter did not have an upper age limit.
- Women – Although the pivotal study was not powered for subgroup analyses, the primary effectiveness data from this study suggest a reduced treatment effect in women, as compared with observed outcomes in men. For further information, see Section 10.3.5 Results (Subgroup Analysis – Gender).

7 DRUG INFORMATION

7.1 Mechanism of Action

The mechanism by which the LUTONIX® Catheter inhibits neointimal growth as seen in preclinical studies has not been established. The LUTONIX® Catheter coating contains paclitaxel, an anti-mitotic pharmaceutical agent that specifically binds to and stabilizes microtubules. Paclitaxel has been reported in prior studies to inhibit smooth muscle cell and fibroblast proliferation and migration as well as secretion of extracellular matrix.

7.2 Drug Interactions

Formal drug interaction studies have not been conducted with the LUTONIX® Catheter, and therefore consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to use the LUTONIX® Catheter. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

7.3 Carcinogenicity, Genotoxicity, and Reproductive Toxicology

No long-term studies in animals have been performed to evaluate the carcinogenic potential of the drug paclitaxel or of the LUTONIX® Catheter, and there are no adequate and well-controlled studies published in pregnant women or in men intending to father children. Paclitaxel inhibits cell proliferation by interacting with microtubules, and one consequence is the loss of whole chromosomes during cell division. This indirect action is consistent with positive responses in vitro and in vivo micronucleus genotoxicity assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT.

Studies performed in rats and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 7 and 22 times the dose provided by the LUTONIX® Catheter coated with 9.7 mg paclitaxel (7mm x 220mm balloon) adjusted for body weight). The drug resulted in increased resorptions and increased fetal deaths. No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (a daily dose of approximately 7 times the dose of the LUTONIX® Catheter (7mm x 220mm), adjusted for bodyweight).

The treating physician should balance the potential medical benefits of the LUTONIX® Catheter against these genotoxic and reproductive risks.

8 POTENTIAL ADVERSE EVENTS

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

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, not described in the above source, which may be unique to the paclitaxel drug coating include:

- Allergic/immunologic reaction to the drug coating (paclitaxel)
- 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

9 PATIENT COUNSELING INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with a PTA procedure
- Discuss the risks associated with a paclitaxel coated PTA catheter
- Discuss the risks/benefits issues for this particular patient
- Post-procedure antithrombotic regimen
- Discuss alteration to current lifestyle immediately following the procedure and over the long term

10 SUMMARY OF CLINICAL STUDIES

10.1 Late Mortality Signal for Paclitaxel-Coated Devices

A meta-analysis of randomized controlled trials published in December 2018 by Katsanos et. al. identified an increased risk of late mortality at 2 years and beyond for paclitaxel-coated balloons and paclitaxel-eluting stents used to treat femoropopliteal arterial disease. In response to these data, FDA performed a patient-level meta-analysis of long-term follow-up data from the pivotal premarket randomized trials of paclitaxel-coated devices used to treat femoropopliteal disease using available clinical data through May 2019. The meta-analysis also showed a late mortality signal in study subjects treated with paclitaxel-coated devices compared to patients treated with uncoated devices. Specifically, in the 3 randomized trials with a total of 1090 patients and available 5-year data, the crude mortality rate was 19.8% (range 15.9% - 23.4%) in patients treated with paclitaxel-coated devices compared to 12.7% (range 11.2% - 14.0%) in subjects treated with uncoated devices. The relative risk for increased mortality at 5 years was 1.57 (95% confidence interval 1.16 – 2.13), which corresponds to a 57% relative increase in mortality in patients treated with paclitaxel-coated devices. As presented at the June 2019 FDA Advisory Committee Meeting, an independent meta-analysis of similar patient-level data provided by VIVA Physicians, a vascular medicine organization, reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80). Additional analyses have been conducted and are underway that are specifically designed to assess the relationship of mortality to paclitaxel-coated devices.

The presence and magnitude of the late mortality risk should be interpreted with caution because of multiple limitations in the available data, including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.
Paclitaxel-coated balloons and stents improve blood flow to the legs and decrease the likelihood of repeat procedures to reopen blocked blood vessels compared to uncoated devices. The benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality).

In the LEVANT 2 randomized study (n=316 DCB and n=160 PTA), Kaplan Meier mortality estimates at 2, 3, and 5 years are 7.4% (95% confidence interval 4.9% - 11.0%), 10.2% (7.2% - 14.2%), and 19.2% (15.1% - 24.2%), respectively, for the Lutonix DCB treatment device and 5.3% (2.7% - 10.3%), 6.0% (3.2% - 11.2%), and 12.3% (8.0% - 18.9%), respectively, for the PTA control device. Additional information regarding long-term outcomes can be found in the sections below.

Clinical Data Overview
The safety and effectiveness of the LUTONIX® Catheter is derived from the pivotal IDE trial, the LEVANT 2 safety studies, LUTONIX® Long Lesion SFA study, and the LUTONIX® SFA ISR study. The LEVANT 1 multicenter randomized European trial and the Global SFA Real-World registry provided additional supporting information but was not considered part of the primary data set supporting approval.

The two-year results from the LEVANT 1 trial, 5 year results from the LEVANT 2 randomized pivotal IDE trial and the Global SFA Real-World registry, the two year results from the LEVANT 2 Safety registry, and the 3 year results from the LUTONIX® Long Lesion SFA study and the LUTONIX® SFA ISR study are presented below.

10.2 LEVANT 1 Multi-Center Clinical Study (Europe)

The LEVANT I trial was performed outside the United States at 9 clinical sites in Belgium and Germany. The objective of this Clinical Study was to assess the safety and effectiveness of the LUTONIX® Catheter for treatment of stenosis of the femoropopliteal arteries by direct comparison to standard balloon angioplasty (POBA). The primary endpoint was angiographic late lumen loss (LLL) at 6 months, as determined by an independent angiographic core lab analysis. Secondary Endpoints were also studied and are as follows Safety (Device related adverse events at 30 days), Device Success; Procedural Success; Primary patency of treated segment at 6, 12 and 24 months; Target Lesion Revascularization (TLR) at 6, 12 and 24 months; Target Vessel Revascularization (TVR) at 6, 12 and 24 months; Change in ankle-brachial index (ABI) from pre-procedure to 6, 12 and 24 months; Change in Rutherford classification from pre-procedure to 6, 12 and 24 months and Changes in Walking Impairment Questionnaire results from pre-procedure to 6, 12 and 24 months.

This trial enrolled subjects presenting with clinical evidence of claudication or critical limb ischemia and an angiographically significant lesion in the femoropopliteal arteries. Pre-dilatation using a standard PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 100% of subjects. After pre-dilatation, subjects were stratified based on pre-defined criteria to undergo stenting with post-dilatation PTA or PTA-only with provisional bail-out stenting. Subjects in each stratification group were then randomized to treatment with either the LUTONIX® Catheter (test arm) or standard balloon angioplasty (POBA control arm). One hundred one (n=101) subjects were enrolled in this study, randomized 1:1 to LUTONIX® Catheter (n=49) and Plain Old Balloon Angioplasty or POBA (n=52). Balloon sizes for the LUTONIX® Catheter ranged from 5.0 – 6.0 mm in diameter and 60 – 100 mm in length.

Safety information at 30 days was available for 97 of 101 subjects, including 49/49 (100%) LUTONIX® Catheter and 48/52 (92%) control POBA subjects. A total of 69 Adverse Events were reported through the 30 day follow-up period. Of these, serious adverse events (SAEs) were reported in 9 (18%) subjects in the LUTONIX® Catheter arm and 10 subjects (19%) in the POBA arm (p = 0.91). There were no Adverse Events through 30 days attributed as “related” or “probably related” to the LUTONIX® Catheter. There was one index limb amputation in the test arm and one death reported in the control arm, both independently adjudicated as unrelated to the device or the procedure.

The Primary Endpoint of mean late lumen loss in the analysis segment at 6 months was 0.46 ± 1.13 mm in the LUTONIX® Catheter arm compared to 1.09 ± 1.07mm in the POBA arm (p = 0.016). The LUTONIX® Catheter demonstrated significantly less late lumen loss at 6 months and similar safety through 24 months by direct comparison to conventional balloon angioplasty. The difference between arms was not significant in the stent group, with late loss of 0.49 ± 1.01 for LUTONIX® vs. 0.90 ± 0.91 for POBA, p = 0.373. Based on freedom from angiographic binary restenosis, primary patency of the treated segment was 28 of 39 (71.8%) for LUTONIX® Catheter and 17 of 35 (48.6%) for POBA at 6 months. The primary objective was met, and the angiographic and clinical results of the LEVANT I trial demonstrate the

feasibility of use of the LUTONIX® Catheter for treatment of femoropopliteal lesions.

The LUTONIX® Catheter performed comparably to conventional POBA in the LEVANT I Trial, with similar AE and SAE rates through 24 months. There were no unanticipated adverse device effects in the drug-coated balloon arm, and overall adverse event rates were similar to conventional uncoated balloon angioplasty. The percentage of subjects with any death, amputation, or target lesion thrombosis was 8% for LUTONIX® Catheter compared to 12% for control POBA at study completion.

10.3 LEVANT 2 Multi-Center Clinical Study (Pivotal Study)

10.3.1 Objective

The primary objective of the LEVANT 2 clinical study was to assess the safety and effectiveness of the LUTONIX® DCB for treatment of stenosis or occlusion of the superficial femoral and popliteal arteries.

10.3.2 Study Design

This study was conducted as a prospective, multicenter, single blind, 2:1 (test:control) randomized trial comparing the LUTONIX® DCB to standard balloon angioplasty for treatment of femoropopliteal arteries.

For the primary endpoints, safety was defined as a composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb reintervention, and index-limb-related death. The primary safety endpoint was tested using Farrington-Manning test for non-inferiority of proportions (a one-sided test at a significance level of 0.025).

H_0: The proportion of subjects with safety events in the Test group through 12-months post-index procedure is clinically inferior to that of the Control group.
H_1: The proportion of subjects with safety events in the Test group through 12-months post-index procedure is clinically non-inferior to that of the Control group.

$$\mathbf{H_0: P_{TEST} - P_{CONTROL} \geq 0.05 \quad vs. \quad H_1: P_{TEST} - P_{CONTROL} < 0.05}$$

Where *P* is the rate of the primary safety endpoint at 12 months post-index procedure.

Effectiveness was defined as 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 effectiveness endpoint was tested for superiority of LUTONIX® DCB compared to the standard PTA, using chi-square test for inequality of binomial proportions at a two-sided significance level of 0.05.

H_0: The proportion of subjects with effectiveness events in the Control group through 12-months post-index procedure is equal to that of the Test group.
H_1: The proportion of subjects with effectiveness events in the Control group through 12-months post-index procedure is not equal to that of the Test group.

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

Where *P* is the rate of the primary patency at 12 months post-index procedure.

Secondary endpoints were also studied and include the following:

Hypothesis Tested Secondary Endpoints:

The following secondary endpoints were prespecified for hypothesis testing if both primary objectives passed. The testing of the secondary objectives were performed in a hierarchical fashion in the order listed below to ensures that the study-wide Type 1 error rate is 0.05 when all of the secondary endpoints are tested at α=0.05.

- Superiority of TLR at 12 months.
- Superiority of TVR at 12 months.
- Superiority of composite events (all-cause death at 30 days, and amputation, index-limb reintervention, and index-limb-related death) at 12 months.
- Non-inferiority (with 5% delta) of the composite events (all-cause death at 30 days, and amputation, index-limb reintervention, and index-limb-related death) at 24 months.
- Superiority of primary patency (absence of target lesion restenosis and freedom from TLR) at 24 months.
- Superiority of TLR at 24 months.
- Superiority of TVR at 24 months.
- Superiority of the composite events (all-cause death at 30 days, and amputation, index-limb reintervention, and index-limb-related death) at 24 months.
- Statistical difference in the number of post-index procedure hospital days for PAD treatment through 24 months.

Effectiveness Secondary Endpoints (Evaluated at 6, 12 and 24 months):

- Acute Device, Technical, and Procedural success
- Primary and Secondary Patency
- Alternative Primary and Secondary Patency based on alternative definitions of Duplex Ultrasound (DUS)-derived patency: PSVR <2.0, <2.5 and <3.0
  - DUS Clinical Patency
- 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
- Change in Walking Impairment Questionnaire from baseline
- Change in Six Minute Walk Test from baseline in a subset of patients
- Change in quality of life from baseline, as measured by EQ-5D and SF36-v2 Surveys

Safety Secondary Endpoints:

- Freedom at 30 days from all-cause death, index limb amputation above the ankle and target vessel revascularization (TVR; VIVA Safety Endpoint)
- Composite of freedom from all-cause perioperative (≤30 day) death and freedom from the following at 1, 6, 24, 36, 48, and 60 months: index limb amputation, index limb re-intervention, and index-limb-related death.
- The following endpoints were to be assessed at 1, 6, 12, 24, 36, 48 and 60 months:
  - All-cause death
  - Amputation (above the ankle)-Free Survival (AFS)
  - Target Vessel Revascularization (TVR)
  - Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature
  - Major vascular complications
  - Readmission for cardiovascular events

10.3.3 Demographics

Following informed consent, 476 subjects were randomized 2:1 to the LUTONIX® DCB (n=316) and PTA (n=160) arms. Of these subjects, frequency of diabetes were similar in both groups (43.4%-DCB vs. 41.9%-PTA), and there was a similar frequency of prior stroke (11.4% -DCB vs. 11.3%-PTA). Overall, comorbidities at baseline was well-matched and representative of the patient population with peripheral vascular disease. **Table 3** presents baseline patient demographics for the LEVANT 2 subjects. Pre-dilatation using a standard PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 100% of subjects.

Table 3. Demographics

Variable	Test DCB	Control PTA	P-value[1]
Age (years), Mean ± SD (n) median (min, max)	67.8 ± 10.0 (316) 68.2 (44.5, 91.4)	69.0 ± 9.0 (160) 69.0 (41.5, 89.4)	0.209
Gender, % (n/N)			0.216
Female	38.9% (123/316)	33.1% (53/160)	
Male	61.1% (193/316)	66.9% (107/160)	
Ethnicity, % (n/N)			0.741
Hispanic or Latino	7.9% (25/316)	8.8% (14/160)	
Not Hispanic or Latino	91.8% (290/316)	91.3% (146/160)	
Patient chose not to respond	0.3% (1/316)	0.0% (0/160)	
Race, % (n/N)			0.160
Asian	1.3% (4/316)	2.5% (4/160)	
Black or African American	3.8% (12/316)	8.1% (13/160)	
Patient chose not to respond	4.1% (13/316)	4.4% (7/160)	
White	90.8% (287/316)	85.0% (136/160)	
Height (cm), Mean ± SD (n) median (min, max)	169.3 ± 10.3 (316) 170.0 (135.0, 194.0)	170.3 ± 10.1 (160) 171.5 (142.0, 190.0)	0.335
Weight (kg), Mean ± SD (n) median (min, max)	83.1 ± 17.0 (316) 82.0 (42.0, 146.0)	82.5 ± 17.1 (160) 80.0 (48.0, 133.0)	0.709
BMI (kg/m^2), Mean ± SD (n) median (min, max)	29.0 ± 5.3 (316) 28.5 (15.8, 52.7)	28.3 ± 4.8 (160) 27.9 (18.1, 48.5)	0.221
BMI>=30, % (n/N)	34.8% (110/316)	30.6% (49/160)	0.360
Smoking, % (n/N)			0.548
Current smoker	35.1% (111/316)	33.8% (54/160)	
Never smoked	20.9% (66/316)	17.5% (28/160)	
Previously smoked	44.0% (139/316)	48.8% (78/160)	
Dyslipidemia/Hypercholesterolemia, % (n/N)	89.6% (283/316)	86.3% (138/160)	0.286
Diabetes Mellitus, % (n/N)	43.4% (137/316)	41.9% (67/160)	0.758
Type			0.034
Type I	9.5% (13/137)	1.5% (1/67)	
Type II	90.5% (124/137)	98.5% (66/67)	
Insulin Dependency	40.9% (56/137)	40.3% (27/67)	0.937
Hypertension, % (n/N)	89.2% (282/316)	87.5% (140/160)	0.572
Renal Failure, % (n/N)	3.5% (11/316)	4.4% (7/160)	0.629
Congestive Heart Failure, % (n/N)	5.7% (18/316)	3.1% (5/160)	0.217
Previous CAD, % (n/N)	49.7% (157/316)	48.1% (77/160)	0.748
Previous MI, % (n/N)	19.9% (63/316)	17.5% (28/160)	0.523
Chronic Angina, % (n/N)	4.7% (15/316)	5.0% (8/160)	0.903
History of Coronary Revascularization, % (n/N)	41.8% (132/316)	38.8% (62/160)	0.526
Type of Coronary Revascularization			0.429
CABG	45.2% (47/104)	52.1% (25/48)	
PCI	54.8% (57/104)	47.9% (23/48)	
Previous Cerebrovascular Event, % (n/N)	11.4% (36/316)	11.3% (18/160)	0.963
Ischemic	75.0% (27/36)	100.0% (18/18)	0.020
Hemorrhagic	5.6% (2/36)	0.0% (0/18)	0.308
Previous Target Limb Intervention, % (n/N)	23.4% (74/316)	17.5% (28/160)	0.137
Target Vessel Type			0.292

Variable	Test DCB	Control PTA	P-value[1]
DeNovo Target Vessel	83.9% (265/316)	87.5% (140/160)	
Restenosed Target Vessel	16.1% (51/316)	12.5% (20/160)	
Rutherford Grade, % (n/N)			0.521
2	29.4% (93/316)	34.4% (55/160)	
3	62.7% (198/316)	57.5% (92/160)	
4	7.9% (25/316)	8.1% (13/160)	
ABI of Target Limb, Mean ± SD (n) median (min, max)	0.74 ± 0.20 (306) 0.73 (0.00, 1.38)	0.73 ± 0.18 (156) 0.73 (0.00, 1.17)	0.467
ABI of Contralateral Limb, Mean ± SD (n) median (min, max)	0.87 ± 0.23 (301) 0.92 (0.00, 1.34)	0.87 ± 0.20 (152) 0.89 (0.00, 1.30)	0.783

[1] T-tests for means and X^2-tests for proportions

Baseline angiographic data indicate that the LUTONIX® DCB and control PTA subjects were well-balanced with respect to lesions treated, lesion length, diameter of stenosis, lesion class, classification, occlusion, location, and other lesion-specific measures. See **Table 4**.

Table 4. Baseline Angiographic Data

Variable[1]	Test DCB	Control PTA	P-value[2]
Number of Lesions Treated, % (n/N)			0.400
1	98.1% (310/316)	96.9% (155/160)	
2	1.9% (6/316)	3.1% (5/160)	
Total Target Lesion Length (mm, core lab), Mean ± SD (n) median (min, max)	62.7 ± 41.4 (315) 51.5 (5.7, 196.7)	63.2 ± 40.4 (160) 51.8 (7.5, 173.7)	0.900
Total Target Lesion Length (mm, site), Mean ± SD (n) median (min, max)	69.6 ± 43.8 (316) 70.0 (1.0, 150.0)	69.6 ± 43.9 (160) 70.0 (2.0, 150.0)	0.987
Treated Length (mm), Mean ± SD (n) median (min, max)	107.9 ± 47.0 (316) 105.3 (29.9, 233.9)	107.9 ± 49.4 (160) 103.4 (23.3, 307.7)	0.988
Maximum Percent Stenosis, %DS, Mean ± SD (n) median (min, max)	80.5 ± 14.8 (316) 81.0 (40.0, 100.0)	80.9 ± 14.9 (160) 82.0 (45.0, 100.0)	0.776
Average RVD (mm), Mean ± SD (n) median (min, max)	4.8 ± 0.8 (316) 4.7 (3.0, 7.5)	4.8 ± 0.8 (160) 4.7 (2.8, 7.1)	0.981
Target Limb, % (n/N)			0.841
Left	52.8% (167/316)	51.9% (83/160)	
Right	47.2% (149/316)	48.1% (77/160)	
Lesion Class TASC II, % (n/N)			0.398
A	76.3% (241/316)	75.6% (121/160)	
B	21.5% (68/316)	23.8% (38/160)	
C	2.2% (7/316)	0.6% (1/160)	
Calcification, % (n/N)	59.2% (187/316)	58.1% (93/160)	0.826
Severe Calcification	10.4% (33/316)	8.1% (13/160)	0.419
Total Occlusion, % (n/N)	20.6% (65/316)	21.9% (35/160)	0.741
Number of Patent Run-Off Vessels, Mean ± SD (n) median (min, max)	2.1 ± 1.0 (316) 2.0 (0.0, 3.0)	1.9 ± 1.0 (160) 2.0 (0.0, 3.0)	0.148
Number of Patent Run-Off Vessels (Categorical), % (n/N)			0.539
0	9.5% (30/316)	13.1% (21/160)	
1	15.2% (48/316)	16.9% (27/160)	
2	35.4% (112/316)	35.0% (56/160)	
3	39.9% (126/316)	35.0% (56/160)	
Most Distal Lesion Location, % (n/N)			0.495
Proximal SFA	9.2% (29/316)	8.1% (13/160)	

Variable[1]	Test DCB	Control PTA	P-value[2]
Mid SFA	51.3% (162/316)	45.6% (73/160)	
Distal SFA	29.7% (94/316)	38.8% (62/160)	
Proximal Popliteal	4.7% (15/316)	4.4% (7/160)	
Mid Popliteal	4.1% (13/316)	2.5% (4/160)	
Distal Popliteal	0.9% (3/316)	0.6% (1/160)	
Most Distal Lesion Location Rank[3], Mean ± SD (n) median (min, max)	2.46 ± 0.94 (316) 2.00 (1.00, 6.00)	2.49 ± 0.85 (160) 2.00 (1.00, 6.00)	0.721

[1]All values per angiographic core lab except where indicated
[2] T-tests for means and X^2-tests for proportions
[3] Lesion locations are ranked 1-6 from least to most distal, in the order displayed.

10.3.4 Methods

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 were enrolled. Study subjects received a baseline angiogram to confirm an angiographically significant lesion in the superficial femoral or popliteal artery. After protocol-defined pre-dilatation, subjects who were likely to have successful revascularization using PTA balloon (i.e., were unlikely to require a stent) were randomized 2:1 to LUTONIX® DCB (test) or standard PTA (control). Subjects who did not meet the protocol-defined criteria after pre-dilatation were treated per standard practice and followed for safety through 30 days. Baseline clinical and angiographic data were collected on a web-based standardized electronic case report forms. Clinical and Angiographic outcomes we assessed by quantitative analysis at a designated (blinded) core laboratory. All suspected SAEs and device failures/malfunctions were adjudicated by an independent (blinded) Clinical Events Committee.

Intent-to-treat (ITT) population, which includes all those who were enrolled and randomized, was pre-specified as the primary analysis population. An analysis based on the per-protocol population, which excludes patients with pre-specified major protocol deviations, was performed as an additional analysis to further support the results from the primary analysis. All ITT patients received the randomized treatment; therefore, the as-treated population, analyzed according to the actual treatment received regardless of the randomization assignment, was the same as the ITT population.

10.3.5 Results

A total of 476 patients (316 LUTONIX® DCB and 160 control PTA) were enrolled and randomized from 54 clinical sites. Balloon sizes for the LUTONIX® DCB ranged from 4.0 – 6.0 mm in diameter and 40 – 100 mm in length.

Results for the primary safety and effectiveness endpoints of The LEVANT 2 clinical study are described and summarized in **Table 5**. Under the ITT population among completers, 84.3% of the patients in the Test LUTONIX® DCB group were free from the primary safety event, compared to 79.5% of the Control PTA group. The lower bound of the 95% confidence interval of the rate difference was greater than -5% (5% non-inferiority margin); therefore, the objective of the primary safety endpoint was met. For the primary effectiveness endpoint, 66.0% of the patients in the LUTONIX® DCB group had primary patency at 12 months compared to 54.0% in the Control PTA group. The 95% confidence interval excluded 0 (no difference); therefore, the objective for the primary effectiveness was met.

In addition, the effect of lesion length on patency was analyzed by comparing the patency rates between the treatment and control groups as a function of lesion length subsets. The results did not indicate any clinically meaningful effect of lesion length on patency out to the maximum indicated lesion length.

Table 5. Summary of Primary Endpoints at 12 Months (ITT completers)

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value
Freedom from Primary Safety Event[1]	84.3% (242/287) [80.1,88.5]	79.5% (116/146) [72.9,86.0]	4.8% [-3.8,3.1]	<0.001[2]
Primary Patency[3]	66.0% (177/268) [60.4, 71.7]	54.0% (74/137) [45.7, 62.4]	12.0% [1.9, 22.1]	0.019 [4]

[1] Primary Safety is defined as a 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.
[2] P-value and CI for difference based on a Farrington-Manning method. Confidence intervals for groups are asymptotic. Margin of non-inferiority 5%.
[3] Primary Patency is defined as freedom from target lesion restenosis (defined by DUS core lab adjudication) and target lesion revascularization (TLR).
[4] Based on asymptotic likelihood ratio test. CIs for groups and difference are asymptotic.

Figure 5 and **Figure 6** provide primary safety and primary patency rates through 24 months (respectively) using a time-to-event Kaplan-Meier survival analysis. Note that the 24 month values are secondary endpoints and that the study was not powered for secondary endpoints. For the primary effectiveness endpoint, the primary patency rate is greater for the LUTONIX® DCB group than the Control PTA group.

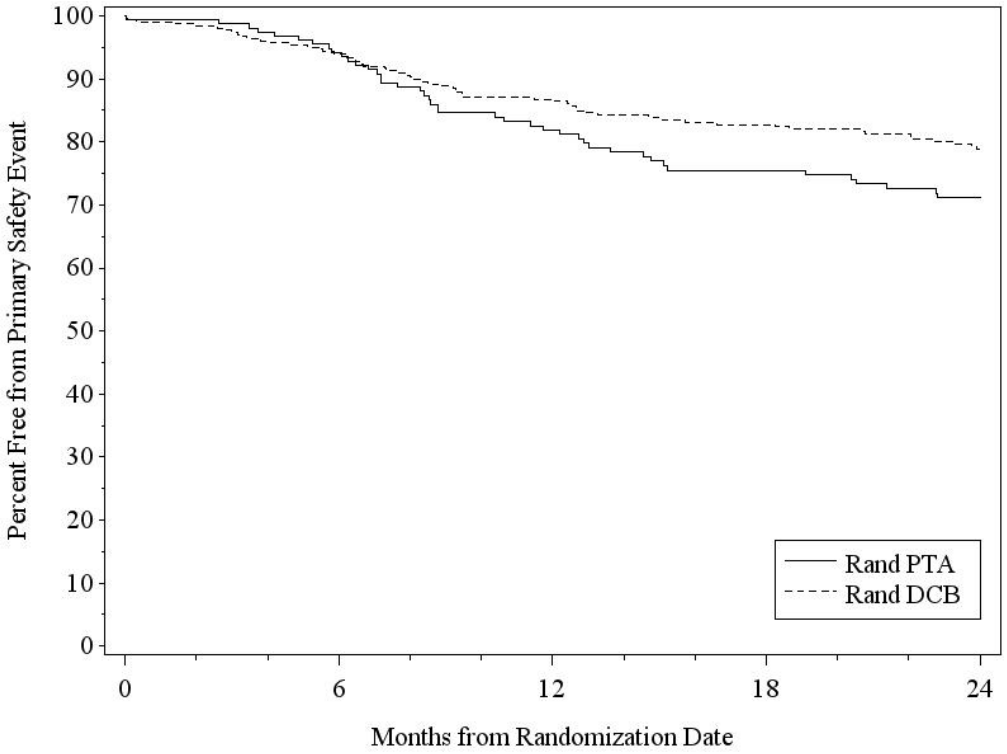


Figure 5. Primary Safety Rate 24 Months by Kaplan-Meier

Table 6. Primary Safety Rate 24 Months by Kaplan-Meier

Time	Test DCB				Control PTA			
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk
30 days	99.0%	3	9	304	99.4%	1	4	155
183 days	94.0%	18	21	277	94.1%	9	11	140
365 days	86.8%	39	33	244	81.9%	27	14	119
730 days	78.9%	60	52	204	71.1%	42	21	97

[1] Survival is the absence of the composite endpoint of failure from all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.

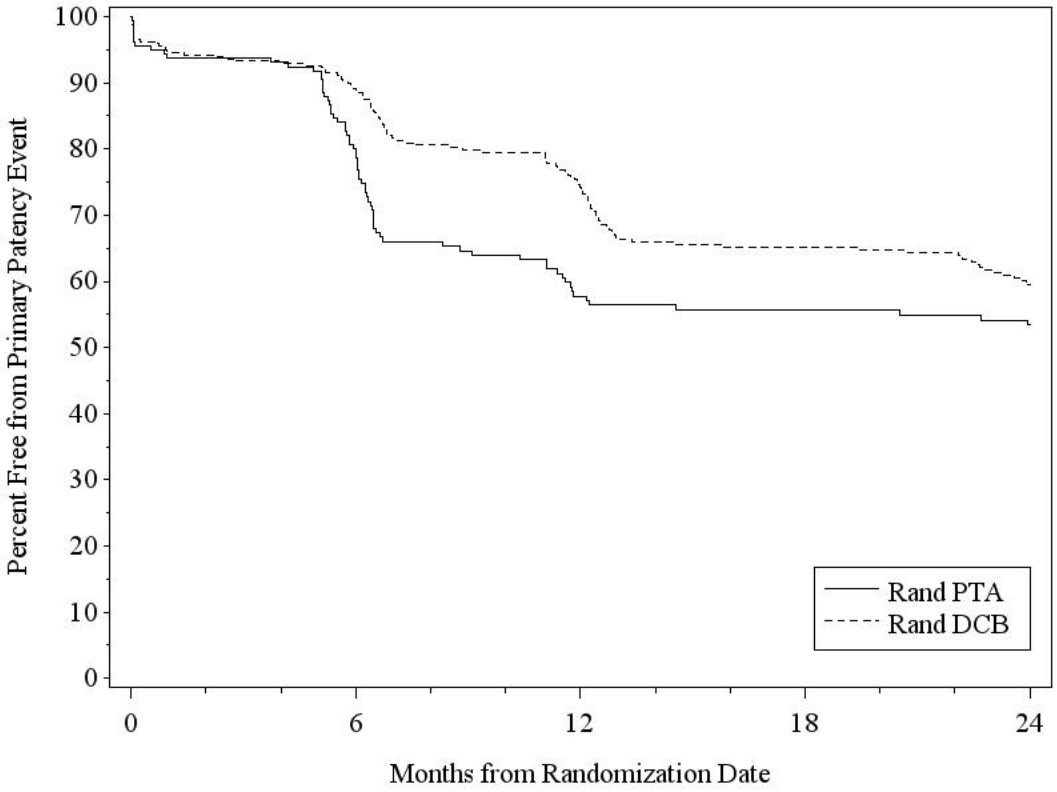


Figure 6. Primary Patency Rate 24 Months by Kaplan-Meier

Table 7. Primary Patency Rate 24 Months by Kaplan-Meier

Time	Test DCB				Control PTA			
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk
30 days	94.6%	17	9	290	93.7%	10	3	147
183 days	88.9%	34	21	261	78.7%	33	9	118
365 days	73.9%	77	32	207	57.8%	64	12	84
730 days	59.0%	117	47	152	53.4%	70	19	71

[1] Survival of Primary Patency is defined as the absence of target lesion restenosis (defined by core lab adjudication) and freedom from target lesion revascularization (TLR).

Table 8 describes results from the first three (ordered) secondary endpoints. Following the hierarchical method, no pre-specified secondary endpoint met their objectives since the first ordered secondary endpoint (Total TLR at 12 months) failed to meet its objective. The results for the next two secondary endpoints are presented for informational purpose only.

Table 8. Summary of Hypothesis Tested Secondary Endpoints at 12 Months

Measure	Test DCB %(n/N)	Control PTA %(n/N)	Difference %
Total TLR	12.2% (35/286)	16.4% (24/146)	-4.2%
Total TVR	13.3% (38/286)	17.8% (26/146)	-4.5%
Composite Safety Events[1]	15.7% (45/287)	20.5% (30/146)	-4.8%

[1] The composite event is all-cause death at 30 days, and amputation, index-limb re-intervention, or index-limb-related death at 12 months. One test patient who exited after a non-TVR safety event is included.

Secondary Descriptive Endpoints

Several secondary endpoints were also analyzed but were not hypothesis tested. Procedural success (< 30% residual stenosis without SAE) was similar for LUTONIX® DCB 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 and 24 months in both treatment groups – see **Table 9** below. Improvements in ABI, six minute walk test, EQ-5D, and SF-36v2 through 24 months were similar for both groups.

Table 9. Secondary Endpoints – Functional Outcomes

Functional Outcome	Device	Scores, Mean (n)		
		Baseline	12 months	24 months
Rutherford Scores	Lutonix DCB	2.8 (316)	0.8 (263)	0.8 (240)
	Control PTA	2.7 (160)	1.0 (131)	1.0 (122)
Walking Impairment Scores	Lutonix DCB	32.3 (312)	57.3 (264)	56.1 (238)
	Control PTA	34.2 (155)	53.8 (133)	52.8 (124)
Ankle-Brachial Index	Lutonix DCB	0.74 (306)	0.91 (264)	0.87 (235)
	Control PTA	0.73 (156)	0.90 (128)	0.91 (116)
Six Minute Walk Test	Lutonix DCB	306.3 (301)	356.3 (252)	366.7 (222)
	Control PTA	295.6 (151)	341.9 (125)	358.6 (110)
Quality of Life (EQ-5D Index)	Lutonix DCB	0.73 (301)	0.82 (263)	0.81 (233)
	Control PTA	0.71 (154)	0.79 (131)	0.80 (123)

Primary patency was also assessed using alternative Doppler thresholds for restenosis – see **Table 10** below. Results of an alternative analysis of primary patency in which only TLRs that were clinically-driven were counted as failures (rather than all TLRs) were identical to the primary effectiveness endpoint analysis at both 12 months and 24 months.

Table 10. Alternate Primary Patency

Primary Patency	Device	Primary Patency, % (n/N)	
		12 months	24 months
Core-Lab adjudicated (Primary Effectiveness)	Lutonix DCB	66.0% (177/268)	53.8% (136/253)
	Control PTA	54.0% (74/137)	47.2% (60/127)
By DUS PSVR ≥ 3.0	Lutonix DCB	69.1% (170/246)	54.0% (116/215)
	Control PTA	57.5% (73/127)	45.7% (48/105)
By DUS PSVR ≥ 2.5	Lutonix DCB	65.2% (161/247)	49.8% (109/219)
	Control PTA	53.1% (69/130)	39.3% (42/107)
By DUS PSVR ≥ 2.0	Lutonix DCB	54.1% (138/255)	40.2% (92/229)
	Control PTA	46.6% (62/133)	33.6% (38/113)

Secondary safety endpoints were similar for both LUTONIX® DCB and control PTA – see **Table 11** below.

Table 11. Secondary Safety Endpoints

Secondary Safety	Visit	Secondary Safety; %(n/N)	
		Lutonix DCB	Control PTA
Freedom from Composite Safety Events[1]	12 Months	84.3% (242/287)	79.5% (116/146)
	24 Months	76.0% (203/267)	67.1% (94/140)
	36 Months	70.6% (180/255)	63.5% (87/137)
	48 Months	66.0% (161/244)	55.6% (74/133)
	60 Months	60.7% (136/224)	53.5% (69/129)
Death, All Cause	12 Months	2.4% (7/291)	2.7% (4/148)
	24 Months	7.5% (21/279)	5.7% (8/141)
	36 Months	10.9% (30/274)	7.2% (10/139)
	48 Months	17.0% (46/271)	10.2% (14/137)
	60 Months	21.1% (55/261)	12.8% (17/133)
Amputation Free Survival	12 Months	97.6% (284/291)	97.3% (144/148)
	24 Months	92.5% (258/279)	94.3% (133/141)
	36 Months	89.1% (244/274)	92.8% (129/139)
	48 Months	82.7% (224/271)	89.1% (122/137)
	60 Months	78.9% (206/261)	86.5% (115/133)

Secondary Safety	Visit	Secondary Safety; %(n/N)	
		Lutonix DCB	Control PTA
Reintervention for Thrombosis	12 Months	0.7% (2/286)	0.7% (1/144)
	24 Months	0.8% (2/261)	0.7% (1/134)
	36 Months	1.2% (3/246)	0.8% (1/131)
	48 Months	1.3% (3/229)	0.8% (1/124)
	60 Months	1.4% (3/208)	0.9% (1/116)
Cardiovascular Hospitalization	12 Months	9.4% (27/286)	6.9% (10/144)
	24 Months	16.6% (44/265)	15.6% (21/135)
	36 Months	18.2% (46/253)	17.4% (23/132)
	48 Months	19.2% (46/240)	18.3% (23/126)
	60 Months	20.5% (46/224)	19.3% (23/119)
Major Vascular Complications	12 Months	7.0% (20/286)	4.8% (7/145)
	24 Months	9.8% (26/266)	7.4% (10/135)
	36 Months	11.9% (30/253)	9.8% (13/132)
	48 Months	13.6% (33/242)	10.3% (13/126)
	60 Months	14.7% (33/224)	10.9% (13/119)

[1] The composite event is all-cause death at 30 days, and amputation, index-limb re-intervention, or index-limb-related death at 12 months.

Subgroup Analysis - Gender

LEVANT 2 pivotal study was not powered to statistically examine differences in results between subgroups. However, the primary effectiveness data from this study suggest a reduced treatment effect in women, as compared with observed outcomes in men. See **Table 12** for Primary Endpoints at 1 year by gender.

Table 12. Primary Endpoints at 1 Year by Gender

Primary Endpoint	Gender	Test DCB %(n/N)	Control PTA %(n/N)	Difference %
Primary Effectiveness	Female	57.3% (59/103)	63.0% (29/46)	-5.7%
	Male	71.5% (118/165)	49.5% (45/91)	22.0%
Primary Safety	Female	80.4% (90/112)	68.1% (32/47)	12.3%
	Male	86.9% (152/175)	84.8% (84/99)	2.1%

Adverse Events - LEVANT 2 Clinical Experience

A total of 476 subjects were enrolled in the LEVANT 2 randomized clinical study at 54 clinical sites across the United States (US) and Europe (EU). The study randomized subjects in 2:1 ratio to the LUTONIX® DCB or standard uncoated PTA. The primary objective of the study was to assess the safety and effectiveness of the LUTONIX® DCB for treatment of stenosis or occlusion of the superficial femoral and popliteal arteries compared to the standard PTA.

Table 13 provides a summary of the Serious Adverse Events (SAE) observed in the LEVANT 2 randomized pivotal trial as determined by the Clinical Events Committee (CEC). A serious adverse event is defined as an event that led to death or led to a serious deterioration in the health of the subject; resulted in a life-threatening illness or injury; resulted in a permanent impairment of a body structure or a body function; required in-subject hospitalization or prolongation of existing hospitalization; or resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

Table 13. Serious Adverse Events at 24 months

Site-Reported Serious Adverse Events		DCB Subjects	Control PTA
AE Category	Event Description	N=316 % (n subjects)	N=160 % (n subjects)
Access Site Complication	Arterial occlusion puncture site	0.3% (1)	0.0% (0)
	Hematoma / bleeding puncture site - major	0.9% (3)	0.6% (1)
	Hematoma / bleeding puncture site - minor	1.3% (4)	0.0% (0)
	Pseudo aneurysm	1.3% (4)	1.3% (2)
	Puncture site infection	0.3% (1)	0.0% (0)
	Vascular perforation / rupture	0.3% (1)	0.0% (0)
	Retroperitoneal bleed	0.3% (1)	0.6% (1)
	Significant blood loss	0.0% (0)	0.0% (0)
Cardiovascular	Acute coronary syndrome	2.2% (7)	1.3% (2)
	Angina, stable	7.9% (25)	5.0% (8)
	Angina, unstable	2.8% (9)	3.1% (5)
	Arrhythmia - Bradycardia	2.2% (7)	1.9% (3)
	Arrhythmia - Tachycardia	0.9% (3)	3.8% (6)
	Arrhythmia - Other	3.8% (12)	6.3% (10)
	Cardiogenic shock	0.6% (2)	0.6% (1)
	Chronic heart failure	5.4% (17)	5.0% (8)
	Death	2.2% (7)	0.6% (1)
	Hypertension	3.2% (10)	6.3% (10)
	Hypotension	1.6% (5)	0.0% (0)
	Myocardial infarction	6.3% (20)	10.6% (17)
	Other Cardiovascular	16.1% (51)	12.5% (20)
Endocrine System	Diabetes Mellitus, Type I	0.3% (1)	0.0% (0)
	Diabetes Mellitus, Type II	1.3% (4)	1.3% (2)
	Hyperthroidism	0.3% (1)	0.0% (0)
	Hypothroidism	0.3% (1)	0.0% (0)
	Other Endocrine system	1.6% (5)	1.3% (2)
Gastrointestinal	Cholecystitis	0.3% (1)	2.5% (4)
	Colon carcinoma	0.0% (0)	1.3% (2)
	Diarrhea	0.6% (2)	3.8% (6)
	Epigastric pain	0.0% (0)	1.9% (3)
	Gastritis	0.6% (2)	0.6% (1)
	Gastrointestinal bleeding	5.1% (16)	5.0% (8)
	Nausea	0.6% (2)	0.6% (1)
	Other infectious / inflammator	0.6% (2)	1.3% (2)
	Pancreatitis	1.3% (4)	1.9% (3)
	Peritonitis	0.0% (0)	0.6% (1)
	Constipation	0.9% (3)	1.3% (2)
	Other Gastrointestinal	6.3% (20)	6.9% (11)
Infectious	Local infection	2.2% (7)	5.0% (8)
	Septicemia / bacteremia	1.6% (5)	0.6% (1)
	Other Infectious	2.5% (8)	1.9% (3)
Neurological / Nervous System	Confusion	0.3% (1)	1.9% (3)
	Death	0.3% (1)	0.0% (0)

Site-Reported Serious Adverse Events		DCB Subjects	Control PTA
AE Category	Event Description	N=316 % (n subjects)	N=160 % (n subjects)
	Depression	0.6% (2)	0.6% (1)
	Dizziness / vertigo	0.6% (2)	0.6% (1)
	Fainting / syncope	1.6% (5)	1.9% (3)
	Peripheral nervous system complication	0.6% (2)	0.6% (1)
	Seizure	0.6% (2)	0.6% (1)
	Stroke - hemorrhagic	0.6% (2)	0.6% (1)
	Stroke - ischemic	4.4% (14)	1.9% (3)
	TIA	2.8% (9)	1.3% (2)
	Other Neurological / nervous system	4.1% (13)	4.4% (7)
Respiratory	Bronchitis	1.6% (5)	1.3% (2)
	Carcinoma	2.8% (9)	1.9% (3)
	COPD	2.5% (8)	1.3% (2)
	Cough	0.3% (1)	0.0% (0)
	Death	0.0% (0)	0.6% (1)
	Dyspnea	2.5% (8)	1.3% (2)
	Hypoxia	2.2% (7)	0.0% (0)
	Other respiratory	5.7% (18)	3.8% (6)
	Pneumonia	9.2% (29)	4.4% (7)
	Pneumothorax	0.3% (1)	0.0% (0)
	Pulmonary edema	0.9% (3)	0.0% (0)
	Pulmonary embolism	0.6% (2)	0.0% (0)
Skeletal, Spine and muscular system	Arthralgia	1.3% (4)	0.0% (0)
	Arthritis	1.3% (4)	1.3% (2)
	Back pain	2.5% (8)	2.5% (4)
	Fracture (bone)	3.5% (11)	6.3% (10)
	Hernia	2.5% (8)	0.0% (0)
	Osteomyelitis	1.3% (4)	1.3% (2)
	Tendonitis	0.3% (1)	0.0% (0)
	Claudication	0.9% (3)	3.8% (6)
	Other Skeletal, spine and muscular system	8.5% (27)	7.5% (12)
Systematic complication	Anaphylatic reaction	0.6% (2)	0.6% (1)
	Other Systematic complication	0.3% (1)	0.0% (0)
Target Lesion	Aneurysm	0.0% (0)	0.6% (1)
	Atherosclerosis	0.9% (3)	1.3% (2)
	Dissection	0.9% (3)	2.5% (4)
	Occlusion / closure	1.9% (6)	1.9% (3)
	Restenosis	18.7% (59)	20.6% (33)
	Thrombus - in-lesion	1.3% (4)	0.6% (1)
	Other Target lesion	0.3% (1)	0.0% (0)
Target vessel	Atherosclerosis	1.3% (4)	2.5% (4)
	Dissection	0.0% (0)	0.0% (0)
	Occlusion / closure	1.9% (6)	3.1% (5)
	Perforation	0.3% (1)	0.0% (0)

Site-Reported Serious Adverse Events		DCB Subjects	Control PTA
AE Category	Event Description	N=316 % (n subjects)	N=160 % (n subjects)
	Restenosis	5.1% (16)	11.3% (18)
	Thrombus - in-lesion	0.0% (0)	1.3% (2)
	Other Target vessel	1.3% (4)	0.6% (1)
Genito-urinary system	Bladder infection	0.9% (3)	0.0% (0)
	Kidney stones	0.9% (3)	0.0% (0)
	Prostate carcinoma	0.6% (2)	0.6% (1)
	Prostate hypertrophy	0.9% (3)	0.0% (0)
	Renal failure / insufficiency	5.1% (16)	5.6% (9)
	Urinary infection	2.2% (7)	3.1% (5)
	Urinary retention	0.3% (1)	0.6% (1)
	Other Genito-urinary system	2.8% (9)	3.1% (5)
Various	Abscess	0.6% (2)	0.0% (0)
	Amputation	0.6% (2)	0.6% (1)
	Atypical chest pain	0.9% (3)	1.3% (2)
	Carcinoma (not specified elsewhere)	7.6% (24)	3.1% (5)
	Death (non-cardiac or neurological)	2.5% (8)	0.6% (1)
	Fatigue	0.3% (1)	1.3% (2)
	Fever	0.6% (2)	0.0% (0)
	Hematuria	0.3% (1)	0.0% (0)
	Sepsis	0.9% (3)	0.6% (1)
	Other	19.0% (60)	13.1% (21)
Vessel specific complications in the leg (not target lesion or target vessel)	Aneurysm	1.3% (4)	0.6% (1)
	Arterial occlusion	3.2% (10)	5.6% (9)
	Arterial thrombosis	1.3% (4)	1.3% (2)
	Atherosclerosis	3.8% (12)	6.9% (11)
	Dissection	0.6% (2)	0.0% (0)
	Embolism	0.6% (2)	0.0% (0)
	Perforation	0.3% (1)	0.0% (0)
	Restenosis	8.2% (26)	13.8% (22)
	Stent thrombosis (definite)	0.6% (2)	1.3% (2)
	Stent thrombosis (possible)	0.3% (1)	0.6% (1)
	Venous occlusion	0.3% (1)	0.0% (0)
	Venous thrombosis	0.3% (1)	1.3% (2)
	Ischemia	0.0% (0)	1.3% (2)
	Stenosis	11.7% (37)	14.4% (23)
	Other Vessel Specific	1.9% (6)	1.3% (2)
Total	Total	78.8% (249)	78.1% (125)

Pharmacokinetics Substudy

The pharmacokinetics of paclitaxel following treatment with the LUTONIX® Catheter was evaluated in a subset of patients randomized to the LUTONIX® Catheter arm in the LEVANT 2 clinical study who received varied doses in the 1.3 mg – 5 mg range (n=22 subjects). All subjects had detectable serum paclitaxel immediately after the index procedure that decreased to less than 3 ng/mL within one hour. The pharmacokinetics of paclitaxel following treatment generally exhibited a bi-exponential decay; characterized by a rapid distribution phase followed by a log-linear elimination phase. Group mean (SD) values for the pharmacokinetic parameters C_{max}, AUC_{all}, and MRT_{last} were 5.10 (3.21) ng/mL, 8.39 (4.00) ng*h/mL, and 2.13 (1.84) h. Mean elimination half-life values were 6.88 h for evaluable subjects.

10.4 LEVANT 2 Safety Registry

10.4.1 Objective

The primary objective of the LEVANT Safety Registry was to collect additional safety and effectiveness data on the LUTONIX® DCB in a large population.

10.4.2 Study Design

The primary endpoint of the LEVANT Safety Registry is to determine the rate of unanticipated device- or drug- related adverse events over time through 60 months. This study is supportive of LEVANT 2 and aimed at identifying any rare unanticipated safety events in addition to serious adverse events reported in LEVANT 2. This includes downstream embolic events and reintervention for thrombotic events. Secondary endpoints include the primary endpoints and most of the secondary endpoints of the LEVANT 2 Randomized Controlled Trial (RCT). Composite safety (freedom from all-cause perioperative death and index limb-related reintervention, amputation, and death) and primary patency are assessed at each time point. Other secondary endpoints include device and procedural success, primary patency based on alternative DUS criteria for restenosis, secondary patency, total and clinically-driven target lesion revascularization (TLR), change-in-Rutherford Class and change-in-ABI. Safety endpoints also include the composite VIVA safety endpoint (freedom from death, amputation, and TVR at 30 days), all-cause death, amputation, AFS, target vessel revascularization (TVR), thrombosis, major vascular complications, and readmission for cardiovascular events.

10.4.3 Demographics

Following informed consent, 657 subjects were enrolled at 63 clinical sites across the United States and Europe (EU). Baseline characteristics and treated lesions were comparable to the randomized LEVANT 2 cohort. **Table 14** and **Table 15** present selected demographics and baseline angiographic data for the LEVANT 2 Randomized and LEVANT Safety Registry cohorts. Note: Data on the 56 LEVANT 2 Roll-in subjects are also included. Pre-dilatation using a standard PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 99.4% of the LEVANT 2 safety registry subjects.

Table 14. Selected Demographics

Variable	LEVANT 2 Roll-in DCB	LEVANT 2 Randomized DCB	LEVANT 2 Safety Registry DCB	All DCB
Age (years), Mean ± SD (n) median (min, max)	69.2 ± 9.6 (56) 68.2 (46.9, 89.3)	67.8 ± 10.0 (316) 68.2 (44.5, 91.4)	68.7 ± 9.5 (657) 68.8 (41.6, 93.8)	68.4 ± 9.7 (1029) 68.6 (41.6, 93.8)
Gender, % (n/N)				
Female	39.3% (22/56)	38.9% (123/316)	36.2% (238/657)	37.2% (383/1029)
Male	60.7% (34/56)	61.1% (193/316)	63.8% (419/657)	62.8% (646/1029)
Ethnicity, % (n/N)				
Hispanic or Latino	3.6% (2/56)	7.9% (25/316)	1.8% (12/657)	3.8% (39/1029)
Not Hispanic or Latino	94.6% (53/56)	91.8% (290/316)	98.2% (645/657)	96.0% (988/1029)
Patient chose not to respond	1.8% (1/56)	0.3% (1/316)	0.0% (0/657)	0.2% (2/1029)
Race, % (n/N)				
American Indian or Alaska native	0.0% (0/56)	0.0% (0/316)	0.2% (1/657)	0.1% (1/1029)
Asian	0.0% (0/56)	1.3% (4/316)	0.3% (2/657)	0.6% (6/1029)
Black or African American	5.4% (3/56)	3.8% (12/316)	5.0% (33/657)	4.7% (48/1029)
Native Hawaiian or other Pacific Islander	0.0% (0/56)	0.0% (0/316)	0.2% (1/657)	0.1% (1/1029)
Patient chose not to respond	0.0% (0/56)	4.1% (13/316)	0.3% (2/657)	1.5% (15/1029)
White	94.6% (53/56)	90.8% (287/316)	94.1% (618/657)	93.1% (958/1029)
Height (cm), Mean ± SD (n) median (min, max)	169.5 ± 10.9 (56) 171.5 (148.0, 188.0)	169.3 ± 10.3 (316) 170.0 (135.0, 194.0)	169.5 ± 9.2 (657) 170.0 (134.0, 193.0)	169.4 ± 9.6 (1029) 170.0 (134.0, 194.0)
Weight (kg), Mean ± SD (n) median (min, max)	80.4 ± 18.3 (56) 81.5 (40.0, 126.0)	83.1 ± 17.0 (316) 82.0 (42.0, 146.0)	80.4 ± 16.7 (657) 79.0 (37.0, 154.0)	81.3 ± 16.9 (1029) 80.0 (37.0, 154.0)
BMI (kg/m^2), Mean ± SD (n) median (min, max)	27.8 ± 5.2 (56) 27.7 (18.1, 47.7)	29.0 ± 5.3 (316) 28.5 (15.8, 52.7)	27.9 ± 5.0 (657) 27.5 (13.0, 46.4)	28.3 ± 5.1 (1029) 27.7 (13.0, 52.7)

Table 15. Baseline Angiographic Data (All DCB Population)

Variable	LEVANT 2 Roll-in DCB	LEVANT 2 Randomized DCB	LEVANT 2 Safety Registry DCB	All DCB
Number of Lesions Treated, % (n/N)				
1	98.2% (55/56)	98.1% (310/316)	94.7% (611/645)	96.0% (976/1017)
2	1.8% (1/56)	1.9% (6/316)	5.3% (34/645)	4.0% (41/1017)

Variable	LEVANT 2 Roll-in DCB	LEVANT 2 Randomized DCB	LEVANT 2 Safety Registry DCB	All DCB
Total Target Lesion Length (mm, core lab), Mean ± SD (n) median (min, max)	83.8 ± 48.0 (56) 74.7 (11.2, 200.0)	62.7 ± 41.4 (315) 51.5 (5.7, 196.7)	55.5 ± 40.3 (645) 43.4 (5.5, 224.8)	59.3 ± 41.6 (1016) 47.9 (5.5, 224.8)
Total Target Lesion Length (mm, site), Mean ± SD (n) median (min, max)	80.9 ± 45.0 (56) 80.0 (1.0, 150.0)	69.6 ± 43.8 (316) 70.0 (1.0, 150.0)	67.3 ± 45.4 (656) 60.0 (3.0, 265.0)	68.8 ± 44.9 (1028) 60.0 (1.0, 265.0)
Treated Length (mm), Mean ± SD (n) median (min, max)	122.6 ± 45.7 (56) 114.1 (39.4, 231.9)	107.9 ± 47.0 (316) 105.3 (29.9, 233.9)	104.9 ± 48.6 (644) 104.6 (30.7, 242.3)	106.8 ± 48.1 (1016) 105.1 (29.9, 242.3)
Maximum Percent Stenosis, %DS, Mean ± SD (n) median (min, max)	83.1 ± 13.6 (56) 83.5 (48.0, 100.0)	80.5 ± 14.8 (316) 81.0 (40.0, 100.0)	82.5 ± 13.5 (645) 83.0 (40.0, 100.0)	81.9 ± 14.0 (1017) 82.0 (40.0, 100.0)
Average RVD (mm), Mean ± SD (n) median (min, max)	4.5 ± 0.7 (56) 4.5 (3.1, 6.6)	4.8 ± 0.8 (316) 4.7 (3.0, 7.5)	4.8 ± 0.7 (645) 4.7 (3.0, 7.1)	4.8 ± 0.8 (1017) 4.7 (3.0, 7.5)
Target Limb, % (n/N)				
Left	50.0% (28/56)	52.8% (167/316)	47.2% (310/657)	49.1% (505/1029)
Right	50.0% (28/56)	47.2% (149/316)	52.8% (347/657)	50.9% (524/1029)
Lesion Class TASC II, % (n/N)				
A	64.3% (36/56)	76.3% (241/316)	79.7% (514/645)	77.8% (791/1017)
B	30.4% (17/56)	21.5% (68/316)	17.8% (115/645)	19.7% (200/1017)
C	5.4% (3/56)	2.2% (7/316)	2.3% (15/645)	2.5% (25/1017)
D	0.0% (0/56)	0.0% (0/316)	0.2% (1/645)	0.1% (1/1017)
Calcification, % (n/N)	60.7% (34/56)	59.2% (187/316)	66.0% (426/645)	63.6% (647/1017)
Severe Calcification	19.6% (11/56)	10.4% (33/316)	13.0% (84/645)	12.6% (128/1017)
Total Occlusion, % (n/N)	26.8% (15/56)	20.6% (65/316)	21.9% (144/657)	21.8% (224/1029)
Number of Patent Run-Off Vessels, Mean ± SD (n) median (min, max)	1.9 ± 1.1 (56) 2.0 (0.0, 3.0)	2.1 ± 1.0 (316) 2.0 (0.0, 3.0)	1.9 ± 1.0 (645) 2.0 (0.0, 3.0)	1.9 ± 1.0 (1017) 2.0 (0.0, 3.0)
Number of Patent Run-Off Vessels (Categorical), % (n/N)				
0	17.9% (10/56)	9.5% (30/316)	13.3% (86/645)	12.4% (126/1017)
1	12.5% (7/56)	15.2% (48/316)	15.3% (99/645)	15.1% (154/1017)
2	30.4% (17/56)	35.4% (112/316)	40.8% (263/645)	38.5% (392/1017)
3	39.3% (22/56)	39.9% (126/316)	30.5% (197/645)	33.9% (345/1017)
Most Distal Lesion Location, % (n/N)				
Proximal SFA	12.5% (7/56)	9.2% (29/316)	8.4% (54/645)	8.8% (90/1017)
Mid SFA	55.4% (31/56)	51.3% (162/316)	41.7% (269/645)	45.4% (462/1017)
Distal SFA	25.0% (14/56)	29.7% (94/316)	35.2% (227/645)	32.9% (335/1017)
Proximal Popliteal	1.8% (1/56)	4.7% (15/316)	8.7% (56/645)	7.1% (72/1017)
Mid Popliteal	5.4% (3/56)	4.1% (13/316)	5.4% (35/645)	5.0% (51/1017)
Distal Popliteal	0.0% (0/56)	0.9% (3/316)	0.6% (4/645)	0.7% (7/1017)
Most Distal Lesion Location Rank[2], Mean ± SD (n) median (min, max)	2.32 ± 0.92 (56) 2.00 (1.00, 5.00)	2.46 ± 0.94 (316) 2.00 (1.00, 6.00)	2.63 ± 0.99 (645) 2.00 (1.00, 6.00)	2.56 ± 0.97 (1017) 2.00 (1.00, 6.00)

[1] All values per angiographic core lab except where indicated.
[2] Lesion locations are ranked 1-6 from least to most distal, in the order displayed

10.4.4 Methods

Similar to the LEVANT 2 Randomized Pivotal study, this registry study enrolled 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 were required to meet the same baseline angiographic and post pre-dilatation criteria prior to receiving LUTONIX® DCB treatment. Subjects with target lesions that, after baseline angiography, do not meet all inclusion/exclusion criteria and are not pre-dilated per protocol were considered screen failures and not enrolled. Subjects were considered enrolled in the study after being consented and the defined pre-dilatation balloon inflation had begun. Subjects that did not meet post-pre-dilatation criteria were not treated with LUTONIX® DCB but instead were treated per standard practice and followed for safety for 30 days. Subjects

treated with the study device were scheduled for clinical visits at 1, 6, 12 and 24 months, and by phone annually through 5 years thereafter. Baseline clinical and angiographic data were collected on a web-based standardized electronic case report forms. Clinical and Angiographic outcomes we assessed by quantitative analysis at a designated core laboratory. All suspected SAEs and device failures/malfunctions were adjudicated an independent Clinical Events Committee.

10.4.5 Results

As this study is on-going, safety related data set are presented at this time and include data from the LEVANT 2 (including Roll-in subjects) and the LEVANT Safety Registry. At this writing, there are no unanticipated device- or drug-related adverse events as of reporting date - for an observed incidence rate of 0%, the upper bound of the one-sided 95% CI = 0.4% at 12 months. Additional, supportive, data are presented below.

10.4.5.1 Secondary Endpoints

Composite safety endpoint results are summarized in **Table 16** by cohort. For all DCB-treated patients, the proportion of subjects meeting the composite safety endpoint was 99.4% at 1 month, 96.0% at 6 months and 90.5% at 12 months.

Table 16. Composite Safety Endpoint Success Rate by Time point (All DCB Population)

Freedom from Safety Event[1]	Roll-in DCB %(n/N) [95% CI][2]	Randomized DCB %(n/N) [95% CI][2]	Registry DCB %(n/N) [95% CI][2]	All DCB %(n/N) [95% CI][2]
1 Month	100.0% (54/54) [100.0, 100.0]	99.0% (305/308) [97.9, 100.0]	98.6% (638/647) [97.7, 99.5]	98.8% (997/1009) [98.1, 99.5]
6 Months	96.1% (49/51) [90.8, 100.0]	92.0% (275/299) [88.9, 95.1]	94.2% (596/633) [92.3, 96.0]	93.6% (920/983) [92.1, 95.1]
12 Months	91.7% (44/48) [83.8, 99.5]	84.3% (242/287) [80.1, 88.5]	84.3% (525/623) [81.4, 87.1]	84.7% (811/958) [82.4, 86.9]
24 Months	86.0% (37/43) [75.7, 96.4]	76.0% (203/267) [70.9, 81.2]	73.3% (434/592) [69.7, 76.9]	74.7% (674/902) [71.9, 77.6]

[1] Composite freedom from safety events, including all-cause peri-operative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death
[2] Asymptotic confidence interval based on the normal approximation.

Secondary endpoints are tabulated in **Table 17** below. For the combined all-DCB cohort, the 12 month rates are death (1.4%), amputation (0.1%), AFS (98.6%), TVR (8.3%), thrombosis (0.1%) and cardiovascular hospitalizations (10.2%), and major vascular complications (3.6%).

Table 17. Secondary Safety Endpoints by Time point (All DCB Population)

Outcome Measure (CEC Adjudicated)	Visit	Roll-in DCB %(n/N)	Randomized DCB %(n/N)	Registry DCB %(n/N)	All DCB %(n/N)
Death	1 Month	0.0% (0/54)	0.0% (0/308)	0.2% (1/647)	0.1% (1/1009)
	6 Months	3.8% (2/53)	0.7% (2/301)	0.6% (4/636)	0.8% (8/990)
	12 Months	6.0% (3/50)	2.4% (7/291)	1.3% (8/626)	1.9% (18/967)
	24 Months	8.5% (4/47)	7.5% (21/279)	3.5% (21/601)	5.0% (46/927)
	36 Months	15.2% (7/46)	10.9% (30/274)	7.6% (45/592)	9.0% (82/912)
	48 Months	17.8% (8/45)	17.0% (46/271)	11.5% (67/585)	13.4% (121/901)
	60 Months	20.0% (9/45)	21.1% (55/261)	14.5% (83/573)	16.7% (147/879)
Major Amputation	1 Month	0.0% (0/54)	0.0% (0/308)	0.0% (0/646)	0.0% (0/1008)
	6 Months	0.0% (0/51)	0.3% (1/299)	0.0% (0/630)	0.1% (1/980)
	12 Months	0.0% (0/48)	0.3% (1/287)	0.0% (0/620)	0.1% (1/955)
	24 Months	0.0% (0/43)	0.4% (1/262)	0.2% (1/585)	0.2% (2/890)
	36 Months	0.0% (0/39)	0.4% (1/247)	0.4% (2/557)	0.4% (3/843)
	48 Months	0.0% (0/37)	0.9% (2/230)	0.8% (4/524)	0.8% (6/791)
	60 Months	0.0% (0/36)	1.0% (2/209)	1.2% (6/495)	1.1% (8/740)
Minor Amputation	1 Month	0.0% (0/54)	0.0% (0/308)	0.2% (1/646)	0.1% (1/1008)
	6 Months	0.0% (0/51)	0.0% (0/298)	0.2% (1/630)	0.1% (1/979)
	12 Months	0.0% (0/48)	0.0% (0/286)	0.2% (1/620)	0.1% (1/954)
	24 Months	0.0% (0/43)	0.4% (1/261)	0.3% (2/584)	0.3% (3/888)
	36 Months	0.0% (0/39)	0.8% (2/246)	0.5% (3/556)	0.6% (5/841)

Outcome Measure (CEC Adjudicated)	Visit	Roll-in DCB %(n/N)	Randomized DCB %(n/N)	Registry DCB %(n/N)	All DCB %(n/N)
	48 Months	2.7% (1/37)	0.9% (2/230)	1.1% (6/523)	1.1% (9/790)
	60 Months	2.8% (1/36)	1.0% (2/208)	1.2% (6/493)	1.2% (9/737)
Amputation-Free Survival (AFS)	1 Month	100.0% (54/54)	100.0% (308/308)	99.8% (646/647)	99.9% (1008/1009)
	6 Months	96.2% (51/53)	99.3% (298/300)	99.4% (632/636)	99.2% (981/989)
	12 Months	94.0% (47/50)	97.6% (284/291)	98.7% (618/626)	98.1% (949/967)
	24 Months	91.5% (43/47)	92.5% (258/279)	96.3% (580/602)	94.9% (881/928)
	36 Months	84.8% (39/46)	89.1% (244/274)	92.2% (547/593)	90.9% (830/913)
	48 Months	82.2% (37/45)	82.7% (224/271)	88.0% (515/585)	86.1% (776/901)
	60 Months	80.0% (36/45)	78.9% (206/261)	84.7% (487/575)	82.7% (729/881)
Total TVR	1 Month	0.0% (0/54)	0.6% (2/308)	0.4% (4/646)	0.6% (6/1008)
	6 Months	3.9% (2/51)	6.7% (20/298)	4.1% (26/632)	4.9% (48/891)
	12 Months	8.3% (4/48)	13.3% (38/286)	13.4% (83/621)	13.1% (125/955)
	24 Months	14.0% (6/43)	21.4% (57/266)	24.4% (144/589)	23.1% (207/898)
	36 Months	15.4% (6/39)	26.5% (67/253)	29.6% (167/565)	28.0% (240/857)
	48 Months	21.6% (8/37)	31.5% (76/241)	33.9% (184/542)	32.7% (268/820)
	60 Months	25.0% (9/36)	37.1% (82/221)	36.7% (192/523)	36.3% (283/780)
Reintervention for Thrombosis	1 Month	0.0% (0/54)	0.6% (2/308)	0.0% (0/646)	0.2% (2/1008)
	6 Months	0.0% (0/51)	0.7% (2/298)	0.0% (0/632)	0.2% (2/981)
	12 Months	0.0% (0/48)	0.7% (2/286)	0.2% (1/620)	0.3% (3/954)
	24 Months	0.0% (0/43)	0.8% (2/261)	0.5% (3/584)	0.6% (5/888)
	36 Months	0.0% (0/39)	1.2% (3/246)	0.7% (4/557)	0.8% (7/842)
	48 Months	0.0% (0/37)	1.3% (3/229)	0.8% (4/523)	0.9% (7/789)
	60 Months	0.0% (0/36)	1.4% (3/208)	1.0% (5/494)	1.1% (8/738)
Cardiovascular Hospitalization	1 Month	1.9% (1/54)	0.0% (0/308)	0.8% (5/647)	0.6% (6/1009)
	6 Months	5.9% (3/51)	5.7% (17/298)	5.2% (33/634)	5.4% (53/983)
	12 Months	8.3% (4/48)	9.4% (27/286)	9.1% (57/623)	9.2% (88/957)
	24 Months	18.6% (8/43)	16.6% (44/265)	10.1% (60/592)	12.4% (112/900)
	36 Months	22.5% (9/40)	18.2% (46/253)	10.6% (60/565)	13.4% (115/858)
	48 Months	23.1% (9/39)	19.2% (46/240)	11.3% (60/533)	14.2% (115/812)
	60 Months	23.7% (9/38)	20.5% (46/224)	11.9% (60/506)	15.0% (115/768)
Major Vascular Complications[1]	1 Month	3.7% (2/54)	4.2% (13/308)	1.9% (12/648)	2.7% (27/1010)
	6 Months	3.8% (2/52)	5.7% (17/298)	3.1% (20/635)	4.0% (39/985)
	12 Months	4.1% (2/49)	7.0% (20/286)	4.7% (29/623)	5.3% (51/958)
	24 Months	13.6% (6/44)	9.8% (26/266)	7.9% (47/592)	8.8% (79/902)
	36 Months	14.6% (6/41)	11.9% (30/253)	9.0% (51/567)	10.1% (87/861)
	48 Months	15.0% (6/40)	13.6% (33/242)	9.8% (53/539)	11.2% (92/821)
	60 Months	15.4% (6/39)	14.7% (33/224)	10.5% (54/513)	12.0% (93/776)

[1] Major Vascular Complication is defined as serious Hematoma 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.

10.5 Global SFA Real-World Registry (Europe)

10.5.1 Objective

The primary objective of the Global SFA Real-World registry was to demonstrate safety and assess the clinical use and outcomes of the LUTONIX® catheter in a heterogeneous patient population in real world clinical practice.

10.5.2 Study Design

The Global SFA Real-World registry is a prospective, global, multicenter, single arm registry with primary effectiveness endpoint of freedom from TLR at 12 month and primary safety endpoint of composite safety at 30 days (VIVA safety endpoint).

Following informed consent, 691 subjects were enrolled at 38 clinical sites across 10 European countries. Patient follow-up compliance through 12-month is 89.9% and follow-up through 24 months is 83.9%.

Table 18. Subject Disposition

Summary	Global SFA Registry
Total Enrolled, n	691
Follow-up by Visit, % (n/N) Month 1 Month 6 Month 12 Month 24	 97.1%, (671/691) 92.6%, (640/691) 89.9%, (621/691) 83.9%, (580/691)
Duration of Follow-up (Days), Mean ± SD (n)	726.4 ± 195.4 (691)

10.5.3 Baseline and Demographics

Table 19 and **Table 20** presents selected demographics and baseline angiographic data. Pre-dilatation using a standard PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 64.9% of subjects and final procedure bailout spot stenting occurred in 25.2% of the subjects.

Table 19. Selected Demographics

Summary	Global SFA Registry (N=691)
Age (Years), Mean ± SD (n)	68.2 ± 9.86 (691)
Gender - Male, % (n/N)	67.9% (469/691)
BMI (kg/m2), Mean ± SD (n)	27.2 ± 4.23 (665)
Smoker, % (n/N) Current Smoker Previous Smoker	 36.9% (254/689) 34.7% (239/689)
Hypertension, % (n/N)	84.9% (587/691)
Dyslipidemia, % (n/N)	70.0% (484/691)
Diabetes, % (n/N)	39.5% (273/691)
History of Vascular Disease, % (n/N)	66.0% (456/691)
Prior PAD intervention in index leg, % (n/N)	53.8% (196/364)
History of Cardiac Diseases, % (n/N)	35.6% (246/691)
History of Chronic Renal Disease, % (n/N)	13.5% (93/691)
Rutherford Category, % (n/N) 0 1 2 3 4 5 6	 1.2% (8/689) 2.3% (16/689) 20.6% (142/689) 66.9% (461/689) 7.4% (51/689) 1.5% (10/689) 0.1% (1/689)
ABI of Target Limb[1], Mean ± SD (n)	0.69 ± 0.24 (470)
ABI of Contralateral Limb[1], Mean ± SD (n)	0.86 ± 0.23 (465)

[1] Pressure ratios > 1.4 were excluded.

Table 20. Baseline Angiographic Data (All DCB Population)

Summary	Global SFA Registry (N=691)
Number of Treated Lesions, % (n/N) 1 2 3 4	 84.4% (583/691) 13.9% (96/691) 1.6% (11/691) 0.1% (1/691)
Total Target Lesion (mm, Site), Mean ± SD (n)	101.2 ± 84.2 (685)

Summary	Global SFA Registry (N=691)
Treated Length (mm, Site), Mean ± SD (n)	136.6 ± 89.7 (689)
Stenosis (%DS, Site), Mean ± SD (n)	90.0 ± 11.0 (686)
CTO, % (n/N)	31.2% (214/686)
Average RVD (mm, Site), Mean ± SD (n)	5.2 ± 0.67 (681)
Calcification, % (n/N)	50.2% (238/474)
TASC II Lesion Class, % (n/N) A B C D	 46.8% (231/494) 33.4% (165/494) 13.2% (65/494) 6.7% (33/494)
Number of Patent Runoff Vessels, Mean ± SD (n)	2.3 ± 0.78 (691)

Table 21. Procedural Data

Summary	Global SFA Registry (N=691)
Contralateral Access, % (n/N)	52.2% (361/691)
Vessel Preparation	
Predilatation Performed, % (n/N)	64.9% (448/690)
%DS Post Predilatation, Mean ± SD (n)	39.2 ± 23.32 (425)
Dissection During Pre-DCB Dilatation, % (n/N)	30.1% (135/448)
Dissection Grade During Pre-DCB Dilatation, % (n/N) A B C D E F	 21.6% (29/134) 35.1% (47/134) 26.9% (36/134) 10.4% (14/134) 5.2% (7/134) 0.7% (1/134)
Atherectomy, % (n/N)	1.3% (9/691)
Others, % (n/N)	0.1% (1/691)
Study Device Treatment	
Inflation Time per Balloon (sec), Mean ± SD (n)	108.4 ± 39.54 (676)
Balloon Pressure (atm), Mean ± SD (n)	9.5 ± 2.16 (674)
Balloon to Vessel Ratio (Inflated Diameter/RVD), Mean ± SD (n)	1.00 ± 0.09 (681)
%DS Post-DCB, Mean ± SD (n)	17.8 ± 20.51 (678)
Dissection Post-Study Treatment, % (n/N)	38.0% (262/690)
Dissection Post-Study Treatment Grade, % (n/N) A B C D E F	 39.5% (103/261) 30.3% (79/261) 19.5% (51/261) 6.1% (16/261) 3.4% (9/261) 1.1% (3/261)
Final Procedure Outcome	
Additional Lesion Treatments, % (n/N)	23.8% (164/690)
%DS Post Procedure, Mean ± SD (n)	14.6 ± 18.69 (680)
Dissection Post-Study Treatment, % (n/N)	18.4% (127/690)
Dissection Post-Study Treatment Grade, % (n/N) A B C D E F	 67.7% (86/127) 18.9% (24/127) 3.9% (5/127) 5.5% (7/127) 2.4% (3/127) 1.6% (2/127)
Bailout Spot Stenting, % (n/N)	25.2% (174/690)

Summary	Global SFA Registry (N=691)
Total Lesion Length of Bailout Spot Stent Patients[1] (mm), Mean ± SD (n)	131.0 ± 97.8 (161)
Total Bailout Spot Stent Length (mm), Mean ± SD (n)	128.5 ± 110.3 (166)

[1]Excludes lesion lengths < 10 mm

10.5.4 Methods

All subjects were consented to be followed for a minimum of 2 years. Subjects were treated per standard of care; there were no additional protocol treatments or exams required within this registry.

This registry was performed with devices approved under the CE Mark in Europe. The study device is the same as the device that is commercially available in the United States, with the exception of a broader indication for the CE Marked product.

This registry study enrolled subjects presenting with stenotic or obstructive lesions of the femoropopliteal artery and a patent outflow artery to the foot. Subjects were considered enrolled in the study after being consented and the treatment device has entered the subject's body. For each subject, clinical data and follow-up information at 1, 6, 12 and 24 months were reported. Subject contact was made either by a clinical visit or telephone.

All required clinical data were collected on a web-based standardized electronic case report forms. Monitoring was performed to ensure compliance. All SAEs were adjudicated by an independent Clinical Events Committee.

10.5.5 Results

Results through the 24 month follow-up are presented below. No hypothesis testing was pre-specified in this study.

10.5.5.1 Primary Effectiveness Endpoint

Primary effectiveness endpoint is defined as freedom from TLR at 12 months. Total of 648 subjects were evaluable for the primary effectiveness endpoint analysis. The 12 month TLR Free rate by subject counts at 12 months was 93.4% and was 89.3% at 24 months. The Kaplan-Meier estimates TLR-Free survival was 94.1% at 12 months and 90.3% at 24 months. TLR-Free survival by lesion location at 12 months was 94.7% (n=483) for SFA, 92.9% (n=86) for popliteal, and 92.3% (n=121) for patients with lesion in both SFA and popliteal.

Table 22. Primary Effectiveness Endpoint

Primary Effectiveness Endpoint	Success % (n/N)	95% CI[1]
Freedom from TLR at 12 months	93.4% (605/648)	91.2%, 95.2%

[1] Exact binomial confidence interval

10.5.5.2 Primary Safety Endpoint

The primary safety endpoint is defined as Freedom at 30 days from TVR, major index limb amputation, and device- and procedure-related death (VIVA safety endpoint). Total of 685 subjects were evaluable for the primary safety endpoint analysis. The success by subject counts was 99.4% for the primary safety endpoint. Freedom from primary safety events by Kaplan Meier estimates for 12 months was 92.1% and at 24 months was 86.7%. Note: Primary safety events beyond 30 days were included in the Kaplan-Meier analyses.

Table 23. Primary Safety Endpoint

Primary Safety Endpoint	Success % (n/N)	95% CI[1]
Freedom from primary safety events at 30-days (VIVA safety endpoint)	99.4% (681/685)	98.5%, 99.8%

[1] Exact binomial confidence interval

10.5.5.3 Secondary Effectiveness Endpoint

Primary Patency of the target lesion is by investigator assessment based on presenting symptoms and clinical exam and by absence of CEC adjudicated TLR event. A total of 614 subjects were evaluable for primary patency at 12 months and 532 subjects at 24 months. The primary patency success rate at 12 months as determined by subject counts was 83.1% and was 71.8% at 24 months. The primary patency rate for all subjects as measured by Kaplan-Meier estimates resulted in 85.4% for 12 months and 75.6% at 24 months.

Table 24. Secondary Endpoint Primary Patency at 12 Months

Secondary Effectiveness Endpoint	Success % (n/N)	95% CI[1]
Primary Patency at 12 Months	83.1% (510/614)	79.9%, 85.9%
Primary Patency at 24 Months	71.8% (382/532)	67.8%, 75.6%

[1] Exact binomial confidence interval

10.5.5.4 Secondary Safety Endpoint

An additional analysis was performed to determine the percent of subjects who were free from composite safety events of all-cause perioperative (≤30 day) death and index limb amputation, index limb re-intervention, and index limb related death at 12 months (LEVANT 2 primary safety endpoint). A total of 652 subjects were evaluable for the secondary safety endpoint analysis. The success rate from the composite safety events by subject count was

86.8% for all subjects at 12 months and was 80.2% at 24 months. The Kaplan –Meier method of analysis for the survival rate from the composite safety events was 88.4% at 12 months and 82.1% at 24 months.

Table 25. Secondary Safety Endpoint

Secondary Safety Endpoint	Success % (n/N)	95% CI[1]
Composite Safety Endpoint at 12 months (LEVANT 2 Primary Safety)	86.8% (566/652)	84.0%, 89.3%
Composite Safety Endpoint at 24 months	80.2% (477/595)	76.7%, 83.3%

[1] Exact binomial confidence interval

10.5.5.5 Subgroup Analysis

Additional analyses were performed to evaluate the outcomes by gender, long lesion, and ISR subgroup. Descriptive statistics of the outcomes are provided below.

Table 26. Subgroup Analysis

Description	Gender Subgroup		Long Lesion Subgroup (≥ 140 mm)	ISR Lesion Subgroup
	Female Gender	Male Gender		
	Success Rate - % (n/N)			
Primary Effectiveness Endpoint (Freedom from TLR @ 12m)	88.6% (186/210)	95.7% (419/438)	93.2% (123/132)	90.7% (78/86)
Freedom from TLR @ 24m	84.3% (161/191)	91.7% (365/398)	88.2% (105/119)	84.6% (66/78)
Primary Safety Endpoint (VIVA Safety Endpoint)	99.5% (217/218)	99.4% (464/467)	99.3% (138/139)	100.0% (88/88)
Secondary Effectiveness Endpoint (Primary patency at 12m)	77.7% (157/202)	85.7% (353/412)	74.6% (91/122)	80.7% (67/83)
Primary patency at 24m	66.7% (120/180)	74.4% (262/352)	61.3% (65/106)	61.1% (44/72)
Composite Safety at 12m (LEVANT 2 primary safety)	83.9% (177/211)	88.2% (389/441)	84.2% (112/133)	86.0% (74/86)
Composite Safety at 24m	76.7% (148/193)	81.8% (329/402)	76.7% (92/120)	75.6% (59/78)

Table 27. Primary Effectiveness Endpoint – Long Lesion Subgroup

Lesion Length	Success % (n/N)	95% CI[1]
Lesions ≥14 - 16 cm	92.3% (36/39)	79.1%, 98.4%
Lesions >16 - 20 cm	92.3% (36/39)	79.1%, 98.4%
Lesions >20 - 25 cm	91.7% (22/24)	73.0%, 99.0%
Lesions > 25 cm	96.7% (29/30)	82.8%, 99.9%
All Long Lesions (≥14 cm)	93.2% (123/132)	87.5%, 96.8%

[1] Exact binomial confidence interval.

Table 28. Primary Safety Endpoint - Long Lesion Subgroup

Lesion Length	Success % (n/N)	95% CI[1]
Lesions ≥14 - 16 cm	100.0% (41/41)	91.4%, 100.0%
Lesions >16 - 20 cm	100.0% (40/40)	91.2%, 100.0%
Lesions >20 - 25 cm	100.0% (27/27)	87.2%, 100.0%
Lesions > 25 cm	96.8% (30/31)	83.3%, 99.9%
All Long Lesions (≥14 cm)	99.3% (138/139)	96.1%, 100.0%

[1] Exact binomial confidence interval.

10.5.6 Discussion

While the defined primary endpoints of the Global SFA registry and the LEVANT 2 pivotal study are different (i.e. Primary effectiveness of Freedom from TLR for Global SFA registry vs. Primary Patency for LEVANT 2, etc), similar safety and effectiveness endpoints were evaluated in both studies – reference the **Table 29** below for comparison of the clinical outcomes.

Table 29. Comparison of Outcomes – Global SFA and LEVANT 2 pivotal study

Description	Global SFA Registry – Lutonix DCB	LEVANT 2 pivotal Study	
		Lutonix DCB	Standard PTA
	Success Rate - % (n/N)		
Freedom from TLR @ 12m	93.4% (605/648)	87.8% (251/286)	83.6% (122/146)
Composite Safety at 30-days (VIVA Safety Endpoint)[1]	99.4% (681/685)	99.4% (306/308)	99.4% (155/156)
Primary patency at 12m	83.1% (510/614)	66.0% (177/268)	54.0% (74/137)
Composite Safety at 12 m (LEVANT 2 primary safety)[2]	86.8% (566/652)	84.3% (242/287)	79.5% (116/146)

[1] Composite safety events (VIVA safety endpoints) are device- or procedure related death, TVR, or major amputation within 30 days.
[2] Composite safety events (LEVANT 2 primary safety) are all-cause perioperative (≤30 day) death and index limb amputation, index limb re-intervention, and index limb related death at 12 months.

As a European real-world registry, follow-ups for the Global SFA registry were performed per standard of care and allowed for clinical assessment by the physicians during clinical visit or by telephone. For the LEVANT 2 pivotal study, clinical visit and DUS evaluation were required through the 24 months follow-up. As compared to the real-world clinical results of the Global SFA registry, the effectiveness outcomes of the LEVANT 2 pivotal study are lower. It is believed that the primary reason for this difference is due to the requirement for DUS follow-ups during the LEVANT 2 pivotal study and the associated more stringent definition of binary restenosis (i.e. PSVR ≥ 2.5 as adjudicated by core-lab). The clinical results of the Global SFA registry represent the more real-world clinical results as the patient evaluation and treatment were performed per the clinically-driven symptoms per the standard of care practices. The LEVANT 2 pivotal study as a stringent controlled study is more robust for comparison between treatment options (LUTONIX® DCB vs. standard PTA).

10.6 LUTONIX® Long Lesion Study (Europe)

10.6.1 Objective

The primary objective of the LUTONIX® Long Lesion SFA study was to demonstrate safety and effectiveness of use of the LUTONIX® DCB for treatment of long TASC II Class C and D lesions (≥ 14 cm) in the femoropopliteal artery.

10.6.2 Study Design

The LUTONIX® Long Lesion SFA study is a prospective, global multicenter, single arm trial with primary effectiveness endpoint of primary patency at 12 month and primary safety endpoint of composite safety at 12 months.

Following informed consent, 118 DCB subjects were enrolled at 14 clinical sites across 5 European countries. Patient follow-up compliance was 89.0% at 12 months, 84.7% at 24 months, and 81.4% at 36 months.

Table 30. Subject Disposition

Summary	DCB Subjects
ITT Subjects (Enrolled Subjects), n	118
Follow-up by Visit, % (n/N) Month 1, % (n/N) Month 6, % (n/N) Month 12, % (n/N) Month 24, % (n/N) Month 36, % (n/N)	 98.3% (116/118) 89.0% (105/118) 89.0% (105/118) 84.7% (100/118) 81.4% (96/118)
Duration of Follow-up (Days), Mean ± SD (n)	978.7 ± 285.82 (118)

10.6.3 Baseline and Demographics

Table 31 and **Table 32** presents selected demographics and baseline angiographic data. Pre-dilatation using a standard PTA catheter was required as part of the clinical study to prepare the vessel and occurred in 98.3% of subjects and post-study device bailout spot stenting occurred in 39.8% of the subjects.

Table 31. Selected Demographics

Summary	DCB Subjects (N=118)
Age (Years), Mean ± SD (n)	67.6 ± 9.23 (118)
Gender - Male, % (n/N)	73.7% (87/118)
BMI (kg/m^2), Mean ± SD (n)	27.1 ± 4.48 (114)
Smoking Current Smoker Past Smoker	 41.5% (49/118) 28.8% (34/118)
Hypertension	86.4% (102/118)
Hyperlipidemia	30.5% (36/118)
Diabetes	36.4% (43/118)
History of Vascular Disease, % (n/N)	86.4% (102/118)
History of Cardiac Disease, % (n/N)	53.4% (63/118)
History of Renal Disease, % (n/N)	27.1% (32/118)
Baseline Target Limb Rutherford Grade, % (n/N) 0 2 3 4 5	 0.9% (1/116) 24.1% (28/116) 69.0% (80/116) 5.2% (6/116) 0.9% (1/116)
Baseline ABI of Target Limb, Mean ± SD (n)	0.69 ± 0.26 (111)

Table 32. Baseline Angiographic Data

Summary	DCB Subjects (N=118)
Number of Treated Lesions, % (n/N) 1 2	 92.4% (109/118) 7.6% (9/118)
Total Lesion Length (mm), Mean ± SD (n)	212.5 ± 68.32 (117)
Stenosis (%DS), Mean ± SD (n)	89.5 ± 14.00 (117)
CTO, % (n/N)	52.1% (61/117)
RVD (mm), Mean ± SD (n)	4.7 ± 0.76 (117)
Any Calcification, % (n/N)	88.1% (104/118)
Highest Severity of Calcification, % (n/N) Mild Moderate Severe	 21.2% (22/104) 57.7% (60/104) 21.2% (22/104)

Summary	DCB Subjects (N=118)
Highest TASC Classification, % (n/N) B C D	 0.8% (1/118) 77.1% (91/118) 22.0% (26/118)
Treated Lesion Locations, % (n/N) SFA, Proximal SFA, Mid SFA, Distal Popliteal, Proximal Popliteal, Mid Popliteal, Distal	 51.3% (60/117) 35.9% (42/117) 14.5% (17/117) 4.3% (5/117) 0.9% (1/117) 0.0% (0/117)
Number of Patent Run-off Vessels 2 3 4	 31.6% (37/117) 34.2% (40/117) 34.2% (40/117)

Table 33. Procedural Data

Summary	DCB Subjects (N=118)
Contralateral Access, % (n/N)	55.6% (65/117)
Vessel Preparation	
Predilatation Performed, % (n/N)	98.3% (116/118)
%DS Post Predilatation, Mean ± SD (n)	45.6 ± 13.8 (101)
Dissection During Pre-DCB Dilatation, % (n/N)	81.2% (82/101)
Dissection Grade During Pre-DCB Dilatation, % (n/N) A B C D	 56.1% (46/82) 30.5% (25/82) 12.2% (10/82) 1.2% (1/82)
Bailout Spot Stenting Performed, % (n/N)	6.9% (8/116)
Study Device Treatment	
Inflation Time per Balloon (sec), Mean ± SD (n)	137.4 ± 47.99 (118)
Transit Time per Balloon (sec), Mean ± SD (n)	30.5 ± 23.04 (112)
Balloon Pressure (atm), Mean ± SD (n)	8.6 ± 1.91 (117)
Treatment Overstretch (Inflated Diameter/RVD), Mean ± SD (n)	1.13 ± 0.19 (117)
Total Length Treated with DCB Balloons (mm, Site), Mean ± SD (n)	248.0 ± 70.48 (118)
%DS Post-DCB, Mean ± SD (n)	37.3 ± 13.91 (116)
Dissection Post-Study Treatment, % (n/N)	81.9% (95/116)
Dissection Grade Post-Study Treatment, % (n/N) A B C D	 50.5% (48/95) 40.0% (38/95) 7.4% (7/95) 2.1% (2/95)
Bailout Spot Stenting Post Study Device, % (n/N)	39.8% (47/118)
Final Procedure Outcome	
Post-DCB Dilation Performed, % (n/N)	58.5% (69/118)
%DS after Post-DCB Dilatation, Mean ± SD (n)	29.2 ± 16.77 (68)
Dissection after Post-DCB Treatment, % (n/N)	63.6% (42/66)
Dissection Grade after Post-DCB Treatment, % (n/N) A B D	 59.5% (25/42) 38.1% (16/42) 2.4% (1/42)
Bailout Spot Stent used Post-DCB Dilatation, % (n/N)	65.2% (45/69)
Final %DS, Mean ± SD (n)	29.5 ± 13.89 (117)

10.6.4 Methods

All subjects were consented to be followed for a minimum of 3 years. Subjects were treated per standard of care; there were no additional protocol treatments or exams required within this study.

This study was performed with devices approved under the CE Mark in Europe. The study device is the same as the device that is commercially available in the United States, with the exception of a broader indication for the CE Marked product.

This study enrolled subjects presenting with stenotic or obstructive long lesions (≥ 14 cm) of the femoropopliteal artery and a patent outflow artery to the foot. Subjects were considered enrolled in the study after being consented and successful pre-dilatation. For each subject, clinical data and follow-up information at 1, 6, 12, 24 and 36 months were reported. Subject contact was by a clinical visit with option of telephone contact for 1-month and 36-months follow-up.

All required clinical data were collected on a web-based standardized electronic case report forms. Monitoring was performed to ensure compliance. All deaths, index limb reinterventions and device related SAEs adjudicated by an independent Clinical Events Committee and DUS was adjudicated by an independent core-lab for determination of binary restenosis.

10.6.5 Results

Results through the 12 month follow-up are presented below. No hypothesis testing was pre-specified in this study.

10.6.5.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was primary patency at 12 months defined as freedom from CEC-adjudicated clinically-driven TLR and from core-lab adjudicated binary restenosis. A total of 103 subjects were evaluable for the primary effectiveness endpoint analysis. The primary patency at 12 months by subject counts at 12 months was 58.3%. The Kaplan-Meier estimates primary patency at 12 months (day 365) was 70.1%.

Table 34. Effectiveness Endpoints

Measure	Success % (n/N)	95% CI[1]
Primary Patency at 12 Months (Primary Endpoint)	58.3% (60/103)	48.1%, 67.9%
Primary Patency at 24 Months	43.9% (43/98)	33.9%, 54.3%

[1] Exact binomial confidence interval

Table 35. Primary Effectiveness Endpoint by Lesion Length (12 Months)

Lesion Length	Success % (n/N)	95% CI[1]
Lesions ≤ 16 cm	62.5% (15/24)	40.6%, 81.2%
Lesions >16 - 20 cm	66.7% (20/30)	47.2%, 82.7%
Lesions >20 - 25 cm	47.4% (9/19)	24.4%, 71.1%
Lesions > 25 cm	50.0% (14/28)	30.6%, 69.4%

[1] Exact binomial confidence interval.

10.6.5.2 Primary Safety Endpoint

The primary safety endpoint is defined as freedom from all-cause peri-procedural (≤30 days) death and freedom at 1 year from index limb amputation (above or below the ankle) and index limb reintervention. A total of 108 subjects were evaluable for the primary safety endpoint analysis. The success by subject counts was 78.7% for the primary safety endpoint. Freedom from primary safety events by Kaplan Meier estimates for 12 months (day 365) was 81.5%.

Table 36. Primary Safety Endpoint

Measure	Success % (n/N)	95% CI[1]
Primary Safety Endpoint	78.7% (85/108)	69.8%, 86.0%

[1] Exact binomial confidence interval

Table 37. Primary Safety Endpoint by Lesion Length

Lesion Length	Success % (n/N)	95% CI[1]
Lesions ≤ 16 cm	80.0% (20/25)	59.3%, 93.2%
Lesions >16 - 20 cm	81.8% (27/33)	64.5%, 93.0%
Lesions >20 - 25 cm	84.2% (16/19)	60.4%, 96.6%
Lesions > 25 cm	72.4% (21/29)	52.8%, 87.3%

[1] Exact binomial confidence interval.

10.6.5.3 Secondary Effectiveness Endpoint

The freedom from clinically-driven TLR-free success rates at 12, 24, and 36 months as determined by subject counts were 84.9%, 72.8%, and 66.7% respectively. The freedom from clinically-driven TLR-free success rates as determined by Kaplan-Meier estimates at 12, 24, and 36 months were 87.4%, 74.9%, and 68.9% respectively.

Table 38. Clinically-Driven TLR-Free Success Rates

Measure	Success % (n/N)	95% CI[1]
Clinically-Driven TLR-Free Success Rates		
12 Months	84.9% (90/106)	76.6%, 91.1%
24 Months	72.8% (75/103)	63.2%, 81.1% [1]
36 Months	66.7% (66/99)	56.5%, 75.8% [1]
Clinically-Driven TLR-Free Success Rates by Kaplan-Meier Estimates		
12 Months	87.4% (n = 97)	79.7%, 92.4% [2]
24 Months	74.9% (n = 78)	65.6%, 82.1% [2]
36 Months	68.9% (n = 67)	59.1%, 76.8% [2]

[1] Exact binomial confidence interval.
[2] TLR-Free response estimate based on Kaplan-Meier estimates

10.6.5.4 Secondary Safety Endpoints

Table 39. Secondary Safety Endpoints with Kaplan-Meier through 36 Months

Measure	Time	N[1]	Survival[2] % [95% CI]
All Cause Death Survival	Month 1 (30 Days)	117	100.0% [NA, NA]
	Month 6 (183 Days)	115	100.0% [%, %]
	Month 12 (365 Days)	108	97.4% [92.1%, 99.1%]
	Month 12 (395 Days)	108	97.4% [92.1%, 99.1%]
	Month 24 (730 Days)	102	95.5% [89.5%, 98.1%]
	Month 36 (1095 Days)	98	92.7% [85.9%, 96.3%]
Major Amputation Free	Month 1 (30 Days)	118	100.0% [NA, NA]
	Month 6 (183 Days)	116	99.1% [94.0%, 99.9%]
	Month 12 (365 Days)	108	99.1% [94.0%, 99.9%]
	Month 12 (395 Days)	108	99.1% [94.0%, 99.9%]
	Month 24 (730 Days)	101	98.2% [93.0%, 99.5%]
	Month 36 (1095 Days)	97	98.2% [93.0%, 99.5%]
Minor Amputation Free	Month 1 (30 Days)	117	99.2% [94.1%, 99.9%]
	Month 6 (183 Days)	115	99.2% [94.1%, 99.9%]
	Month 12 (365 Days)	106	98.2% [93.1%, 99.6%]
	Month 12 (395 Days)	106	98.2% [93.1%, 99.6%]
	Month 24 (730 Days)	100	98.2% [93.1%, 99.6%]
	Month 36 (1095 Days)	96	98.2% [93.1%, 99.6%]
Total TLR-Free	Month 1 (30 Days)	118	100.0% [NA, NA]
	Month 6 (183 Days)	114	97.4% [92.2%, 99.2%]
	Month 12 (365 Days)	97	87.4% [79.7%, 92.4%]
	Month 12 (395 Days)	97	85.5% [77.5%, 90.9%]
	Month 24 (730 Days)	78	74.9% [65.6%, 82.1%]
	Month 36 (1095 Days)	67	68.9% [59.1%, 76.8%]
TVR-Free	Month 1 (30 Days)	118	100.0% [NA, NA]
	Month 6 (183 Days)	114	97.4% [92.2%, 99.2%]
	Month 12 (365 Days)	95	85.6% [77.6%, 90.9%]
	Month 12 (395 Days)	95	83.7% [75.4%, 89.4%]
	Month 24 (730 Days)	77	74.1% [64.7%, 81.4%]
	Month 36 (1095 Days)	66	68.0% [58.2%, 76.0%]
Any Target Limb Reintervention Free	Month 1 (30 Days)	118	100.0% [NA, NA]
	Month 6 (183 Days)	112	95.7% [90.0%, 98.2%]
	Month 12 (365 Days)	93	83.9% [75.7%, 89.6%]
	Month 12 (395 Days)	93	82.0% [73.5%, 88.0%]
	Month 24 (730 Days)	75	71.4% [61.8%, 79.0%]
	Month 36 (1095 Days)	63	65.3% [55.3%, 73.5%]
Composite Safety Survival	Month 1 (30 Days)	116	98.3% [93.4%, 99.6%]
	Month 6 (183 Days)	110	93.1% [86.7%, 96.5%]
	Month 12 (365 Days)	92	81.5% [73.1%, 87.5%]
	Month 12 (395 Days)	92	79.6% [71.0%, 86.0%]
	Month 24 (730 Days)	74	69.2% [59.6%, 76.9%]
	Month 36 (1095 Days)	63	64.2% [54.3%, 72.4%]

[1] Subjects ongoing without a failure at the beginning of the visit window
[2] Survivor rate based on Kaplan-Meier estimates
[3] Subjects ongoing without an event at visit day

10.6.6 Discussion

The LUTONIX® Long Lesion SFA study, with exception of lesion length, enrolled similar patients and used similar evaluation methodologies and follow-up protocol as the LEVANT 2 pivotal study. Both studies had similar inclusion/exclusion criteria and used the same core-lab for adjudication.

Given that the lesion length in the Long Lesion SFA study is almost 3.5X the lesion length in the LEVANT 2 study (212.5 mm for Long Lesion vs. 62.7 mm for LEVANT 2 DCB and 63.2 mm for LEVANT 2 PTA), a lower than LEVANT 2 primary patency of the DCB cohorts would be expected, as depicted in **Table 39**. Note that only clinical comparisons may be made since no hypothesis testing was planned or performed.

Table 39: Primary Patency – Long Lesion/LEVANT 2 Comparison

Measure	Long Lesion DCB	LEVANT 2 Pivotal Study	
		DCB Arm	PTA Arm
Primary Patency	58.3% (60/103)	66.0% (177/268)	54.0% (74/137)

For the effectiveness endpoint of clinically driven TLR, a comparison of the TLR-free rate in the Long Lesion DCB population to that of the LEVANT 2 DCB and PTA arm is provided in **Table 40** below.

Table 40: Clinically Driven TLR – Long Lesion/LEVANT 2 Comparison

Measure	Long Lesion DCB	LEVANT 2 Pivotal Study	
		DCB Arm	PTA Arm
Clinically Drive TLR-Free at 12 Months	84.9% (91/106)	87.8% (251/286)	83.6% (122/146)

For primary safety events, the results of the Long Lesion DCB as compared to the LEVANT 2 PTA and the LEVANT 2 DCB can be seen in **Table 41** below. A minor decrease in the primary safety survival rate was seen for the Long Lesion DCB population as compared to the LEVANT 2 DCB population, as expected, given the significant difference in the lesion length.

Table 41: Primary Safety Events – Long Lesion/LEVANT 2 Comparison

Measure	Long Lesion DCB	LEVANT 2 Pivotal Study	
		DCB Arm	PTA Arm
Freedom from Primary Safety Events	78.7% (85/107)	84.3% (242/287)	79.5% (116/146)

10.7 SFA ISR IDE Study

10.7.1 Objective

The primary objective of the LUTONIX® SFA ISR study is to demonstrate effectiveness and safety of the LUTONIX® 035 Drug Coated Balloon for treatment of SFA ISR.

10.7.2 Study Design

The SFA ISR study was originally designed as a randomized controlled trial and amended to a single-arm study design. No subjects have been enrolled under the single arm study design.

The SFA ISR study was initially designed as a prospective, multicenter, single-blind, randomized, controlled trial comparing the LUTONIX® Drug Coated Balloon to standard balloon angioplasty for treatment of femoropopliteal in-stent restenosis. The study results provided are interim results of the 82 randomized patients enrolled from across 20 investigational sites in the U.S. Patient follow-up compliance through 12-month is 86.6%.

Table 42. Subject Disposition

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Intent-to-Treat Subjects (ITT), n	53	29
Follow-up by Visit, % (n/N) Month 1 Month 6 Month 12 Month 24 Month 36	 96.2%, (51/53) 94.3%, (50/53) 92.5%, (49/53) 81.1%, (43/53) 79.2%, (42/53)	 96.6%, (28/29) 75.9%, (22/29) 79.3%, (23/29) 69.0%, (20/29) 69.0%, (20/29)
Duration of Follow-up (Days), Mean ± SD (n)	1029 ± 247.4 (53)	868.5 ± 388.2 (29)

10.7.3 Baseline and Demographics

Table 43 and **Table 44** present selected demographics and baseline angiographic data. Pre-dilatation using a standard PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 100% of subjects and none of the subjects required bailout spot stenting occurred in this study.

Table 43. Selected Demographics

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Age (Years), Mean ± SD (n)	68.9 ± 9.35 (53)	67.0 ± 8.64 (29)
Gender - Male, % (n/N)	56.6% (30/53)	41.4% (12/29)
BMI (kg/m^2), Mean ± SD (n)	28.6 ± 5.38 (53)	29.5 ± 5.65 (28)

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Smoker, % (n/N) Current Smoker Former Smoker	 37.7% (20/53) 54.7% (29/53)	 13.8% (4/29) 75.9% (22/29)
Hypertension, % (n/N)	96.2% (51/53)	93.1% (27/29)
Dyslipidemia/Hypercholesterolemia, % (n/N)	98.1% (52/53)	96.6% (28/29)
Diabetes, % (n/N)	37.7% (20/53)	55.2% (16/29)
Previous lower extremity artery revascularization, % (n/N)	100% (53/53)	100.0% (29/29)
Ischemic Heart Disease, % (n/N)	16.0% (8/50)	24.1% (7/29)
Renal Insufficiency/Failure or on Dialysis, % (n/N)	5.7% (3/53)	6.9% (2/29)
Baseline Target Limb Rutherford Grade, % (n/N) 2 3 4	 17.0% (9/53) 77.4% (41/53) 5.7% (3/53)	 13.8% (4/29) 75.9% (22/29) 10.3% (3/29)
Baseline ABI of Target Limb, Mean ± SD (n)	0.76 ± 0.15 (48)	0.76 ± 0.20 (26)

Table 44. Baseline Angiographic Data (All DCB Population)

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Number of Treated Lesions, % (n/N) 1 2 3	 94.3% (50/53) 5.7% (3/53) 0.0% (0/53)	 96.6% (28/29) 0.0% (0/29) 3.4% (1/29)
Total Target Lesion Length (mm), Mean ± SD (n)	117.8 ± 72.7 (53)	104.2 ± 67.9 (29)
Target Lesion Stenosis (%), Mean ± SD (n)	77.1 ± 15.1 (53)	73.5 ± 14.2 (29)
CTO, % (n/N)	9.4% (5/53)	6.9% (2/29)
RVD (mm), Mean ± SD (n)	4.7 ± 0.66 (53)	4.7 ± 0.52 (29)
MLD (mm), Mean ± SD (n)	1.1 ± 0.73 (53)	1.3 ± 0.69 (29)
Calcification, % (n/N)	47.2% (25/53)	71.4% (20/28)
TASC Classification, % (n/N) A B C	 35.8% (19/53) 34.0% (18/53) 30.2% (16/53)	 48.3% (14/29) 27.6% (8/29) 24.1% (7/29)

Table 45. Procedural Data

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Contralateral Access, % (n/N)	92.5% (49/53)	96.6% (28/29)
Vessel Preparation		
Pre-dilatation Performed, % (n/N)	100.0% (53/53)	100.0% (29/29)
%DS Post Pre-dilatation, Mean ± SD (n)	34.6 ± 12.1 (47)	34.2 ± 13.2 (26)
Dissection During Pre-dilatation, % (n/N)	12.8% (6/47)	7.7% (2/26)
Study Device Treatment		
Inflation Time per Balloon (sec), Mean ± SD (n)	139.8 ± 89.5 (53)	181.8 ± 188 (28)
Balloon Pressure (atm), Mean ± SD (n)	8.8 ± 2.24 (53)	10.5 ± 3.43 (28)
Treated Length (mm), Mean ± SD (n)	152.4 ± 62.5 (50)	142.0 ± 74.7 (27)
%DS Post-Study Treatment, Mean ± SD (n)	22.2 ± 13.3 (50)	23.3 ± 6.97 (27)
Dissection Post-Study Treatment, % (n/N)	28.0% (14/50)	25.9% (7/27)
Bailout Stent Post Study Device, % (n/N)	0.0% (0/53)	0.0% (0/29)
Final Procedure Outcome		

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Post-Study Balloon Dilatation Performed, % (n/N)	13.2% (7/53)	3.4% (1/29)
%DS after Post-Dilatation, Mean ± SD (n)	28.9 ± 5.55 (7)	26.0 (1)
Dissection after Post-Dilatation, % (n/N)	28.6% (2/7)	0.0% (0/1)
Bailout Stent used Post-Dilatation, % (n/N)	0.0% (0/6)	0.0% (0/1)
Final %DS, Mean ± SD (n)	20.7 ± 11.3 (50)	23.4 ± 6.98 (27)

10.7.4 Methods

Subjects presenting with claudication or ischemic rest pain and an angiographically significant in-stent lesion (4 – 22 cm in length) in the superficial femoral or popliteal artery and a patent outflow artery to the foot were enrolled. After protocol-defined pre-dilatation, subjects with successful pre-dilatation were randomized 2:1 to LUTONIX® DCB (test) or standard PTA (control).

All required clinical data were collected on a web-based standardized electronic case report forms. Monitoring was performed to ensure compliance. All deaths, index limb reinterventions and device related SAEs were adjudicated by an independent Clinical Events Committee and DUS/angiograms were adjudicated by an independent core-lab for determination of binary restenosis.

10.7.5 Results

Interim results of the randomized cohort through the 12 month follow-up are presented below.

10.7.5.1 Primary Effectiveness Endpoint

Primary effectiveness endpoint is primary patency defined as freedom from CEC-adjudicated clinically-driven TLR and from core-lab adjudicated binary restenosis at 12 months. A total of 78 subjects were evaluable for the primary patency survival analysis. The Kaplan-Meier estimates of primary patency at 12 months was 67.0% in the DCB group and 49.6% in the PTA group .

Table 46. Primary Effectiveness Endpoint, Kaplan-Meier

Group	Time	N[1]	Survival % [95% CI]	Cumulative Information at Visit Day		
				Subjects with Events	Subjects Censored	Subjects at Risk
LTX DCB	Month 1 (30 Days)	50	94.1% [83.0%, 98.1%]	3	1	47
	Month 6 (183 Days)	43	92.1% [80.4%, 97.0%]	4	8	39
	Month 12 (365 Days)	32	67.0% [50.5%, 79.1%]	14	14	23
	Month 24 (730 Days)	13	28.9% [14.5%, 45.0%]	26	20	5
Std PTA	Month 1 (30 Days)	26	96.3% [76.5%, 99.5%]	1	2	24
	Month 6 (183 Days)	20	77.0% [53.1%, 89.8%]	5	6	16
	Month 12 (365 Days)	8	49.6% [26.2%, 69.2%]	10	9	8
	Month 24 (730 Days)	5	31.0% [1, 52.5%]	13	10	4

[1] Subjects with follow-up reaching the beginning of the 12-month window without a prior event.

10.7.5.2 Primary Safety Endpoint

The primary safety endpoint is defined as Freedom from all-cause peri-procedural (≤30 days) death and freedom at 1 year from index limb amputation (above or below the ankle), index limb reintervention, and index-limb related death. Total of 82 subjects were evaluable for the primary safety endpoint survival analysis. Freedom from primary safety events by Kaplan Meier estimates for 12 months (day 365) was 73.1% for LUTONIX® DCB and 64.0% for control PTA.

Table 47. Primary Safety Endpoint

Group	Time	N[1]	Survival % [95% CI]	Cumulative Information at Visit Day		
				Subjects with Events	Subjects Censored	Subjects at Risk
LTX DCB	Month 1 (30 Days)	52	96.2% [85.7%, 99.0%]	2	1	50
	Month 6 (183 Days)	47	88.5% [76.2%, 94.7%]	6	1	46
	Month 12 (365 Days)	41	73.1% [58.9%, 83.1%]	14	1	38
	Month 24 (730 Days)	29	60.7% [45.9%, 72.7%]	20	4	29
Std PTA	Month 1 (30 Days)	28	100.0% [NA, NA]	0	1	28
	Month 6 (183 Days)	26	92.7% [73.9%, 98.1%]	2	2	25
	Month 12 (365 Days)	16	64.0% [42.0%, 79.5%]	9	6	14

Group	Time	N[1]	Survival % [95% CI]	Cumulative Information at Visit Day		
				Subjects with Events	Subjects Censored	Subjects at Risk
	Month 24 (730 Days)	10	54.4% [32.6%, 71.9%]	11	8	10

[1] Subjects with follow-up in window or longer.

10.7.5.3 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint of freedom from clinically driven TLR success rate by Kaplan-Meier estimate at 12 months (Day 365) was 78.9% for LUTONIX® DCB and 64.0% for control PTA.

Table 48. Clinically-Driven TLR-Free Endpoint

Group	Time	Survival % [95% CI]	Cumulative Information at Visit Day		
			Subjects with Events	Subjects Censored	Subjects at Risk
LTX DCB	Month 1 (30 Days)	96.2% [85.7%, 99.0%]	2	1	50
	Month 6 (183 Days)	94.3% [83.4%, 98.1%]	3	1	49
	Month 12 (365 Days)	78.9% [65.1%, 87.7%]	11	1	41
	Month 24 (730 Days)	64.5% [49.6%, 76.0%]	18	4	31
	Month 36 (1095 Days)	43.6% [22.6%, 62.9%]	13	10	6
Std PTA	Month 1 (30 Days)	100.0% [NA, NA]	0	1	28
	Month 6 (183 Days)	92.7% [73.9%, 98.1%]	2	2	25
	Month 12 (365 Days)	64.0% [42.0%, 79.5%]	9	6	14
	Month 24 (730 Days)	54.4% [32.6%, 71.9%]	11	8	10
	Month 36 (1095 Days)	43.6% [22.6%, 62.9%]	13	10	6

[1] Subjects with follow-up reaching the beginning of the 12-month window without a prior event.

10.7.6 Discussion

The SFA ISR study assessed the safety and effectiveness of the LUTONIX® Drug Coated Balloon for treatment of SFA in-stent restenosis. Enrollment in the RCT trial was terminated and no patients were enrolled into the study that was redesigned as a single arm trial.

The 12 month primary patency rate by Kaplan-Meier estimates is 67.0% in the DCB group and 49.5% in the PTA group at 365 Days.

The primary safety endpoint by Kaplan-Meier estimates is 73.1% for the DCB subjects and 64.0% for the PTA subjects. There were no procedure or device related deaths and no unanticipated adverse events reported.

The study results for the SFA ISR study demonstrate with reasonable assurance the safety and effectiveness of the LUTONIX® 035 Drug Coated Balloon in patients with challenging ISR lesions.

11 HOW SUPPLIED

- Sterile: This device is sterilized with ethylene oxide gas. Do not use if package is opened or damaged. For one use only. Do not resterilize.
- The LUTONIX® Catheter has a protective sheath placed over the balloon, is stored within a standard dispensing hoop, and is sterilized within a dual chamber pouch. The dual chamber pouch contains both a catheter compartment and desiccant compartment. The compartments are separated by a sterile barrier. The desiccant compartment contains packets used to help control package environment and should not be opened.
- Contents: One (1) LUTONIX® 035 Drug Coated Balloon PTA Catheter.
- Storage: Store in a dry, dark place. Store at 15-30°C (59-86°F). Do not store near radiation or ultra-violet light sources.

12 DIRECTIONS FOR USE

12.1 Equipment

In addition to the LUTONIX® Catheter, the following standard materials may also be required:

- 0.035″ Guidewire
- Introducer sheath
- Predilatation PTA catheter
- Contrast medium
- Sterile saline
- Inflation device with manometer
- Luer lock syringe for purging
- Catheter Stabilization Device

12.2 Inspection Prior to Use

Prior to angioplasty, carefully examine all equipment to be used during the procedure, including the dilatation catheter, to verify proper function. Verify that the catheter and sterile packaging have not been damaged in shipment.

Warning: Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use.

12.3 Use of Multiple LUTONIX® Catheters

If multiple LUTONIX® Catheters are required to complete treatment of a lesion, the sequentially used LUTONIX® Catheter should be minimally sized and angiographically positioned so that the marker bands of consecutively placed balloons overlap as necessary to cover the lesion and margins of the predilatation/injury segment. The LUTONIX® Catheter should extend a minimum of 5 mm proximally and distally from the lesion and injury segment. Care should be taken not to extend the entire injury segment(s) unnecessarily. The use of a radiopaque ruler is recommended to ensure appropriate placement of the LUTONIX® Catheter. See **Figure 7**.

Precaution: The safety and effectiveness of using more than four LUTONIX® drug coated balloons or a maximum drug coating quantity of approximately 15.1 mg paclitaxel in a patient has not been clinically evaluated.

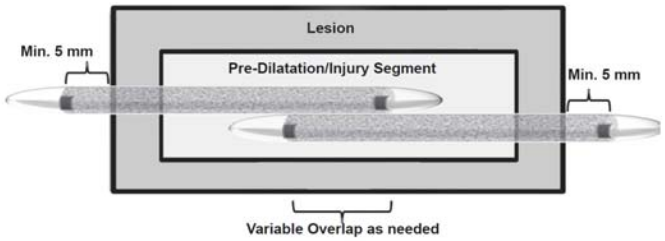


Figure 7. Balloons are appropriately sized to minimize overlap but are consecutively placed by angiography with as much overlap as necessary to treat lesion appropriately

12.4 Target Lesion Vessel Preparation

1. Vessel preparation of the target lesion, using the appropriate vessel preparation method as determined by the treating physician, is required prior to the use of the LUTONIX® Catheter.

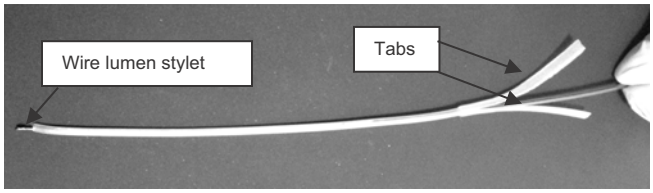
12.5 LUTONIX® Catheter Preparation

1. Remove the device from the packaging.
2. Verify the balloon size is suitable for the procedure and the selected accessories are compatible with the catheter as labeled.
3. Prepare the inflation device/syringe with diluted contrast medium.

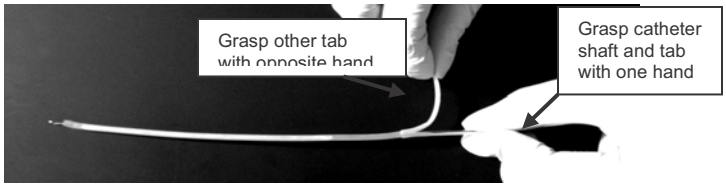
   Warning: Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon.
4. Prior to use, the air in the balloon catheter should be removed. To facilitate purging, select a syringe or inflation device with a 10 ml or larger capacity and fill approximately half of it with the recommended diluted contrast medium.
5. Connect a stopcock to the balloon inflation female luer hub on the dilatation catheter.
6. Connect the syringe to the stopcock.
7. Hold the syringe with the nozzle pointing downward, open the stopcock and aspirate for approximately 15 seconds. Release the plunger.
8. Repeat step 7 above as needed until bubbles no longer appear during aspiration (negative pressure). Once completed, evacuate all air from the barrel of the syringe/inflation device.

12.6 Use of the LUTONIX® Catheter

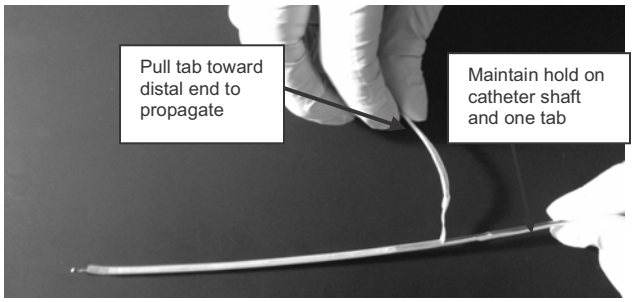
1. Perform the following steps to remove the balloon protector. Shown below is a catheter and Peel Away balloon protector when removed from the catheter hoop.

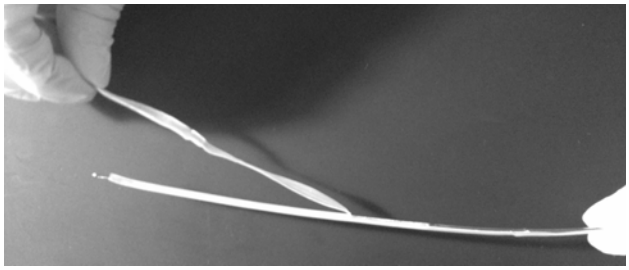


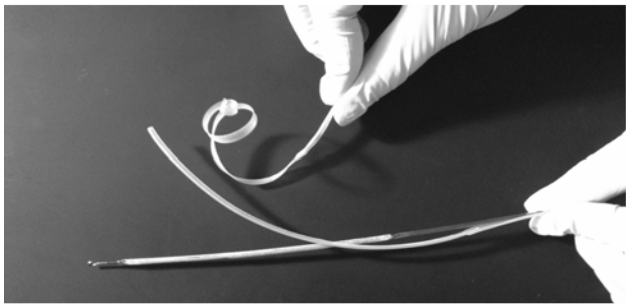
Step 1- Leaving the wire lumen stylet in place; use one hand to grasp both a single tab of the balloon protector and the catheter shaft as shown below. Caution should be taken to not kink or crush the catheter shaft. Using the opposite hand, grasp the other tab of the balloon protector



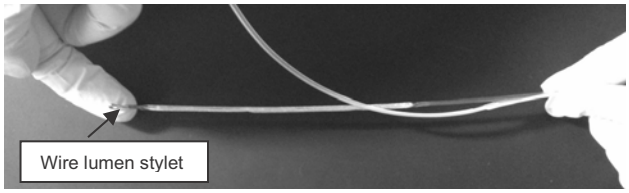
Step 2- With the hand holding the balloon protector tab only; gently pull the balloon protector tab toward the distal end of the balloon. Continue to pull the tab and hold the other balloon protector tab with the catheter shaft until the balloon protector fully propagates and separates into two pieces.





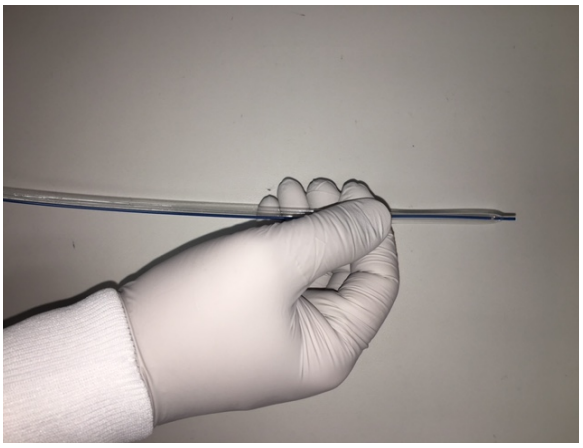


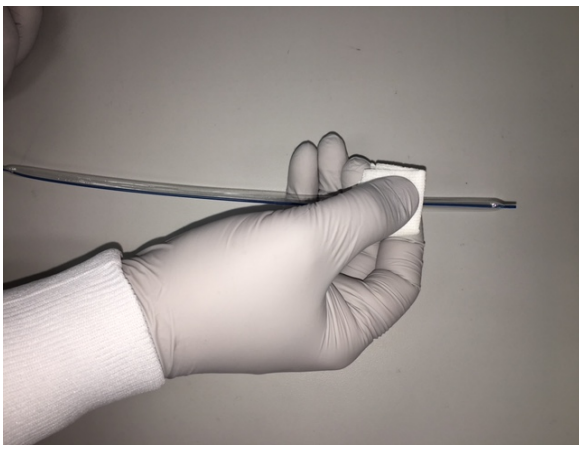
Step 3- Maintaining the grasp on the catheter shaft with one hand; use the opposite hand to remove the wire lumen stylet. Do this by gently pulling the hoop of the wire lumen stylet protruding from the distal end of the balloon.



Step 4- Discard both the balloon protector and wire lumen stylet.

2. With the catheter tip oriented down/vertically, flush the wire lumen.
3. Backload the distal tip of the dilatation catheter onto the guidewire.
4. While the balloon is still fully deflated and under negative pressure, advance the LUTONIX® Catheter through the introducer sheath and over the wire to the site of inflation.
5. The balloon may be handled using dry gloves or gauze to help facilitate advancement through the introducer sheath.





To aid in insertion of longer balloons, hold the balloon one inch from the distal tip and gently insert the balloon in one inch intervals. During catheter advancement, inspect the catheter shaft for damage.

6. To ensure therapeutic drug delivery, the LUTONIX® Catheter should be advanced to the target site in the shortest possible time (i.e. ~30 seconds) and immediately inflated to appropriate pressure to ensure full wall apposition (balloon to artery ratio ≥ 1:1). If the time to deployment of the LUTONIX® Catheter exceeds 3 minutes, the catheter requires replacement with a new unit.
7. Position the balloon relative to the lesion, ensuring coverage of at least 5mm proximally and distally beyond the margins of the lesion segment. Refer to Compliance Chart included on product label. The use of a radiopaque ruler is recommended to ensure appropriate placement of the LUTONIX® Catheter.

   Warning: Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended.
8. Maintain balloon inflation for a minimum of 2 minutes (120 seconds). The balloon may remain inflated as long as is required by the standard of care to achieve a good angioplasty outcome.
9. Apply negative pressure to fully deflate the LUTONIX® Catheter. Prior to removal, confirm that the balloon is fully deflated under fluoroscopy.
10. Perform angiography to confirm dilatation of the lesion.
11. Best outcomes are obtained when the final % diameter stenosis is 0 – 20%. To achieve the suggested % diameter stenosis, if needed, post-dilatation is allowed with another PTA catheter or used LUTONIX® catheter.
12. Withdraw the LUTONIX® Catheter from the body under negative pressure. Maintain the guidewire across the stenosis.
13. After confirming that a satisfactory dilatation was achieved, remove all equipment from the body and close access site per standard clinical practice.
14. Refer to **Section 5.5** for Pre- and Post-Procedure Antiplatelet Regimen for the dual antiplatelet pharmacological therapy recommended with use of the LUTONIX® Catheter.
15. After use, this product may be a potential biohazard. Handle and dispose of in accordance with acceptable medical practices and applicable laws and regulations.

13 DISCLAIMER OF WARRANTY

LUTONIX, INC. WARRANTS TO THE FIRST PURCHASER OF THIS PRODUCT, THAT THIS PRODUCT WILL BE FREE FROM DEFECTS IN MATERIALS AND WORKMANSHIP FOR A PERIOD OF ONE YEAR FROM THE DATE OF FIRST PURCHASE AND LIABILITY UNDER THIS LIMITED PRODUCT WARRANTY WILL BE LIMITED, TO REPAIR OR REPLACEMENT OF THE DEFECTIVE PRODUCT, IN LUTONIX'S SOLE DISCRETION, OR REFUNDING YOUR NET PRICE PAID. WEAR AND TEAR FROM NORMAL USE OR DEFECTS RESULTING FROM MISUSE OF THIS PRODUCT IS NOT COVERED BY THIS LIMITED WARRANTY.

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