LUTONIX® 035 Drug Coated Balloon PTA Catheter

INSTRUCTIONS FOR USE

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

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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. The balloon is coated with a specialized formulation that includes the drug, paclitaxel. The LUTONIX® Catheter is 0.035" guidewire compatible, with a low profile, semi-compliant balloon formed to a low profile tapered tip to facilitate advancement of the catheter to and through the stenotic region of the vessel. Two radiopaque marker bands delineate the working length of the balloon and are located under the proximal and distal ends of the balloon to facilitate fluoroscopic visualization of the balloon during delivery and placement. The proximal portion of the catheter includes an inflation female luer lock hub and a guidewire female luer lock hub. Each product is packaged with a balloon protector that has been positioned over the balloon and a disposable wire lumen stylet, both of which are to be removed prior to use.

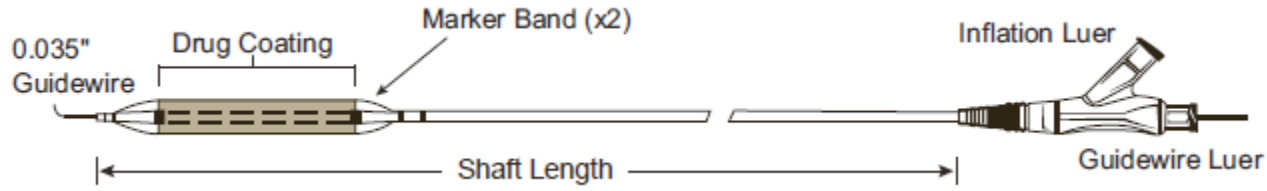


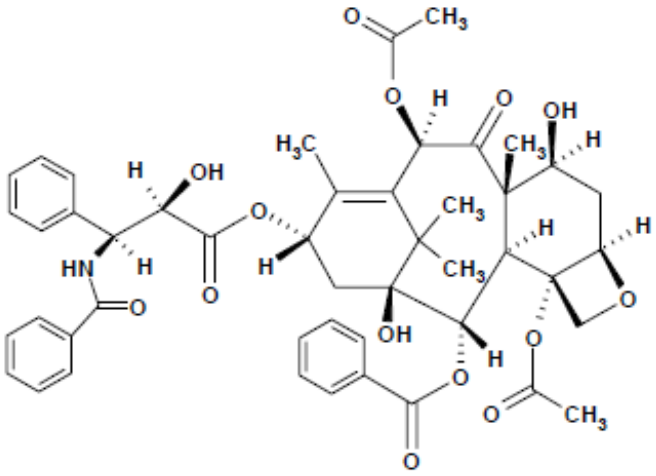
Figure 1. Lutonix® 035 Drug Coated Balloon PTA Catheter, Model 9004

Table 1. Lutonix® 035 Drug Coated Balloon PTA Catheter Product Description

Attribute	Peripheral (PTA)
Model Number	9004
Catheter Configuration	Over-the-Wire (OTW)
Available Balloon Diameters	4.0, 5.0, 6.0 mm
Available Balloon Lengths	40, 60, 80, 100 mm
Effective Catheter Length	75, 100, 130 cm
Radiopaque Marker Bands	2
Nominal Balloon Pressure	6 atm for 4.0 – 5.0 mm diameter balloon 7 atm for 6.0 mm diameter balloon
Balloon Rated Burst Pressure	12 atm
Maximum Guidewire	0.035"
Minimum Introducer Sheath	5F for 4.0 – 5.0 mm diameter balloon 6F for 6.0 mm diameter balloon
Crossing Profile	4.0 mm diameter balloon: 5.0F (1.7 mm) 5.0 mm diameter balloon: 5.3F (1.8 mm) 6.0 mm diameter balloon: 6.0F (2.0 mm)
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 2**. The key functional characteristic of the formulation is to allow for release of paclitaxel to the tissue of the vascular wall during inflation.

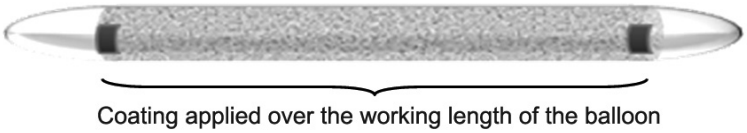


Figure 2. Drug Coating Distribution

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
4.0	1.0	1.5	2.0	2.5
5.0	1.3	1.9	2.5	3.1
6.0	1.5	2.3	3.0	3.8

2 INDICATIONS FOR USE

The Lutonix 035 Drug Coated Balloon PTA catheter is indicated for percutaneous transluminal angioplasty, after pre-dilatation, of de novo or restenotic lesions up to 150mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-6mm.

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

- 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 two Lutonix drug coated balloons (i.e., a maximum drug coating quantity of approximately 7.6 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.

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 and wire lumen stylet 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 after flexing, 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® Drug Coated Balloon prior to reaching the target lesion.
  - The LUTONIX® Catheter should be advanced to the target site as fast as possible and immediately inflated to appropriate pressure to ensure full wall apposition (balloon to artery ratio of 1:1). If the deployment of the LUTONIX Catheter exceeds 3 minutes, the catheter requires replacement with a new unit.
- Maintain balloon inflation for a minimum of 30 seconds. The balloon may remain inflated as long as is required by the standard of care to achieve a good angioplasty outcome.
- Predilatation with an uncoated PTA catheter is required prior to use of 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.

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 10.2.5 (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 genotoxitiy 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 18 and 55 times the dose provided by the LUTONIX® Catheter coated with 3.8 mg paclitaxel (6mm x 100mm 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 18 times the dose of the LUTONIX® Catheter (6mm x 100mm), 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
- Arrythmias
- 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

The safety and effectiveness of the LUTONIX® Catheter is derived from the pivotal IDE trial and the LEVANT 2 safety studies. The LEVANT 1 multicenter randomized European trial provided additional supporting information but was not considered part of the primary data set supporting approval.

The two-year final results from the LEVANT 1 trial, the one year results from the LEVANT 2 randomized pivotal IDE trial, and the LEVANT 2 Safety registry results are presented below. Patient follow-up for the LEVANT 2 trials are planned out to 5-years and are ongoing.

10.1 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. 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).

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.

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

10.2.1 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.

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

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

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

10.2.3 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.

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)	

Variable	Test DCB	Control PTA	P-value[1]
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
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

Variable[1]	Test DCB	Control PTA	P-value[2]
Proximal SFA	9.2% (29/316)	8.1% (13/160)	
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.

10.2.4 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.

10.2.5 Results

A total of 476 patients (316 Lutonix DCB and 160 control PTA) were enrolled and randomized from 54 clinical sites.

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% of the patients in the Test Lutonix DCB group were free from the primary safety event, compared to 79% 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, 65% of the patients in the Lutonix DCB group had primary patency at 12 months compared to 53% 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]	83.9% (240/286) [79.7,88.2]	79.0% (113/143) [72.3,85.7]	4.9% [-2.6,12.3]	0.005 [2]
Primary Patency[3]	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015 [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 3 and Figure 4 provide primary safety and primary patency rates at 12 Months (respectively) using a time-to-event Kaplan-Meier survival analysis. For the primary effectiveness endpoint, the primary patency rate is greater for the Lutonix DCB group than the Control PTA group.

Figure 3: Primary Safety Rate 12 Months by Kaplan-Meier

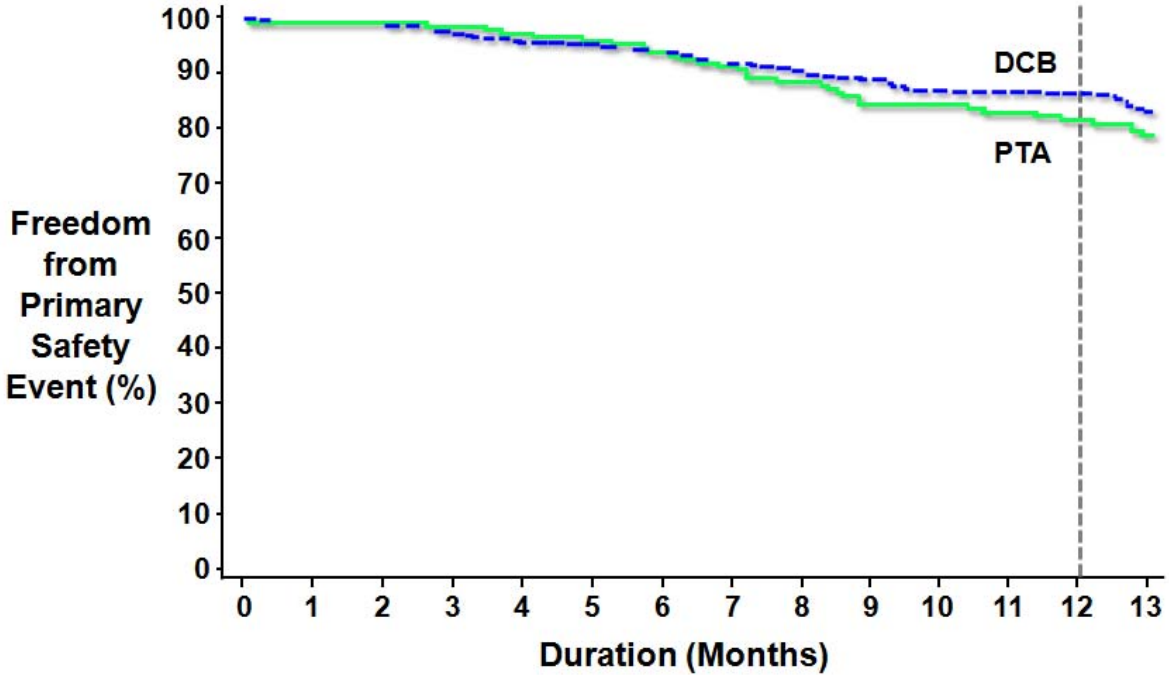


Table 6. Primary Safety Rate 12 Months by Kaplan-Meier

	Test DCB				Control PTA			
Time	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk
30 days	99.4%	2	9	305	99.4%	1	5	154
183 days	94.0%	18	21	277	94.1%	9	13	138
365 days	86.7%	39	66	211	81.5%	27	35	98

[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 4: Primary Patency Rate 12 Months by Kaplan-Meier

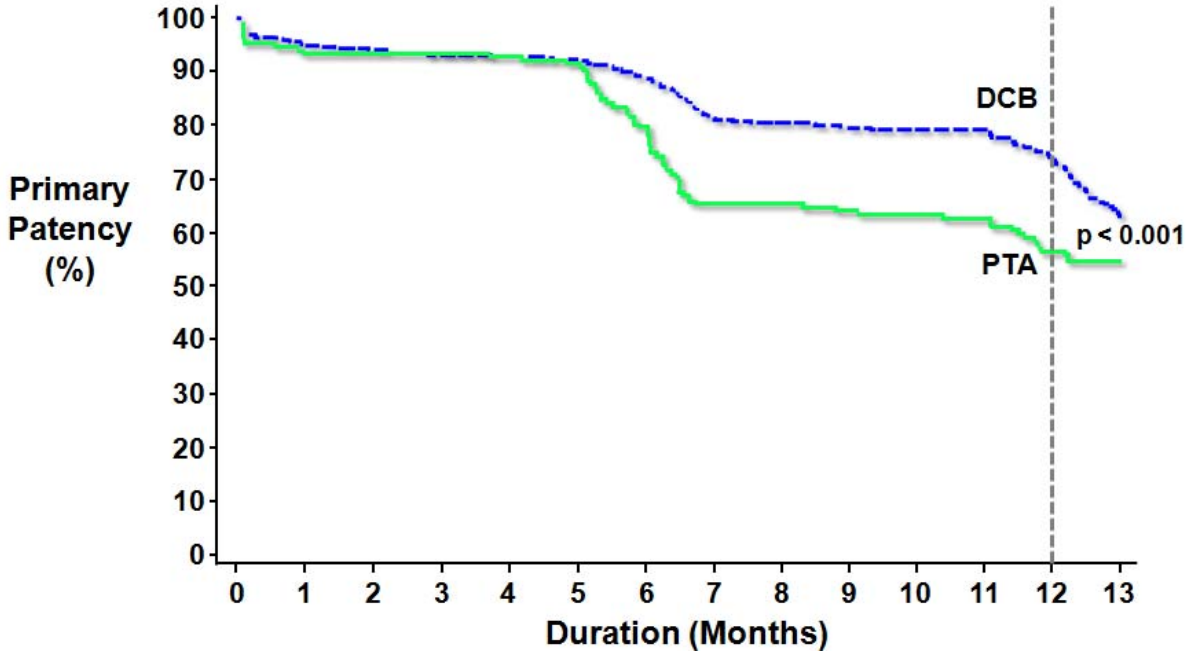


Table 7. Primary Patency Rate 12 Months by Kaplan-Meier

	Test DCB				Control PTA			
Time	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk
30 days	94.9%	16	9	291	93.7%	10	4	146
183 days	88.8%	34	21	261	78.5%	33	11	116
365 days	73.5%	77	60	179	56.8%	64	27	69

[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	12.3% (35/285)	16.8% (24/143)	-4.5%
Total TVR	13.3% (38/285)	18.2% (26/143)	-4.8%
Composite Safety Events[1]	16.1% (46/286)	21.0% (30/143)	-4.9%

[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 in both treatment groups. At 12 months, 88.2% of Lutonix DCB patients and 82.4% of control PTA patients had improved Rutherford Class compared to baseline. Mean improvement in the WIQ total score was 23.9 ± 27.6% for Lutonix DCB compared to 19.2 ± 26.5% for control PTA, and improvement in WIQ walking distance was 31.5 ± 37.0% vs. 22.2 ± 35.4%, respectively. Improvements in ABI, six minute walk test, EQ-5D, and SF-36v2 through 12 months were similar for both groups.

Primary patency was also assessed using alternative Doppler thresholds for restenosis. For Lutonix DCB vs. control PTA respectively, primary patency at 12 months was 68.3% vs. 56.1% based on PSVR ≥ 3.0 indicating restenosis, 64.0% vs. 51.2% based on PSVR ≥ 2.5 indicating restenosis, and 53.2% vs. 45.0% based on PSVR ≥ 2.0 indicating restenosis. 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 (65.2% vs. 52.6%).

Secondary safety endpoints were similar for both Lutonix DCB and control PTA. These included, respectively, all-cause death (2.4% vs. 2.8%), amputation (0.3% vs. 0.0%), amputation-free survival (97.6% vs. 97.2%), thrombosis (0.4% vs. 0.7%), cardiovascular hospitalization (9.1% vs. 7.1%), and major vascular complications (6.3% vs. 4.9%; defined as hematoma >5 cm, false aneurysm, AV fistula, retroperitoneal bleed, peripheral ischemia/nerve injury, transfusion).

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 9 for Primary Endpoints at 1 year by gender.

Table 9: Primary Endpoints at 1 Year by Gender

Primary Endpoint	Gender	Test DCB %(n/N)	Control PTA %(n/N)	Difference %
Primary Effectiveness	Female	56.4% (57/101)	61.4% (27/44)	-4.9%
	Male	70.6% (115/163)	48.4% (44/91)	22.2%
Primary Safety	Female	80.4% (90/112)	67.4% (31/46)	13.0%
	Male	86.2% (150/174)	84.5% (82/97)	1.7%

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 10 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 10. Serious Adverse Events @ 12 months

AE Category	Event Description	Test DCB N=316* % (n subjects)	Control PTA N=160* % (n subjects)
Cardiac Events	Angina	4.1% (13)	1.3% (2)
	Atrial Fibrillation	0.9% (3)	1.3% (2)
	Other Arrhythmia, specify:	0.3% (1)	1.3% (2)
	Cardiac arrest/failure	0.3% (1)	0.0% (0)
	Hypertension (req. therapy)	0.3% (1)	0.6% (1)
	Hypotension (Sustained, req. pressors and/or IABP)	0.3% (1)	0.0% (0)
	MI: Q-wave (STEMI)	0.0% (0)	0.6% (1)
	MI: Non Q-wave (NSTEMI)	0.6% (2)	0.0% (0)
	MI: Unknown	0.9% (3)	1.3% (2)
	CHF: After discharge	1.9% (6)	0.0% (0)
	Other Cardiac, specify:	0.9% (3)	0.6% (1)

AE Category	Event Description	Test DCB N=316* % (n subjects)	Control PTA N=160* % (n subjects)
Clinical Events	Contrast media allergic reaction	0.3% (1)	0.0% (0)
	Fever, unknown etiology	0.3% (1)	0.0% (0)
	Groin infection, local (req. antibiotics)	0.3% (1)	0.0% (0)
	Skin infection, local (req. antibiotics)	0.6% (2)	0.6% (1)
	Other infection, local (req. antibiotics), specify:	1.9% (6)	0.6% (1)
	Infection, systemic (req. antibiotics)	0.6% (2)	0.6% (1)
	Renal insufficiency (> 0.5 increase in Cr from preprocedure/baseline)	0.9% (3)	0.6% (1)
	Renal failure (requiring new dialysis or prolonged hospitalization with dialysis)	0.0% (0)	0.0% (0)
	Respiratory failure: Exacerbation of COPD	1.6% (5)	0.6% (1)
	Pneumonia	2.2% (7)	1.3% (2)
	Neoplasia	3.5% (11)	5.0% (8)
	Pulmonary Embolism	0.3% (1)	0.0% (0)
	Other Clinical, specify:	2.8% (9)	2.5% (4)
	Orthopaedic Injury	1.6% (5)	2.5% (4)
	Orthopaedic Disease	1.9% (6)	1.9% (3)
	Musculoskeletal Pain	0.6% (2)	0.0% (0)
	Arthritis/gout	0.0% (0)	0.6% (1)
	Other Renal Events	0.9% (3)	0.0% (0)
	Gastrointestinal Disorder	1.9% (6)	3.8% (6)
	Inguinal hernia	0.6% (2)	0.0% (0)
	Cholelithiasis	0.0% (0)	0.6% (1)
	Benign Prostatic Hypertrophy	0.3% (1)	0.0% (0)
	Cataracts	1.3% (4)	1.3% (2)
	Electrolyte Abnormality	0.9% (3)	0.0% (0)
	Dyspnea	0.3% (1)	0.0% (0)
	Non-Cardiac Chest Pain	0.9% (3)	0.0% (0)
	Cholecystitis	0.3% (1)	0.6% (1)

AE Category	Event Description	Test DCB N=316* % (n subjects)	Control PTA N=160* % (n subjects)
Hemorrhagic Events	Access site: Hematoma	0.9% (3)	0.0% (0)
	Access site: Significant hemorrhage req. transfusion	0.9% (3)	0.0% (0)
	Access site: Pseudoaneurysm	1.3% (4)	1.9% (3)
	Bleeding/Hemorrhage from anticoagulants	0.3% (1)	0.0% (0)
	Bleed, Gastrointestinal	1.3% (4)	0.6% (1)
	Bleed, Retroperitoneal	0.3% (1)	0.6% (1)
	Anemia, general (req. blood transfusion)	0.3% (1)	0.6% (1)
	Other Hemorrhage, specify:	0.9% (3)	0.6% (1)
Neurological Events	TIA (Focal deficit resolving within 24 hours)	0.3% (1)	0.0% (0)
	Stroke (Focal deficit lasting over 24 hours)	2.8% (9)	0.6% (1)
	Other Neurologic, specify:	1.3% (4)	1.9% (3)
	Hearing loss	0.3% (1)	0.0% (0)
	syncope/near syncope/dizziness/vertigo	1.3% (4)	0.0% (0)
Angiographic Events	Target vessel injury/dissection with study treatment	1.9% (6)	3.8% (6)
	Target vessel injury/dissection with post-treatment	0.3% (1)	1.3% (2)
	Distal embolization with study treatment	0.3% (1)	0.6% (1)
	Distal embolization with post-treatment	0.0% (0)	0.6% (1)
	Clot/Thrombus formation (thrombosis)	0.3% (1)	1.3% (2)
	Distal embolization (non-index procedure)	0.3% (1)	0.0% (0)

AE Category	Event Description	Test DCB N=316* % (n subjects)	Control PTA N=160* % (n subjects)
Vascular Events	Restenosis of the study lesion	1.6% (5)	3.8% (6)
	Restenosis of the study vessel	0.3% (1)	1.3% (2)
	Restenosis of the non-study vessel	7.0% (22)	6.3% (10)
	Clinically-driven target (study) lesion revascularization (TLR)	0.6% (2)	0.6% (1)
	Target (study) vessel revascularization (TVR)	0.0% (0)	0.0% (0)
	Non-target extremity revascularization	0.3% (1)	0.6% (1)
	Non-target acute limb ischemia	0.6% (2)	0.0% (0)
	Target (study) acute limb ischemia	0.3% (1)	0.0% (0)
	Target extremity pain	2.8% (9)	2.5% (4)
	Target extremity ischemic ulcer-New	0.6% (2)	0.0% (0)
	Non-target extremity pain	1.6% (5)	1.3% (2)
	Non-target extremity ischemic ulcer-New	0.0% (0)	0.6% (1)
	Other Vascular, specify:	0.6% (2)	1.3% (2)
	Bilateral lower extremity pain	0.3% (1)	1.9% (3)
	Non target limb aneurysm	0.3% (1)	0.0% (0)
	Claudication	12.0% (38)	16.3% (26)
Other Events	Other, specify:	0.3% (1)	0.0% (0)
Non-Event/ Death Outcomes	Accidental death	0.0% (0)	0.6% (1)
	Unknown cause of death	1.3% (4)	0.6% (1)
	Death (not otherwise specified-NOS)	0.0% (0)	0.0% (0)
Total	Total	50.6% (160)	48.8% (78)

* Event counts are for all events from all randomized patients through 12 month follow-up. Denominator for percentage calculation includes all randomized patients.

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.

10.3 LEVANT Safety Registry

10.3.1 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.

10.3.2 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)[1], all-cause death, amputation, AFS, target vessel revascularization (TVR), thrombosis, major vascular complications, and readmission for cardiovascular events.

10.3.3 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 11 and Table 12 presents 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.

Table 11: 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)

[1] Rocha-Singh, K.J., et al., *Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease.* Catheter Cardiovasc Interv, 2007. **69**(6): p. 910-9.

Variable	LEVANT 2 Roll-in DCB	LEVANT 2 Randomized DCB	LEVANT 2 Safety Registry DCB	All DCB
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 Hawiian 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 12: 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)
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)

Variable	LEVANT 2 Roll-in DCB	LEVANT 2 Randomized DCB	LEVANT 2 Safety Registry DCB	All DCB
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

10.3.4 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.

10.3.5 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.

10.3.5.1 Secondary Endpoints

Composite safety endpoint results are summarized in Table 13 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 13: 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]	99.4% (306/308) [98.5, 100.0]	99.4% (643/647) [98.8, 100.0]	99.4% (1003/1009) [98.9, 99.9]
6 Months	96.1% (49/51) [90.8, 100.0]	92.0% (275/299) [88.9, 95.1]	98.0% (582/594) [96.8, 99.1]	96.0% (906/944) [94.7, 97.2]
12 Months	91.7% (44/48) [83.8, 99.5]	84.0% (241/287) [79.7, 88.2]	94.6% (423/447) [92.5, 96.7]	90.5% (708/782) [88.5, 92.6]

[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 14 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 14: 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]	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)	0.3% (2/632)	0.6% (6/986)
	12 Months	6.0% (3/50)	2.4% (7/291)	0.4% (2/500)	1.4% (12/841)

Outcome Measure (CEC Adjudicated)	Visit	Roll-in DCB %(n/N)	Randomized DCB %(n/N)	Registry DCB %(n/N)	All DCB %(n/N)
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% (0/498)	0.1% (1/833)
Minor 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)	0.0% (0/298)	0.0% (0/630)	0.0% (0/979)
	12 Months	0.0% (0/48)	0.0% (0/286)	0.0% (0/498)	0.0% (0/832)
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)	99.7% (630/632)	99.4% (979/985)
	12 Months	94.0% (47/50)	97.6% (284/291)	99.6% (498/500)	98.6% (829/841)
Total TVR	1 Month	0.0% (0/54)	0.3% (1/308)	0.5% (3/646)	0.4% (4/1008)
	6 Months	3.9% (2/51)	6.7% (20/298)	1.9% (11/593)	3.5% (33/942)
	12 Months	8.3% (4/48)	13.3% (38/286)	5.2% (23/446)	8.3% (65/780)
Reintervention for Thrombosis	1 Month	0.0% (0/54)	0.3% (1/308)	0.0% (0/646)	0.1% (1/1008)
	6 Months	0.0% (0/51)	0.3% (1/298)	0.0% (0/630)	0.1% (1/979)
	12 Months	0.0% (0/48)	0.3% (1/286)	0.0% (0/498)	0.1% (1/832)
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% (33/632)	5.4% (53/981)
	12 Months	8.3% (4/48)	9.4% (27/286)	10.8% (55/511)	10.2% (86/845)
Major Vascular Complications[2]	1 Month	3.7% (2/54)	4.2% (13/308)	1.2% (8/648)	2.3% (23/1010)
	6 Months	3.8% (2/52)	5.4% (16/298)	1.4% (9/632)	2.7% (27/982)
	12 Months	4.1% (2/49)	6.3% (18/286)	2.0% (10/501)	3.6% (30/836)

[1]An additional 4 deaths in the Registry population have not yet been CEC adjudicated. Including all site-reported deaths, there have been a total of 6 deaths (1.2%) in the Registry and 16 (1.9%) for pooled DCB cohorts through 12 months. The single perioperative death was a murder on day 20.

[2] 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.

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

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 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 5**.

Precaution: The safety and effectiveness of deploying more than two Lutonix Catheters (i.e., a maximum drug coating quantity of approximately 7.6 mg paclitaxel) in a patient has not been established.

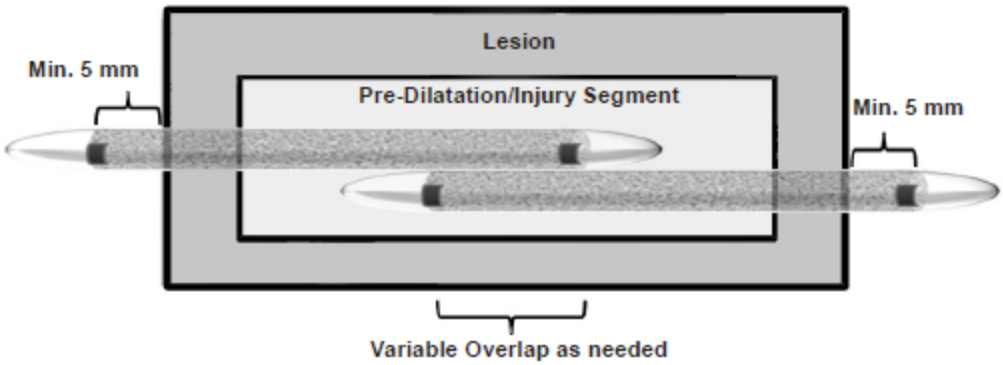


Figure 5: Balloons are appropriately sized to minimize overlap but are consecutively placed by angiography with as much overlap as necessary to treat lesion appropriately

12.4 Predilatation of Target Lesion

1. Predilatation of the target lesion with an uncoated PTA catheter is required prior to the use of the Lutonix Catheter.
2. Predilate the target lesion to at least 1mm of the reference vessel diameter.

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.

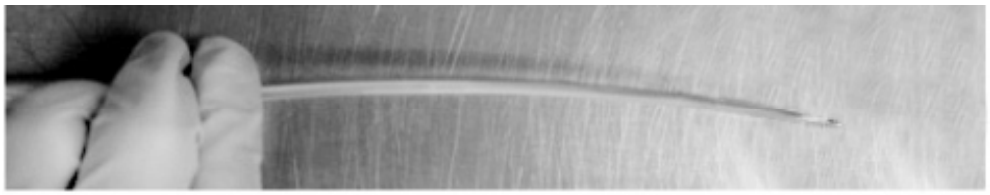
   Warning: Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon.

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 from **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.

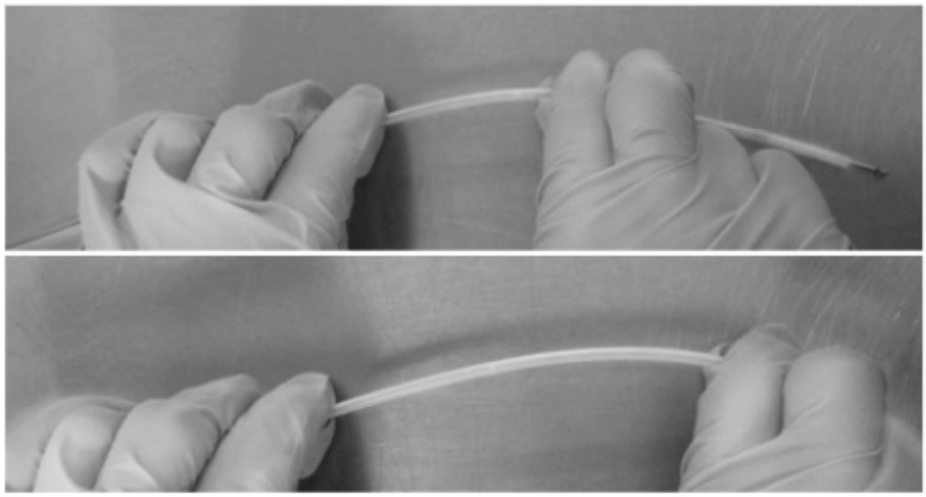
12.6 Use of the Lutonix® Catheter

1. While under negative pressure and before removing the balloon protector and wire lumen stylet, perform the following steps to reduce friction between the balloon protector and the balloon and remove the balloon protector:

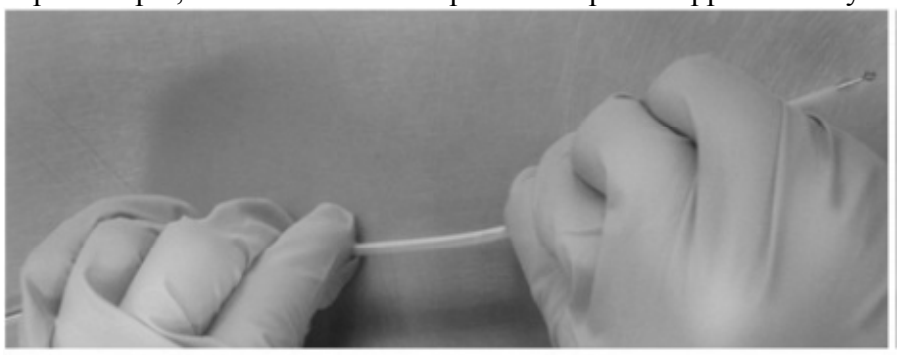
Step 1- Leaving the wire lumen stylet in place; grasp the proximal end of the balloon protector with one hand.

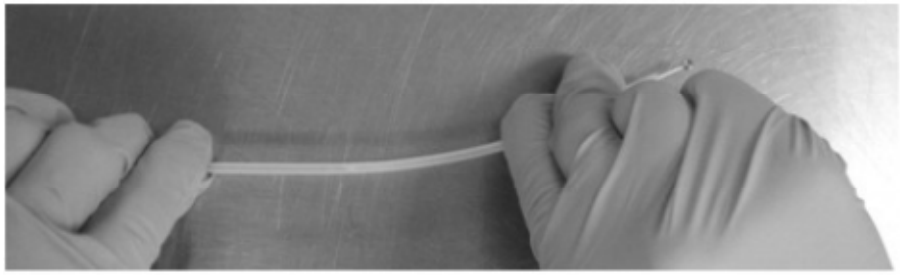


Step 2- Using the opposite hand, gently slide the thumb and forefinger from the proximal end of the balloon protector out toward the distal end of the balloon protector while flexing the balloon slightly downward approximately 15 degrees.

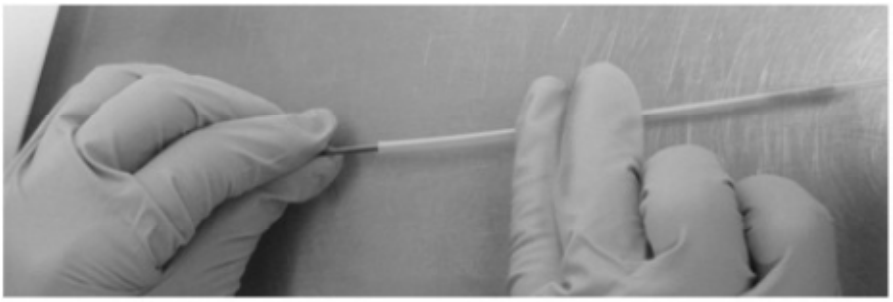


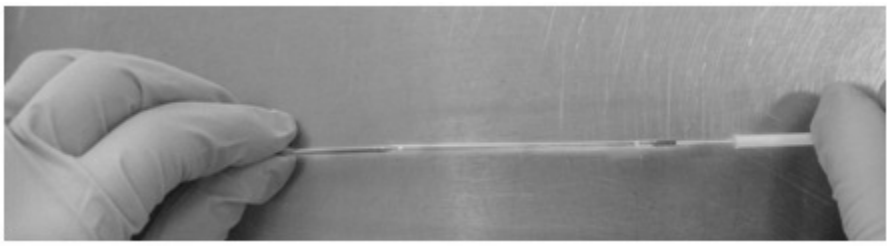
Step 3- Repeat Step 2, but flex the balloon protector upward approximately 15 degrees.





Step 4- Grasp the balloon protector at roughly the midpoint of the balloon protector and pull it away from the balloon catheter. The balloon protector and wire lumen stylet should be removed together.





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, slowly advance the Lutonix® Catheter through the introducer sheath and over the wire to the site of inflation. During catheter advancement, inspect the catheter shaft for damage.
5. To ensure therapeutic drug delivery, the Lutonix® Catheter should be advanced to the target site in the shortest possible time. If the deployment of the Lutonix Catheter exceeds 3 minutes, the catheter requires replacement with a new unit.
6. Position the balloon relative to the lesion, ensuring coverage of at least 5mm proximally and distally beyond the margins of the lesion segment, and immediately inflate to appropriate pressure to achieve full wall apposition (balloon to artery ratio of 1:1). 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.

7. Apply negative pressure to fully deflate the LUTONIX® Catheter. Prior to removal, confirm that the balloon is fully deflated under fluoroscopy.
8. Perform angiography to confirm dilatation of the lesion.
9. Withdraw the LUTONIX® Catheter from the body under negative pressure. Maintain the guidewire across the stenosis.
10. Whenever possible, the LUTONIX® Catheter should be the final treatment of the vessel; however, post-dilatation is allowed with another PTA catheter or used LUTONIX® catheter.
11. After confirming that a satisfactory dilatation was achieved, remove all equipment from the body and close access site per standard clinical practice.
12. 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.
13. 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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