1 Summary of Safety and Effectiveness Data (SSED)

1.1 General Information

Device Generic Name: Drug Coated Balloon Percutaneous Transluminal Angioplasty Catheter

Device Trade Name: LUTONIX® 035 Drug Coated Balloon PTA Catheter

Applicant's Name and Address: Lutonix, Inc.
9409 Science Center Drive
New Hope, MN 55428

Date of Panel Recommendation: [TBD]

Premarket Approval Application (PMA) number: P130024

Date of FDA Notice of Approval: [TBD]

1.2 Indications for Use

The LUTONIX® 035 Drug Coated Balloon PTA Catheter is indicated for improving luminal diameter for the treatment of obstructive de novo or non-stented restenotic lesions (≤ 15 cm in length) in native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm.

1.3 Contraindications

The LUTONIX® 035 Drug Coated Balloon PTA Catheter is contraindicated for use in:

- Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
- Patients with known hypersensitivity or contraindication to paclitaxel or paclitaxel-related compounds.
- 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.

1.4 Warnings and Precautions

The warnings and precautions can be found in the LUTONIX® 035 Drug Coated Balloon PTA Catheter labeling.

1.5 Device Description

The LUTONIX® 035 Drug Coated Balloon PTA Catheter (LUTONIX® DCB) is an over-the-wire (OTW) percutaneous transluminal angioplasty (PTA) catheter with the Lutonix's paclitaxel-based drug coating on the surface of the balloon. The LUTONIX® DCB is 0.035" guidewire

compatible and has balloon size range from 4.0mm – 6.0mm in diameter and 40mm – 100mm in length. The LUTONIX® DCB is available in 75cm, 100cm and 130cm in working length.

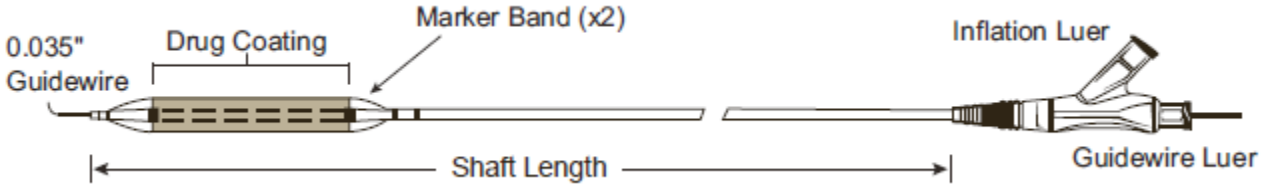


Figure 1. Lutonix® 035 Drug Coated Balloon PTA Catheter, Model 9004

The LUTONIX DCB contains paclitaxel, a well-known anti-proliferative drug, as the active pharmaceutical ingredient (API), and excipients – polysorbate and sorbitol. The balloon is coated with a constant 2µg/mm^2 of paclitaxel and the total dosage of paclitaxel per balloon size is correlated to the balloon surface area and is shown in **Table 1** below.

Table 1. Total Drug Dosage (Paclitaxel) by Balloon Size

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

1.5.1 Drug Component Description

Paclitaxel is a cytotoxic anticancer drug substance, which is originally a naturally occurring product obtained by extraction and successive purifications from yew tree species (Taxus brevifolia, Taxus yunnanensis, etc). The present manufacture of paclitaxel drug substance is a semi-synthetic process using 10-deacetylbaccatin III as natural starting material and an oxazolidine carboxylate derivative, (1S,2R,5S)-(+)-menthyl (4S,5R)-3-benzoyl-2-methoxy-4-phenyloxazolidine-5-carboxylate, as chemical starting material. Paclitaxel drug substance is described in the United States Pharmacopoeia (*Paclitaxel*). Details of the paclitaxel drug substance are provided below.

Nomenclature:

- United States Adopted Name (USAN): Paclitaxel
- Chemical Name:

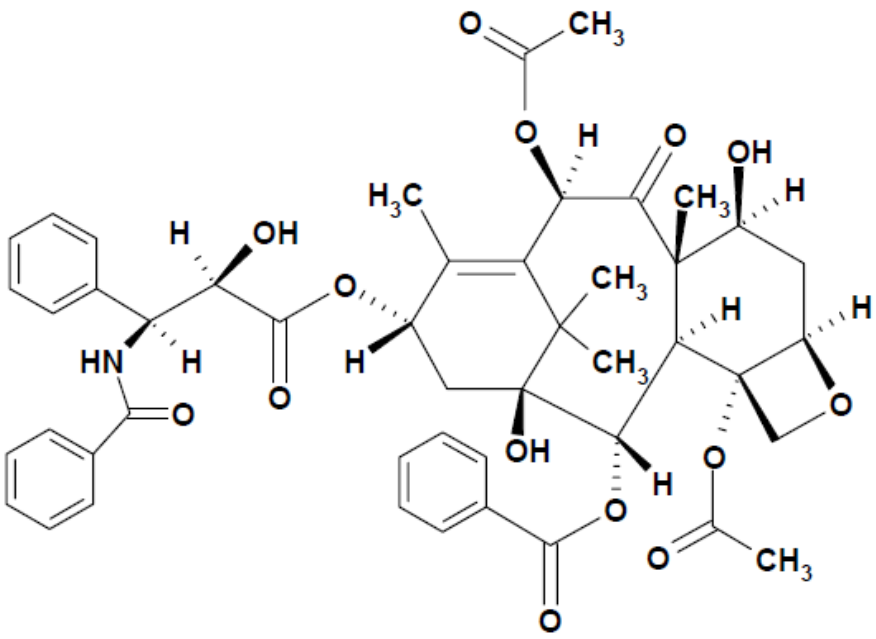
  (2aR,4S,4aS,6R,7E,9S,11S,12S,12aR,12bS)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-7,11-methano-1H-cyclodeca[[d]benzoxetine-6,9,12,12b-tetrayl 6, 12b-diacetate 12-benzoate 9 -[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate] or 5β,20-epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate

2-benzoate 13-[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate]

- CAS Registry Number: 33069-62-4
- Compendial Name (USP): Paclitaxel

Structure

- Molecular Formula: $C_{47}H_{51}NO_{14}$
- Relative Molecular Mass: M_r: 854
- Structural Formula:



1.5.2 Mechanism of Action

The mechanism by which the LUTONIX DCB inhibits neointimal growth as seen in preclinical and clinical studies has not been established. Paclitaxel is an antimitotic agent that prevents microtubule deconstruction[1], and paclitaxel inhibits restenosis by preventing migration and proliferation of smooth muscle cells, inflammatory cells, and fibroblasts, and by preventing secretion of extracellular matrix proteins[2]. Paclitaxel is very lipophilic, and it binds tightly to vessel wall tissue and resists wash out into aqueous blood. Paclitaxel has been shown to diffuse transmurally after endoluminal delivery to the vessel wall and to reach concentrations in smooth muscle cell and adventitial cell layers that are 5 to 20-fold higher than at the luminal source[3]. Paclitaxel delivered by LUTONIX DCB has been shown to have a residence time on the order of months in the treated arteries.

[1] Schiff. Promotion of microtubule assembly in vitro by taxol. *Nature* 277, no. 5698 (1979): 665-667.
[2] Waksman. Drug-eluting stents: from bench to bed. *Cardiovascular Radiation Medicine* 3 (2002): 226-241
[3] Creel. Arterial paclitaxel distribution and deposition. Circ Res." *Circ Res* 86, no. 8 (2000): 879-884.

1.6 Alternative Practices and Procedures

There are several other alternatives for the treatment of femoropopliteal artery atherosclerotic disease, including:

- Non-invasive treatment (exercise and/or drug therapy),
- Minimally invasive treatment (plain old balloon angioplasty (POBA), endovascular stent, directional atherectomy), and
- Surgical treatment (surgical bypass).

1.7 Marketing History

The LUTONIX 035 Drug Coated Balloon PTA Catheter has been commercially available outside of the US, including Europe and other countries, for use in treatment of lower limb vascular disease. To date, one recall has occurred for retrieval of products with weak sterile pouch seal from the pouch supplier; 21 units were identified to be potentially affected which required recall of 165 units in total from the field. This recall was completed on March 2014.

1.8 Potential Adverse Effects of the Device on Health

Potential adverse events which may be associated with a percutaneous peripheral balloon angioplasty procedure include, but are not limited to, the following:

- Additional intervention
- Allergic reaction to drugs or contrast medium
- 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

Potential adverse events that may be unique to the LUTONIX DCB include, but are not limited to, the following:

- Allergic/immunologic reaction to drug coating

For the specific adverse events that occurred in the IDE clinical study reference **Table 19** (Summary of Clinical Study) below.

1.9 Summary of Preclinical Studies

1.9.1 Laboratory Studies

1.9.1.1 Catheter Bench Testing

LUTONIX DCBs were subjected to the mechanical bench testing per the FDA Guidance on PTCA catheters and Lutonix's internal requirements. Summary of the results is provided in **Table 2** below.

In conclusion, the results confirm that the LUTONIX DCB meets all the requirements of the catheter bench testing.

Table 2. Catheter Bench Test Summary

Test	Description of Test	Test Results
Catheter Engineering Tests		
Dimensional and Functional Attributes	The catheter is dimensionally measured and functionally tested with accessory devices to confirm their compatibility with the catheter. The device met the established acceptance criteria.	Pass
Minimum Balloon Burst Strength	Testing is performed to confirm with 95% confidence and 99.9% reliability that the balloons will not rupture below the labeled rated burst pressure (RBP). The device met the established acceptance criteria.	Pass
Balloon Compliance	Testing is performed to determine the relation of the balloon diameter with the balloon pressure. The device met the established acceptance criteria.	Pass
Balloon Inflation and Deflation Time	Testing is performed to confirm the inflation and deflation times of the balloon. The device met the established acceptance criteria.	Pass
Balloon Fatigue	Testing is performed to confirm with 95% confidence and 90% reliability that the balloon will not rupture when inflated and deflated to RBP for up to 20 cycles. The device met the established acceptance criteria.	Pass
Tensile Strength	Testing is performed to confirm the tensile strength of the catheter. The device met the established acceptance criteria.	Pass
Flexibility and Shaft Kink	Testing is performed on the catheter shaft to determine its bend radius before kink occurs. The device met the established acceptance criteria.	Pass
Torque Strength	Testing is performed in a simulated use tracking model to determine the rotation of the catheter until damage. The device met the established acceptance criteria.	Pass

Test	Description of Test	Test Results
Balloon Preparation, Delivery and Retrieval	Testing is performed in a simulated use track model to confirm the catheter preparation and track/retrieval without damage. The device met the established acceptance criteria.	Pass
Radiopacity	The radiopacity of the catheter markers are confirmed to be acceptably visible under fluoroscopic imaging. The device met the established acceptance criteria.	Pass
Coating Characterization Testing		
Coating Durability and Particulate Generation	Testing is performed using a simulated use tracking model to quantify and analyze the particulate matter generated during the simulated use procedure. The device met the established acceptance criteria.	Pass
Coating Uniformity	Consistency of the drug coating on the balloon is measured to confirm its uniformity. The device met the established acceptance criteria.	Pass

1.9.1.2 Sterilization

The LUTONIX DCB is sterilized using ethylene oxide (EO) sterilization. The cycle is validated per the ISO 11135-1:2007 (Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization). Results show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, the amount of EtO residual and bacterial endotoxin was verified to be within the specification limits.

1.9.1.3 Coating Characterization Testing

The following coating tests were performed to characterize the drug coating on the LUTONIX DCB.

Test	Test Description
Particulate Release	Simulated use test was performed to quantify the particulate matter during the tracking and deployment of the Lutonix DCB.
Coating Physical Properties	Tests were performed to characterize the physical properties of the coating including: • Coating thickness • Coating uniformity
Coating Dwell Time Study	In-vivo study was performed to confirm the quantity of the coating retained after tracking and retrieval to the target anatomy.
Coating Durability	Tests were performed to confirm the coating durability/adhesion to the balloon surface after inflation/deflation and insertion through hemostasis valve in dry air. In conclusion, durability testing showed that ≤ 0.1% content is lost during the respective testing.

1.9.1.4 Chemistry, Manufacturing and Controls (CMC) Testing

The following analytical testing was performed on the Lutonix DCB as part of CMC.

Test	Preliminary Acceptance Criteria
Appearance	Visual inspection was conducted to verify that the Lutonix DCB drug coating meets the appearance specification.
Identification	Assays are conducted to verify the identity of the paclitaxel drug on the Lutonix DCB using two different methods.
Assay	Assays are conducted to verify that the total amount of drug on the Lutonix DCB met specification.
Content Uniformity	Multiple catheters are tested for assay content to verify the uniformity of the drug content across the individual catheters.
Related Substances	Assays are conducted to verify the amount and type of degradation products on the Lutonix DCB.
Residual Solvent	The amount of residual solvent is verified to be within the established specification limits.
Dissolution	Dissolution tests are performed to verify the drug release profile of the Lutonix DCB.
Particulate Matter	Simulated use particulate release tests are performed to verify the simulated use drug release profile of the Lutonix DCB.

1.9.1.5 Stability/Shelf-Life

A stability study was conducted to establish a shelf-life/expiration date for the LUTONIX DCB. Functional testing was performed on the aged Lutonix DCB and packaging and analytical testing was performed to confirm the stability of the drug coating.

1.9.1.6 Biocompatibility

The biological effects of the LUTONIX DCB were assessed in accordance with the recommended biocompatibility tests in ISO 10993-1:2009 (*Biological Evaluation of Medical Devices – General Requirements*) for an externally communicating device with limited contact duration (< 24 hours) with circulating blood, and the FDA guidance documents on drug eluting stents *(Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies*, Mar 2008) and PTCA Catheters (*Class II Special Controls Guidance Document for Certain PTCA Catheters*, Sept 2010).

Lutonix conducted a number of biocompatibility tests to establish the safety profile of the materials used in the LUTONIX DCB on both the uncoated PTA catheter and the drug coated balloon component. The components were separately tested due to the potential of paclitaxel, a known cytotoxic active pharmaceutical ingredient, to impact the biocompatibility assessment results of the catheter materials and manufacturing processes. Using the same approach, extraction followed by chemical identification of the compounds extracted and a toxicological assessment of these compounds were also performed. Summary of results are provided below.

Table 3. Biocompatibility Summary – Group 1 (Uncoated PTA Catheter)

Test Name	Acceptance Criteria	Results
Cytotoxicity Study ISO 10993-5: 2009, MEM Elution	The biological response of the test sample must be ≤ to grade 2 (mild).	Acceptable
Maximization Sensitization ISO 10993-10: 2002, Sodium Chloride & Sesame Oil	Consideration is given to the overall pattern, intensity, duration, and character of reactions of the test as compared to the control conditions.	Acceptable
Intracutaneous ISO 10993-10: 2002, Sodium Chloride & Sesame Oil	The difference between the test extract mean score and corresponding control mean score is 1.0 or less.	Acceptable
Systemic Toxicity ISO 10993-11: 2006, Sodium Chloride & Sesame Oil	None of the mice treated with the test extract show a significantly greater reaction than the corresponding control mice.	Acceptable
Pyrogen Study, Material Mediated ISO 10993-11: 2006, Sodium Chloride	No single animal shows an increase of 0.5°C or more above its baseline temperature.	Acceptable
ASTM Hemolysis ASTM F756-00 (2008)	A hemolytic index of 2% or less will be considered to be nonhemolytic	Acceptable
C3A Complement Activation Assay ISO 10993-4: 2002 Enzyme Immunossay	If the C3a concentration of the test sample is statistically higher than both the activated normal human serum (NHS) and negative control, then the sample is considered positive and an activator of the complement system.	Acceptable
SC5b-9 Complement Activation Assay ISO 10993-4: 2002 Enzyme Immunossay	If the SC5b-9 concentration of the test sample is statistically higher than both the activated NHS and negative control, then the sample is considered positive and an activator of the complement system.	Acceptable

Table 4. Chemical Characterization Summary – Group 1 (Uncoated PTA Catheter)

Test Name	Results
USP Physicochemical Testing Infrared Analysis – Infrared Analysis – Purified Water (PW), Isopropanol(IPA), & Hexane Extract	Because of low toxicity, based on biocompatibility test results, the levels of non-volatile organic compounds detected do not cause any toxicological concerns.
Fourier Transform Infrared Spectroscopy (FTIR) of the Extraction Residues Infrared Analysis – PW, IPA, & Hexane Extract	The compounds detected in the residue from the uncoated PTA catheter are what would be expected from a device containing PEBAX polymers.
Inductively Coupled Plasma (ICP) Spectroscopy Exhaustive Extraction – Lipophilic Extractables in IPA	The levels of calcium, iron, and potassium detected in the PW extracts are lower than the levels of these elements endogenously present in human tissues. No other element/metallic species were detected in the PW extracts.
Gas Chromatography – Mass Spectrometry (GC/MS) Determination of Extractable Semi Volatile Organic compounds by GC/MS – PW, IPA, & Hexane Extract	The PW extract had a single semi-volatile organic species while the IPA and hexane extracts contained more extractables. The detected compounds appear to be structurally related to the plastics, balloon manufacturing process and the Loctite adhesive.
Liquid Chromatography/Mass Spectrometry (LC/MS) LC/MS Screen for Extracts – PW, IPA & Hexane extract.	Because of low toxicity, based on biocompatibility test results, the levels of non-volatile organic compounds detected do not cause any toxicological concerns.

Table 5. Biocompatibility Summary - Group 2 (Drug Coated Balloon Component)

Test Name	Acceptance Criteria	Results
Cytotoxicity Study ISO 10993-5: 2009, MEM Elution & Agarose Overlay Method	The biological response of the test sample must be ≤ to grade 2 (mild).	Acceptable
Maximization Sensitization ISO 10993-10: 2002, Sodium Chloride & Sesame Oil	Consideration is given to the overall pattern, intensity, duration, and character of reactions of the test as compared to the control conditions.	Acceptable
Intracutaneous ISO 10993-10: 2002, Sodium Chloride & Sesame Oil	The difference between the test extract mean score and corresponding control mean score is 1.0 or less.	Acceptable
Systemic Toxicity ISO 10993-11: 2006, Sodium Chloride & Sesame Oil	None of the mice treated with the test extract show a significantly greater reaction than the corresponding control mice.	Acceptable
USP Pyrogen Study, Material Mediated ISO 10993-11: 2006, Sodium Chloride	No single animal shows an increase of 0.5°C or more above its baseline temperature.	Acceptable
ASTM Hemolysis ASTM F756-00 (2008)	A hemolytic index of 2% or less will be considered to be nonhemolytic	Acceptable
C3a Complement Activation Assay ISO 10993-4: 2002, Enzyme Immunoassay	If the C3a concentration of the test sample is statistically higher than both the activated NHS and negative control, then the sample is considered positive and an activator of the complement system.	Acceptable
SC5b-9 Complement Activation Assay ISO 10993-4: 2002, Enzyme Immunoassay	If the SC5b-9 concentration of the test sample is statistically higher than both the activated NHS and negative control, then the sample is considered positive and an activator of the complement system.	Acceptable

Table 6. Chemical Characterization Summary – Group 2 (DCB Component)

Test Name	Results
USP Physicochemical Testing Infrared Analysis – Infrared Analysis – Purified Water (PW), Isopropanol(IPA), & Hexane Extract	Because of low toxicity, based on biocompatibility test results, the levels of non-volatile organic compounds detected do not cause any toxicological concerns.
Fourier Transform Infrared Spectroscopy (FTIR) of the Extraction Residues Infrared Analysis – PW, IPA, & Hexane Extract	The compounds detected in the FTIR spectra from the extraction residues were consistent with the chemical composition of the materials used to construct the device components and coating.
Inductively Coupled Plasma (ICP) Spectroscopy Exhaustive Extraction – Lipophilic Extractables in IPA	The levels of calcium, iron, and potassium detected in the PW extracts are lower than the levels of these elements endogenously present in human tissues. No other element/metallic species were detected in the PW extracts.
Gas Chromatography – Mass Spectrometry (GC/MS) Determination of Extractable Semi Volatile Organic compounds by GC/MS – PW, IPA, & Hexane Extract	The PW extract had a single semi-volatile organic species while the IPA and hexane extracts contained more extractables. The detected compounds appear to be structurally related to the plastics, balloon manufacturing process and the Loctite adhesive.
Liquid Chromatography/Mass Spectrometry (LC/MS) LC/MS Screen for Extracts – PW, IPA & Hexane extract.	Because of low toxicity, based on biocompatibility test results, the levels of non-volatile organic compounds detected do not cause any toxicological concerns.

Table 7. *In Vivo* Thromboresistance Study – Group 3 (Complete DCB Catheter)

Test Name	Test Method	Results
Hemocompatibility Thrombogenicity	ISO 10993-4: 2002, In-Vivo Thromboresistance Analysis in Dogs	Non-significant thrombosis

1.9.2 Animal Studies

Detailed arterial histopathology information is not attainable through human clinical trials so a series of animal studies were conducted to evaluate the safety of the Lutonix DCB.

Safety, Safety Margin and Pharmacokinetics studies were conducted with the LUTONIX DCB in accordance with FDA 21 CFR Part 58 GLP Regulations. In addition, a supplementary non-GLP Surface Deposition PK study was performed for evaluation of surface versus tissue-associated drug in treated arteries. Reference **Table 8** below.

Table 8. Animal Study Overview

Description / Study #	Animal Model	Devices	Study Design	Time points	Endpoints
Safety Study	22 Domestic Swine	Test – Nominal Dose Lutonix DCB Control- uncoated balloon	Single balloon treatment in Femoral Arteries	28, 90, 180 Days	• Quantitative Angiography • Clinical Safety • Histopathology/SEM • Device handling
Safety Margin Study	23 Domestic Swine	Test – 2x Dose Lutonix DCB Control- uncoated balloon	Two balloons 100% overlapped (4x Dose) in Femoral Arteries	28, 90, 180 Days	• Quantitative Angiography • Clinical Safety • Histopathology/SEM
Pharmacokinetics Study	39 Domestic Swine	Test – Nominal Dose Lutonix DCB	Single balloon treatment in Femoral Arteries	3min, 1hr, 24hr, 7d, 30d, 60d, 90d, & 180d	• Tissue Levels • Organ Levels • Plasma Levels

1.10 Summary of Clinical Studies

The safety and effectiveness of the LUTONIX® Catheter is derived from the LEVANT 2 prospective, multicenter single blind, randomized, controlled IDE trial and the LEVANT I multicenter, randomized, controlled European trial.

The one year results from the LEVANT 2 pivotal trial and the two-year final results from the LEVANT I trial are presented here. Patient follow-up for the LEVANT 2 trial is ongoing and is planned out to 5-years.

1.10.1 LEVANT 2 Randomized Pivotal Trial

1.10.1.1 Study Design

The LEVANT 2 Randomized clinical trial is a prospective, multicenter, single blind, randomized, controlled trial comparing the LUTONIX 035 Drug Coated Balloon PTA Catheter vs. standard balloon angioplasty for treatment of de novo or non-stented restenotic lesions in native femoropopliteal arteries.

The LEVANT 2 Randomized clinical trial recruited patients with denovo or restenotic lesion in the femoropopliteal artery. After baseline angiogram and 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 treatment with either the LUTONIX 035 Drug Coated Balloon PTA Catheter (Test Arm) or standard PTA catheter (Control Arm). Subjects who did not meet the protocol-defined criteria after pre-dilatation were treated per standard practice and followed for safety through 30 days.

Overview of the study flowchart is provided in the **Figure 2** and the overview of the LEVANT 2 study design if provided in **Table 9** below.

Figure 2: Study Flow Chart

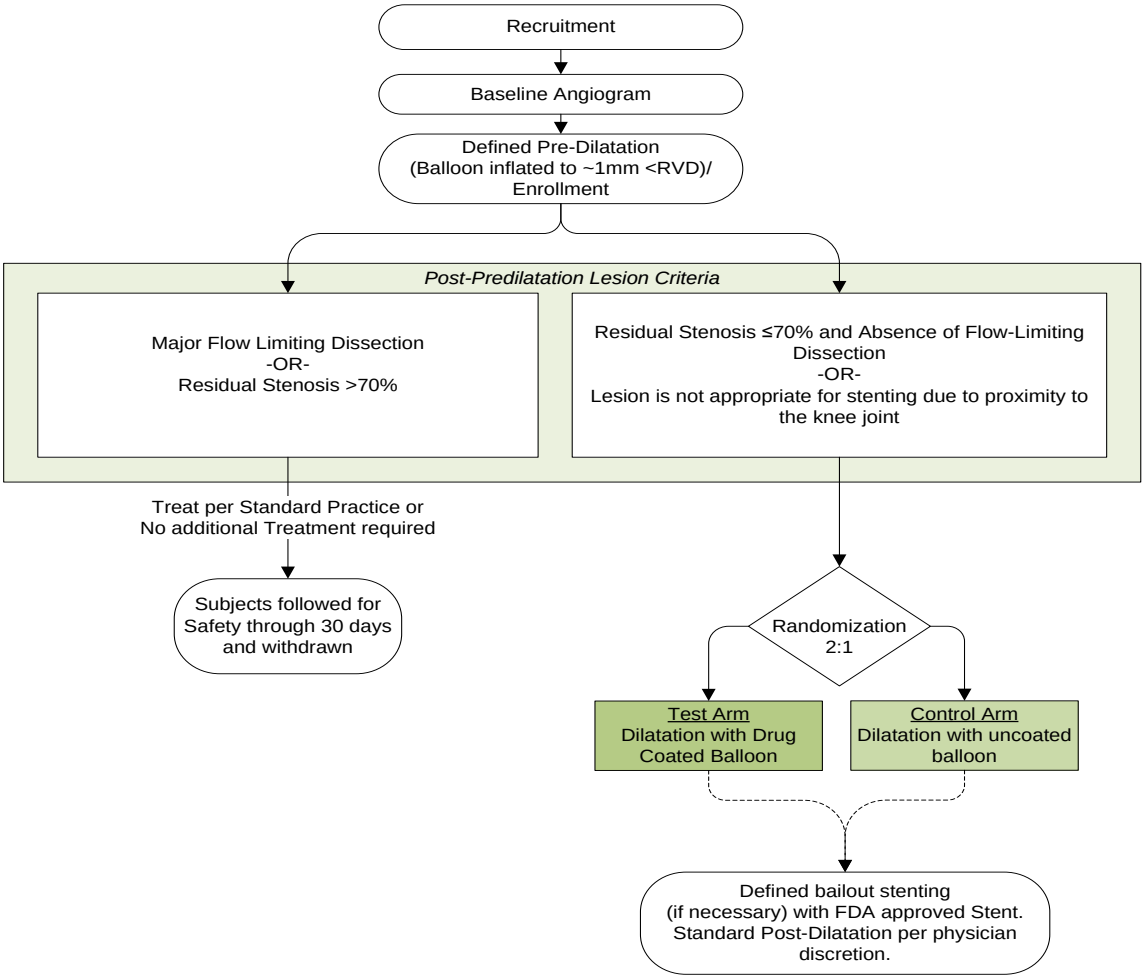


Table 9. LEVANT 2 Randomized Clinical Trial Study Design

Item	Description
Study Type/Design	Prospective, Multicenter, Single Blind, Randomized, Safety and Efficacy
Number of Subjects Enrolled	Total: 543 Standard Practice: 11 / Randomized(2:1): 476 / Roll-in: 56 Test Arm (DCB): 316 / Control Arm (POBA): 160

Treatment Lesion	De novo or restenotic angiographically significant lesion in the superficial femoral or popliteal artery with lesion length of ≤ 15 cm in length and reference vessel of 4 mm – 6 mm in diameter.
Treatment Device	Test Arm: Lutonix 035 Drug Coated Balloon PTA Catheter (formerly known as Moxy Drug Coated Balloon) Control Arm: Non-coated standard percutaneous transluminal angioplasty balloon catheter (standard PTA catheter)
Balloon Sizes	Balloon Diameters: 4 mm, 5 mm, & 6 mm Balloon Lengths: 40 mm, 60 mm and 100 mm in length.
Concomitant Medication	Appropriate antiplatelet therapy (clopidogrel or prasugrel) for at least 1 month and aspirin indefinitely. Anticoagulation was per hospital standard practice.
Primary Endpoints	Safety 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 re-intervention, and index-limb-related death. Efficacy Primary Patency of the target lesion at 1 year. Primary Patency is defined as the absence of target lesion restenosis (as adjudicated by blinded core-lab) and freedom from target lesion revascularization (TLR).
Randomized Subject Follow-Up Schedule	*Clinical*: 6, 12, and 24 Months *Duplex Ultrasound (DUS):* 0-30 days, 6 months, 12 months, and 24 months *Telephone:* 1, 36, 48 and 60 Months
PK Study	Pharmacokinetic testing for up to 30-days from up to 30 subjects treated with the Lutonix DCB.
Status	One year results reported

1.10.1.2 Clinical Inclusion/Exclusion Criteria

Enrollment in the LEVANT 2 Randomized clinical trial was limited to subjects who met the eligibility criteria and who provided a signed informed consent form prior to enrollment. Subjects had to be at least 18 years old, be presenting with claudication or ischemic rest pain, have an angiographically significant lesion in the femoropopliteal artery, and have an outflow artery to the foot. Female subjects with childbearing potential had to have a negative pregnancy test within 30-days of the index procedure.

Clinical Inclusion Criteria

1. Male or non-pregnant female ≥18 years of age;
2. Rutherford Clinical Category 2-4;

3. Subject is willing to provide informed consent, is geographically stable and comply with the required follow up visits, testing schedule and medication regimen;

Angiographic Inclusion Criteria

1. Lesion Length ≤15 cm;
2. Up to two focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. two discrete segments, separated by several cm, but both falling within a composite length of ≤15 cm);
3. ≥70% stenosis by visual estimate;
4. Lesion location starts ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the TP trunk;
5. *de novo* lesion(s) or non-stented restenotic lesion(s) >90 days from prior angioplasty procedure
6. Lesion is located at least 3 cm from any stent, if target vessel was previously stented;
7. Target vessel diameter between ≥4 and ≤6 mm and able to be treated with available device size matrix;
8. Successful, uncomplicated (without use of a crossing device) antegrade wire crossing of lesion;
9. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions);
   NOTE: Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication.
10. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure);
11. Contralateral limb lesion(s) cannot be treated within 2 weeks before and/or planned 30 days after the protocol treatment in order to avoid confounding complications;
12. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment.

Exclusion Criteria:

1. Pregnant or planning on becoming pregnant or men intending to father children;
2. Life expectancy of <5 years;
3. Patient is currently participating in an investigational drug or other device study or previously enrolled in this study;
   NOTE: Enrollment in another clinical trial during the follow up period is not allowed.
4. History of hemorrhagic stroke within 3 months;
5. Previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the index procedure;
6. History of MI, thrombolysis or angina within 2 weeks of enrollment;
7. Rutherford Class 0, 1, 5 or 6;

8. Renal failure or chronic kidney disease with MDRD GFR ≤30 ml/min per 1.73 m^2 (or serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis);
9. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion;
10. Inability to take required study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication;
11. Anticipated use of IIb/IIIa inhibitor prior to randomization;
12. Ipsilateral retrograde access;
13. Composite lesion length is >15 cm or there is no normal proximal arterial segment in which duplex flow velocity can be measured;
14. Significant inflow disease. Successful treatment of inflow disease allowed prior to target lesion treatment;
15. Known inadequate distal outflow (>50% stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion;
16. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;
17. Severe calcification that renders the lesion undilatable;
18. Use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).

1.10.1.3 Clinical Primary Endpoints

The primary efficacy endpoint for the LEVANT 2 Randomized clinical trial is primary patency of the target lesion at 1 year with primary patency defined as:

- Absence of target lesion restenosis (as adjudicated by blinded core-lab), and
- Freedom from target lesion revascularization (TLR).

The primary safety endpoint is the 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 re-intervention, and
- Index-limb-related death.

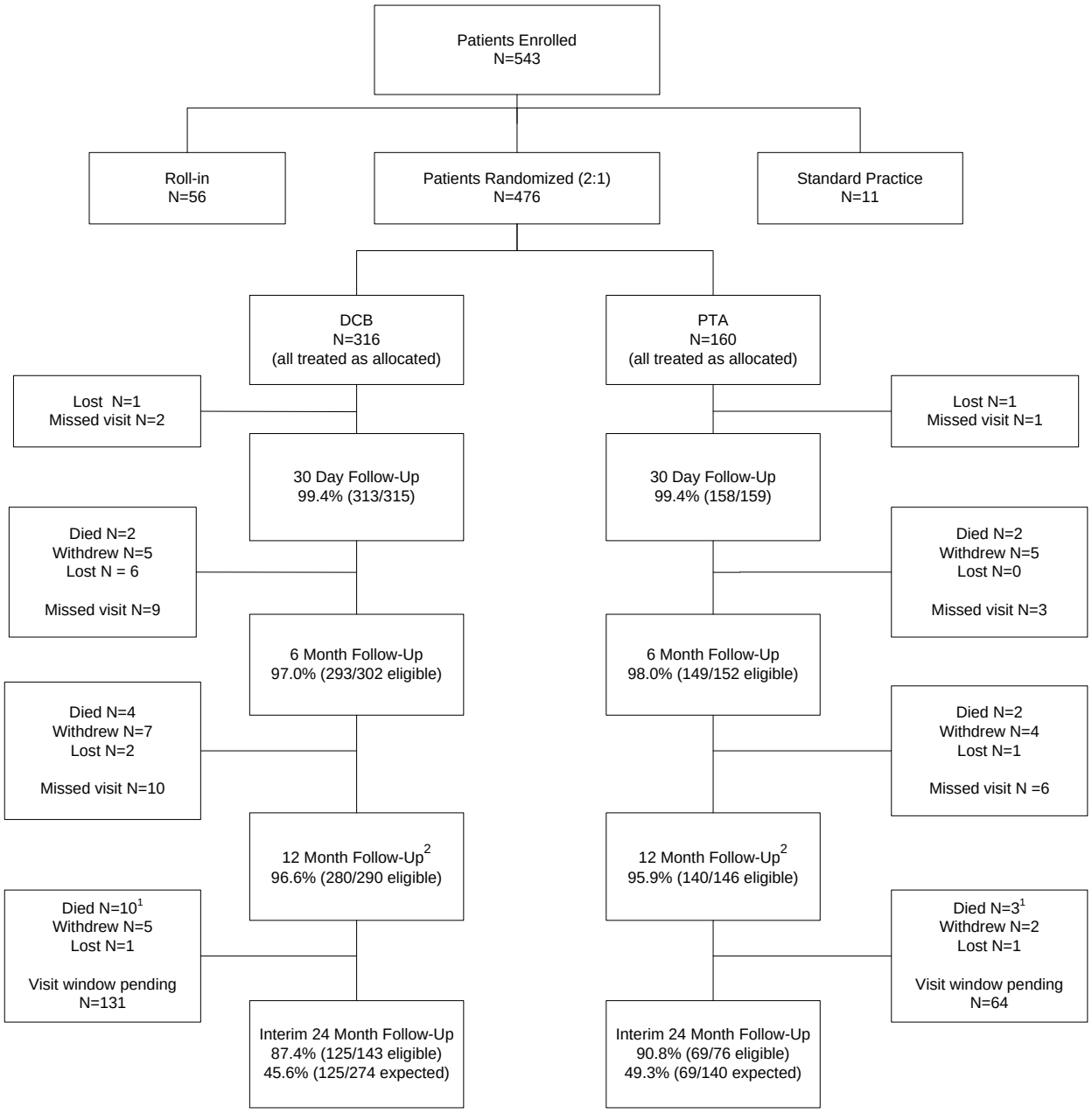
1.10.1.4 Accountability of Subjects

Five hundred forty-three (543) subjects were enrolled into the LEVANT 2 Randomized clinical trial of which four hundred seventy-six (n=476) subjects were randomized 2:1 to Lutonix Drug Coated Balloon (n=316) and PTA (n=160). Fifty-six (56) subjects were roll-in subjects and treated with Lutonix DCB (53 as site training cases and 3 as live-cases in Europe). Eleven (11) subjects did not meet the post pre-dilatation inclusion criteria and were treated per standard practice and followed for safety only for 30 days. Reference **Figure 3** for the LEVANT 2 subject enrollment.

At the time of database lock on Feb 26, 2014, of the 476 randomized subjects enrolled and per intent-to-treat (ITT) analysis, 471 subjects (98.9% ITT) completed the 30-day follow-up; 442

subjects (92.9% ITT) completed the 6-month follow-up, and 420 subjects (88.2% ITT) completed the 12-month follow-up. Reference **Table 10** for the subject disposition and **Table 11** for subject disposition of evaluable subjects for primary endpoint analyses.

Figure 3. LEVANT 2 Subjects Enrolled



[1] One DCB subject died within the 12-month follow-up window after a 12-month follow-visit and is shown as exiting between 12 and 24 months. Deaths between 12 and 24 months include (n =6 DCB vs 2 PTA) that have not yet been CEC adjudicated. Exit reason "other" (n=2 vs. 1) are included as lost.

[2] Telephone contact with family/physicians was obtained for two patients (1 DCB and 1 PTA) exiting in the 12 month window; these are included in the Consort diagram **Figure 2** as exiting between 12 and 24 months.

Table 10. Subject Disposition

Variable	Test DCB (N=316)	Control PTA (N=160)
Roll-in, N	56	0
ITT (Randomized), N	316	160
As-Treated, N	316	160
Per-Protocol, N	291	122
Follow-up Information Obtained (ITT)		
1-Month[1]	99.1% (313/316)	98.8% (158/160)
Clinical visit completed[1]	50.0% (158/316)	49.4% (79/160)
6-Month[2]	92.7% (293/316)	93.1% (149/160)
Clinical visit completed	90.8% (287/316)	91.3% (146/160)
Analyzable DUS	74.1% (234/316)	75.6% (121/160)
12-Month[3]	88.6% (280/316)	87.5% (140/160)
Clinical visit completed	85.1% (269/316)	84.4% (135/160)
Analyzable DUS	74.4% (235/316)	68.8% (110/160)
24-Month	39.6% (125/316)	43.1% (69/160)
Clinical visit completed	38.3% (121/316)	41.9% (67/160)
Analyzable DUS	25.0% (79/316)	23.8% (38/160)
Discontinuation Reasons (ITT)		
Subject died[4]	5.1% (16/316)	4.4% (7/160)
Subject refused further participation	5.7% (18/316)	6.9% (11/160)
Subject is lost to follow-up	2.5% (8/316)	1.3% (2/160)
Other[5]	0.6% (2/316)	0.6% (1/160)

[1] One-month visit could also be completed via telephone (49.7% test DCB, 50.3% control PTA).
[2] Information obtained by telephone for 6 (1.9%) test and 3 (1.9%) control subjects with missed visits.
[3] Information obtained by telephone for 11 (3.5%) test and 5 (3.1%) control subjects with missed visits.
[4] Includes 6 test and 2 control deaths between 12 and 24 months include that have not yet been CEC adjudicated.
[5] Discontinuation Reason "Other" is included as "lost" in the Consort Flow Diagram (**Figure 2** above).

Table 11. Evaluable Subjects for Primary Endpoint Analyses (ITT Population)

Information Source	Test DCB	Control PTA
Analyzable for 12 month Primary Efficacy Endpoint (Primary Patency)	**83.5% (264/316)**	**84.4% (135/160)**
In-window Clinical Visit with analyzable DUS Completed, without TLR prior to end of 12m window	64.6% (204/316)	58.1% (93/160)
TLR prior to end of 12m window	11.1% (35/316)	15.0% (24/160)
Binary restenosis adjudicated on most recent prior DUS without TLR or evaluable 12m DUS	3.5% (11/316)	6.3% (10/160)
Freedom from TLR and absence of binary restenosis determined by subsequent visit with analyzable DUS	4.4% (14/316)	5.0% (8/160)
Analyzable for 12 month Primary Safety Endpoint	**90.5% (286/316)**	**89.4% (143/160)**
In-window Clinical Visit and/or failed prior to 395 days	81.0% (256/316)	78.8% (126/160)
Freedom from safety events through 395 days demonstrated by subsequent contact	9.5% (30/316)	10.6% (17/160)

1.10.1.5 Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral arterial disease study performed in the US and the baseline patient characteristics were similar between the Lutonix DCB and PTA control treatment groups.

Demographics (**Table 12**), medical history (**Table 13**) and clinical characteristics (**Table 14**) were similar for the two treatment groups. There were similar frequency of diabetes treated in both groups (43.4% vs. 41.9%), although a higher percentage of these were Type I for the Lutonix DCB arm (9.5% vs. 1.5%, p=0.03), and there was a similar frequency of prior stroke (11.4% vs. 11.3%), although a lower percentage of these were ischemic in the Lutonix DCB arm (75% vs. 100%, p=0.02). Overall, comorbidities at baseline was well-matched and representative of the patient population with peripheral vascular disease.

Similarly, baseline angiographic data (**Table 15**) 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.

Table 12. Demographics

Variable	Test DCB	Control PTA	P-value[1]	Pooled
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	68.2 ± 9.7 (476) 68.4 (41.5, 91.4)
Gender, % (n/N)			0.216	
Female	38.9% (123/316)	33.1% (53/160)		37.0% (176/476)
Male	61.1% (193/316)	66.9% (107/160)		63.0% (300/476)
Ethnicity, % (n/N)			0.741	
Hispanic or Latino	7.9% (25/316)	8.8% (14/160)		8.2% (39/476)
Not Hispanic or Latino	91.8% (290/316)	91.3% (146/160)		91.6% (436/476)
Patient chose not to respond	0.3% (1/316)	0.0% (0/160)		0.2% (1/476)
Race, % (n/N)			0.160	
Asian	1.3% (4/316)	2.5% (4/160)		1.7% (8/476)
Black or African American	3.8% (12/316)	8.1% (13/160)		5.3% (25/476)
Patient chose not to respond	4.1% (13/316)	4.4% (7/160)		4.2% (20/476)
White	90.8% (287/316)	85.0% (136/160)		88.9% (423/476)
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	169.6 ± 10.2 (476) 170.0 (135.0, 194.0)
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	82.9 ± 17.0 (476) 82.0 (42.0, 146.0)
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	28.7 ± 5.2 (476) 28.1 (15.8, 52.7)

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

Table 13. Medical History

Variable	Test DCB	Control PTA	P-value[1]	Pooled
BMI>=30, % (n/N)	34.8% (110/316)	30.6% (49/160)	0.360	33.4% (159/476)
Smoking, % (n/N)			0.548	
Current smoker	35.1% (111/316)	33.8% (54/160)		34.7% (165/476)
Never smoked	20.9% (66/316)	17.5% (28/160)		19.7% (94/476)
Previously smoked	44.0% (139/316)	48.8% (78/160)		45.6% (217/476)
Dyslipidemia/Hypercholesterolemia, % (n/N)	89.6% (283/316)	86.3% (138/160)	0.286	88.4% (421/476)
Diabetes Mellitus, % (n/N)	43.4% (137/316)	41.9% (67/160)	0.758	42.9% (204/476)
Type			0.034	
Type I	9.5% (13/137)	1.5% (1/67)		6.9% (14/204)
Type II	90.5% (124/137)	98.5% (66/67)		93.1% (190/204)
Insulin Dependency	40.9% (56/137)	40.3% (27/67)	0.937	40.7% (83/204)

Variable	Test DCB	Control PTA	P-value[1]	Pooled
Hypertension, % (n/N)	89.2% (282/316)	87.5% (140/160)	0.572	88.7% (422/476)
Renal Failure, % (n/N)	3.5% (11/316)	4.4% (7/160)	0.629	3.8% (18/476)
Congestive Heart Failure, % (n/N)	5.7% (18/316)	3.1% (5/160)	0.217	4.8% (23/476)
Previous CAD, % (n/N)	49.7% (157/316)	48.1% (77/160)	0.748	49.2% (234/476)
Previous MI, % (n/N)	19.9% (63/316)	17.5% (28/160)	0.523	19.1% (91/476)
Chronic Angina, % (n/N)	4.7% (15/316)	5.0% (8/160)	0.903	4.8% (23/476)
History of Coronary Revascularization, % (n/N)	41.8% (132/316)	38.8% (62/160)	0.526	40.8% (194/476)
Type of Coronary Revascularization			0.429	
CABG	45.2% (47/104)	52.1% (25/48)		47.4% (72/152)
PCI	54.8% (57/104)	47.9% (23/48)		52.6% (80/152)
Previous Cerebrovascular Event, % (n/N)	11.4% (36/316)	11.3% (18/160)	0.963	11.3% (54/476)
Ischemic	75.0% (27/36)	100.0% (18/18)	0.020	83.3% (45/54)
Hemorrhagic	5.6% (2/36)	0.0% (0/18)	0.308	3.7% (2/54)
Previous Target Limb Intervention, % (n/N)	23.4% (74/316)	17.5% (28/160)	0.137	21.4% (102/476)
Target Vessel Type			0.292	
DeNovo Target Vessel	83.9% (265/316)	87.5% (140/160)		85.1% (405/476)
Restenosed Target Vessel	16.1% (51/316)	12.5% (20/160)		14.9% (71/476)

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

Table 14. Clinical Characteristics

Variable	Test DCB	Control PTA	P-value[1]	Pooled
Rutherford Grade, % (n/N)			0.521	
2	29.4% (93/316)	34.4% (55/160)		31.1% (148/476)
3	62.7% (198/316)	57.5% (92/160)		60.9% (290/476)
4	7.9% (25/316)	8.1% (13/160)		8.0% (38/476)
ABI of Target Limb[2], 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	0.74 ± 0.20 (462) 0.73 (0.00, 1.38)
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	0.87 ± 0.22 (453) 0.91 (0.00, 1.34)

[1] T-tests for means and X2-tests for proportions

[2] Pressures > 1.4 were excluded from this analysis (n = 3 for Lutonix DCB, n = 1 for control PTA) per the Measurement and Interpretation of the Ankle-Brachial Index guidelines from the American Heart Association.

Table 15. Baseline Angiographic Data

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
Number of Lesions Treated, % (n/N)			0.400	
1	98.1% (310/316)	96.9% (155/160)		97.7% (465/476)
2	1.9% (6/316)	3.1% (5/160)		2.3% (11/476)
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	62.8 ± 41.0 (475) 51.6 (5.7, 196.7)
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	69.6 ± 43.8 (476) 70.0 (1.0, 150.0)
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	107.9 ± 47.8 (476) 104.9 (23.3, 307.7)
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	80.6 ± 14.8 (476) 81.0 (40.0, 100.0)
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	4.8 ± 0.8 (476) 4.7 (2.8, 7.5)
Target Limb, % (n/N)			0.841	
Left	52.8% (167/316)	51.9% (83/160)		52.5% (250/476)
Right	47.2% (149/316)	48.1% (77/160)		47.5% (226/476)
Lesion Class TASC II, % (n/N)			0.398	
A	76.3% (241/316)	75.6% (121/160)		76.1% (362/476)
B	21.5% (68/316)	23.8% (38/160)		22.3% (106/476)
C	2.2% (7/316)	0.6% (1/160)		1.7% (8/476)
Calcification, % (n/N)	59.2% (187/316)	58.1% (93/160)	0.826	58.8% (280/476)
Severe Calcification	10.4% (33/316)	8.1% (13/160)	0.419	9.7% (46/476)
Total Occlusion, % (n/N)	20.6% (65/316)	21.9% (35/160)	0.741	21.0% (100/476)
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	2.0 ± 1.0 (476) 2.0 (0.0, 3.0)
Number of Patent Run-Off Vessels (Categorical), % (n/N)			0.539	
0	9.5% (30/316)	13.1% (21/160)		10.7% (51/476)
1	15.2% (48/316)	16.9% (27/160)		15.8% (75/476)
2	35.4% (112/316)	35.0% (56/160)		35.3% (168/476)

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
3	39.9% (126/316)	35.0% (56/160)		38.2% (182/476)
Most Distal Lesion Location, % (n/N)			0.495	
Proximal SFA	9.2% (29/316)	8.1% (13/160)		8.8% (42/476)
Mid SFA	51.3% (162/316)	45.6% (73/160)		49.4% (235/476)
Distal SFA	29.7% (94/316)	38.8% (62/160)		32.8% (156/476)
Proximal Popliteal	4.7% (15/316)	4.4% (7/160)		4.6% (22/476)
Mid Popliteal	4.1% (13/316)	2.5% (4/160)		3.6% (17/476)
Distal Popliteal	0.9% (3/316)	0.6% (1/160)		0.8% (4/476)
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	2.47 ± 0.91 (476) 2.00 (1.00, 6.00)

[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.

1.10.1.6 Safety and Effectiveness Results

1.10.1.6.1 Primary Safety Endpoint

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

Overall, 90.5% (286/316) Lutonix DCB subjects and 89.4% (143/160) control PTA subjects were evaluable for primary safety endpoint testing. Missing subjects included 7.3% (23) Lutonix DCB and 8.1% (13) control PTA subjects who either died, withdrew, or were lost-to-follow-up without prior safety events and 2.2% (7) Lutonix DCB and 2.5% (4) control PTA subjects with missed visits at 12 month and had no prior safety events or later evidence of success.

The proportion of subjects that had freedom from any safety events in the Lutonix DCB group was 83.9% compared to 79.0% in the standard PTA group at 12 months, and non-inferior safety was demonstrated (p = 0.005) with a non-inferiority margin of 5% - see **Table 16**.

Table 16. Primary Safety Endpoint at 1 year (ITT Population)

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
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

[1] Composite freedom from safety events, including all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or 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%.

Table 17. Safety Events through 1 year (ITT Population)

Safety Event *(subject may have more than one event)*	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**	**Difference[1] % [95% CI]**
Perioperative (≤30) Death	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%
Index Limb Related Death at 12 Months	0.0% (0/285) [0.0, 0.0]	0.0% (0/140) [0.0, 0.0]	0.0%
Amputation at 12 Months	0.3% (1/286) [0.0, 1.0]	0.0% (0/140) [0.0, 0.0]	0.3% [-0.3, 1.0]
Target Limb Revascularization 12 months	15.4% (44/285) [11.2, 19.6]	21.0% (30/143) [14.3, 27.7]	-5.5% [-13.4, 2.3]

[1] Nominal CI for difference based on a Farrington-Manning method are provided but were not prespecified for hypothesis testing and are not adjusted for multiplicity. CI for groups are asymptotic.

Kaplan-Meier survival analysis

The primary safety endpoint was also analyzed using time-to-event Kaplan-Meier survival analysis as one of the sensitivity analyses to address the issue of missing data.

Kaplan-Meier analysis confirmed the safety of the Lutonix DCB compared to control PTA through 1 year (**Figure 4** and **Table 18**). At 365 days, 86.7% of Lutonix DCB subjects and 81.5% of standard PTA subjects were free from safety events.

Figure 4. Kaplan-Meier Graph of Primary Safety Endpoint Success Rate (ITT Population)

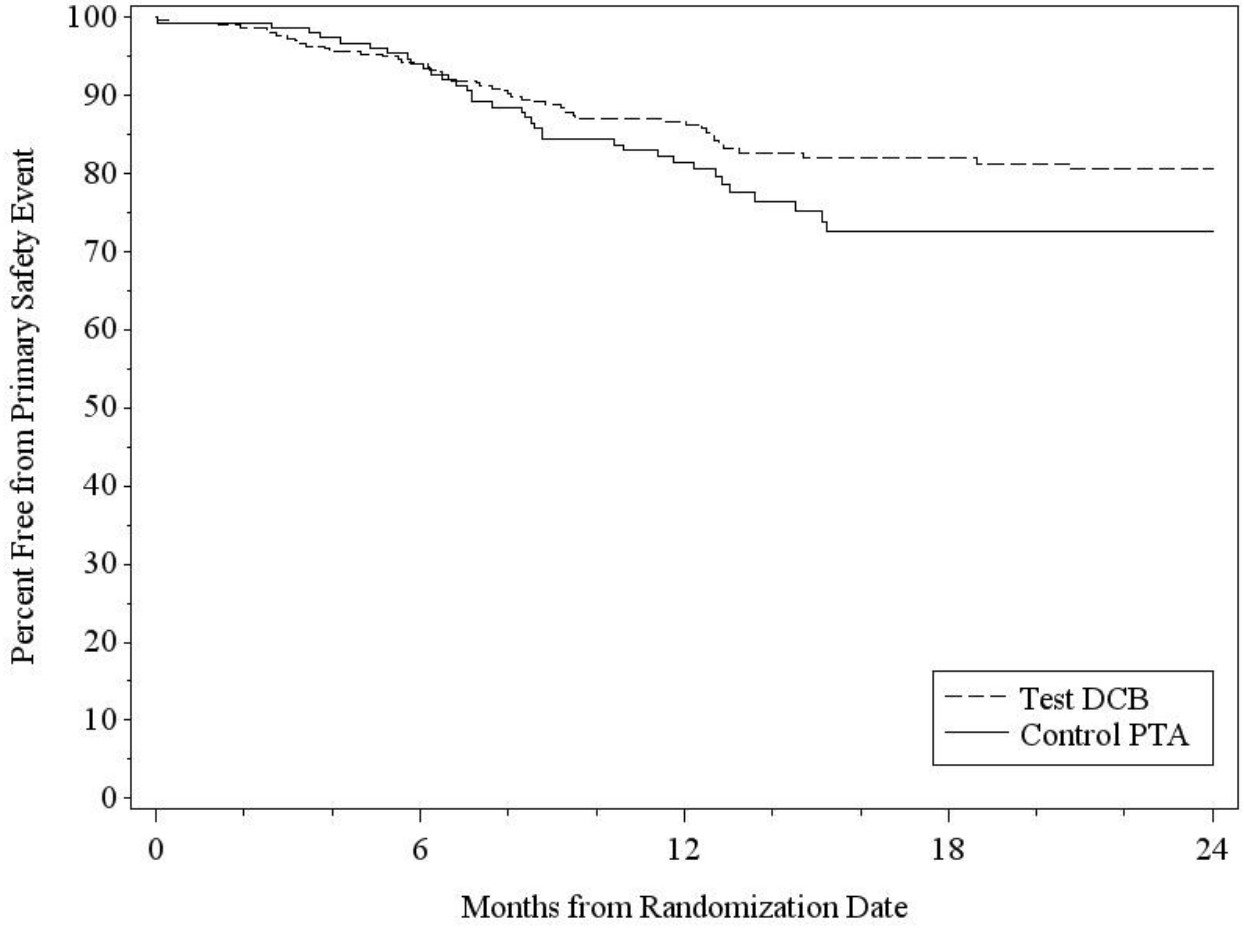


Table 18. Freedom from Primary Safety Endpoint by Kaplan-Meier (ITT Population)

Time	Test DCB				Control PTA			
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival %	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
730 days	80.6%	50	226	40	72.6%	35	108	17

[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.

SAE Listing

Serious adverse events are summarized in **Table 19**. Roughly half of the subjects in each treatment group experienced at least one SAE during the study. While differences in incidence in Lutonix DCB and control PTA subjects can be observed for some events, the disparity in incidence was not statistically or clinically significant. Overall, there was no evidence that treatment with the Lutonix DCB led to increased risk of any SAE.

Table 19. CEC-adjudicated Serious Adverse Events Through the 24-Month Follow-up Window (AT Population)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
1 Cardiac Events	1.01 Angina	15	4.4% (14)	3	1.9% (3)
	1.02 Atrial Fibrillation	3	0.9% (3)	2	1.3% (2)
	1.05 Other Arrhythmia, specify:	1	0.3% (1)	2	1.3% (2)
	1.06 Cardiac arrest/failure	1	0.3% (1)	0	0.0% (0)
	1.07 Hypertension (req. therapy)	1	0.3% (1)	1	0.6% (1)
	1.08 Hypotension (Sustained, req. pressors and/or IABP)	2	0.6% (2)	0	0.0% (0)
	1.09 MI: Q-wave (STEMI)	0	0.0% (0)	1	0.6% (1)
	1.10 MI: Non Q-wave (NSTEMI)	4	0.9% (3)	1	0.6% (1)
	1.11 MI: Unknown	4	1.3% (4)	2	1.3% (2)
	1.13 CHF: After discharge	9	1.9% (6)	0	0.0% (0)
	1.14 Other Cardiac, specify:	5	1.3% (4)	1	0.6% (1)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
2 Clinical Events	2.01 Contrast media allergic reaction	1	0.3% (1)	0	0.0% (0)
	2.05 Fever, unknown etiology	1	0.3% (1)	0	0.0% (0)
	2.06 Groin infection, local (req. antibiotics)	1	0.3% (1)	0	0.0% (0)
	2.07 Skin infection, local (req. antibiotics)	2	0.6% (2)	1	0.6% (1)
	2.08 Other infection, local (req. antibiotics), specify:	6	1.9% (6)	1	0.6% (1)
	2.09 Infection, systemic (req. antibiotics)	2	0.6% (2)	1	0.6% (1)
	2.10 Renal insufficiency (> 0.5 increase in Cr from preprocedure/baseline)	3	0.9% (3)	1	0.6% (1)
	2.11 Renal failure (requiring new dialysis or prolonged hospitalization with dialysis)	0	0.0% (0)	0	0.0% (0)
	2.12 Respiratory failure: Fluid volume overload	0	0.0% (0)	0	0.0% (0)
	2.13 Respiratory failure: Exacerbation of COPD	8	1.6% (5)	1	0.6% (1)
	2.16 Pneumonia	8	2.5% (8)	2	1.3% (2)
	2.17 Neoplasia	15	3.8% (12)	9	5.0% (8)
	2.18 Pulmonary Embolism	2	0.6% (2)	0	0.0% (0)
	2.19 Other Clinical, specify:	13	3.2% (10)	6	2.5% (4)
	2.20 Orthopaedic Injury	5	1.6% (5)	4	2.5% (4)
	2.21 Orthopaedic Disease	7	1.9% (6)	5	2.5% (4)
	2.22 Musculoskeletal Pain	2	0.6% (2)	0	0.0% (0)
	2.23 Arthritis/gout	0	0.0% (0)	1	0.6% (1)
	2.24 Other Renal Events	6	0.9% (3)	0	0.0% (0)
	2.25 Gastrointestinal Disorder	6	1.9% (6)	8	4.4% (7)
	2.26 Inguinal hernia	2	0.6% (2)	0	0.0% (0)
	2.27 Cholelithiasis	0	0.0% (0)	1	0.6% (1)
	2.28 Benign Prostatic Hypertrophy	1	0.3% (1)	0	0.0% (0)
	2.29 Cataracts	5	1.3% (4)	3	1.3% (2)
	2.32 Electrolyte Abnormality	3	0.9% (3)	0	0.0% (0)
	2.33 Dyspnea	1	0.3% (1)	0	0.0% (0)
	2.34 Non-Cardiac Chest Pain	4	1.3% (4)	0	0.0% (0)
	2.38 Cholecystitis	1	0.3% (1)	1	0.6% (1)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
3 Hemorrhagic Events	3.01 Access site: Hematoma	3	0.9% (3)	0	0.0% (0)
	3.02 Access site: Significant hemorrhage req. transfusion	4	0.9% (3)	0	0.0% (0)
	3.03 Access site: Pseudoaneurysm	4	1.3% (4)	3	1.9% (3)
	3.06 Bleeding/Hemorrhage from anticoagulants	2	0.6% (2)	0	0.0% (0)
	3.07 Bleed, Gastrointestinal	4	1.3% (4)	1	0.6% (1)
	3.09 Bleed, Retroperitoneal	2	0.6% (2)	1	0.6% (1)
	3.10 Anemia, general (req. blood transfusion)	4	0.9% (3)	1	0.6% (1)
	3.11 Other Hemorrhage, specify:	5	1.3% (4)	1	0.6% (1)
4 Neurological Events	4.01 TIA (Focal deficit resolving within 24 hours)	2	0.6% (2)	0	0.0% (0)
	4.02 Stroke (Focal deficit lasting over 24 hours)	9	2.8% (9)	1	0.6% (1)
	4.03 Other Neurologic, specify:	4	1.3% (4)	4	2.5% (4)
	4.05 Hearing loss	1	0.3% (1)	0	0.0% (0)
	4.06 syncope/near syncope/dizziness/vertigo	4	1.3% (4)	0	0.0% (0)
5 Angiographic Events	5.02 Target vessel injury/dissection with pre-treatment	0	0.0% (0)	0	0.0% (0)
	5.03 Target vessel injury/dissection with study treatment	6	1.9% (6)	6	3.8% (6)
	5.04 Target vessel injury/dissection with post-treatment	1	0.3% (1)	2	1.3% (2)
	5.07 Distal embolization with study treatment	1	0.3% (1)	1	0.6% (1)
	5.08 Distal embolization with post-treatment	0	0.0% (0)	1	0.6% (1)
	5.10 Arterial rupture	1	0.3% (1)	0	0.0% (0)
	5.11 Clot/Thrombus formation (thrombosis)	1	0.3% (1)	2	1.3% (2)
	5.15 Access Site Dissection	1	0.3% (1)	0	0.0% (0)
	5.17 Distal embolization (non-index procedure)	1	0.3% (1)	0	0.0% (0)

AE Category	Event code	DCB Subjects		PTA Subjects	
		n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
6 Vascular Events	6.02 Restenosis of the study lesion	5	1.6% (5)	7	3.8% (6)
	6.03 Restenosis of the study vessel	1	0.3% (1)	2	1.3% (2)
	6.04 Restenosis of the non-study vessel	24	7.0% (22)	10	6.3% (10)
	6.05 Clinically-driven target (study) lesion revascularization (TLR)	6	1.9% (6)	2	1.3% (2)
	6.06 Incidental target (study) lesion revascularization (TLR)	0	0.0% (0)	1	0.6% (1)
	6.07 Target (study) vessel revascularization (TVR)	0	0.0% (0)	0	0.0% (0)
	6.09 Target (study) extremity revascularization (non-study lesion/vessel)	0	0.0% (0)	1	0.6% (1)
	6.10 Non-target extremity revascularization	5	1.3% (4)	6	3.8% (6)
	6.11 Non-target acute limb ischemia	2	0.6% (2)	0	0.0% (0)
	6.12 Target (study) acute limb ischemia	1	0.3% (1)	0	0.0% (0)
	6.17 Non-target extremity minor/major amputation, toe(s)	0	0.0% (0)	0	0.0% (0)
	6.22 Target extremity pain	12	3.2% (10)	5	3.1% (5)
	6.24 Target extremity ischemic ulcer-New	2	0.6% (2)	0	0.0% (0)
	6.25 Non-target extremity pain	9	2.8% (9)	4	2.5% (4)
	6.27 Non-target extremity ischemic ulcer-New	0	0.0% (0)	1	0.6% (1)
	6.28 Other Vascular, specify:	2	0.6% (2)	2	1.3% (2)
	6.29 Bilateral lower extremity pain	1	0.3% (1)	3	1.9% (3)
	6.31 Deep vein thrombosis	0	0.0% (0)	0	0.0% (0)
	6.32 Non target limb aneurysm	1	0.3% (1)	0	0.0% (0)
	6.35 Claudication	50	12.3% (39)	40	16.9% (27)
7 Other Events	7.01 Other, specify:	1	0.3% (1)	0	0.0% (0)
8 Non-Event/ Death Outcomes	8.01 Accidental death	0	0.0% (0)	1	0.6% (1)
	8.03 Cardiac death	1	0.3% (1)	0	0.0% (0)
	8.04 Sudden cardiac death	0	0.0% (0)	1	0.6% (1)
	8.06 Unknown cause of death	4	1.3% (4)	1	0.6% (1)
	8.07 Death (not otherwise specified-NOS)	0	0.0% (0)	0	0.0% (0)
	8.08 Death from neoplasia	1	0.3% (1)	0	0.0% (0)
Total	Total	338	53.5% (169)	169	50.0% (80)

1.10.1.6.2 Primary Efficacy Endpoint Evaluation

The Primary Efficacy Endpoint is primary patency defined as the absence of binary restenosis and absence of clinically-driven target lesion revascularizaton (TLR) at 12 months.

Overall, 83.5% (264/316) Lutonix DCB subjects and 84.4% (135/160) control PTA subjects were evaluable for the primary efficacy endpoint testing. Missing subjects included 7.9% (25) Lutonix DCB and 6.9% (11) control PTA subjects who either died, withdrew, or were lost-to-follow-up without prior efficacy failures, 6.0% (19) Lutonix DCB and 5.6% (9) control PTA subjects with 12-month clinical follow-up but non-analyzable or missing DUS, and 2.5% (8) Lutonix DCB and 3.1% (5) control PTA subjects with missed visits at 12 months and no prior failure.

The proportion of subjects with primary patency at 12 months was 65.2% in the Lutonix DCB group and 52.6% in the standard PTA group, and superior efficacy (p = 0.015) of Lutonix DCB over control PTA was demonstrated – see **Table 20**.

Table 20. Primary Patency of Target Lesion (ITT Population)

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
Primary Patency[1]	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015

[1]Primary Patency is defined freedom from target lesion restenosis (defined by DUS core lab adjudication) and target lesion revascularization (TLR).
[2]Based on asymptotic likelihood ratio test. CIs for groups and difference are asymptotic.

Kaplan-Meier survival analysis

Primary patency has also been analyzed using time-to-event Kaplan-Meier survival analysis as part of the sensitivity analyses to address missing data. Primary patency by Kaplan-Meier analysis (**Table 21** and **Figure 5**) was consistent with the superiority of primary patency of Lutonix DCB over control PTA that was demonstrated by proportion-based hypothesis testing. At 365 days, the primary patency rate was 73.5% for the Lutonix DCB group compared to 56.8% for the control PTA group.

Figure 5. Kaplan-Meier Graph of Primary Patency (ITT Population)

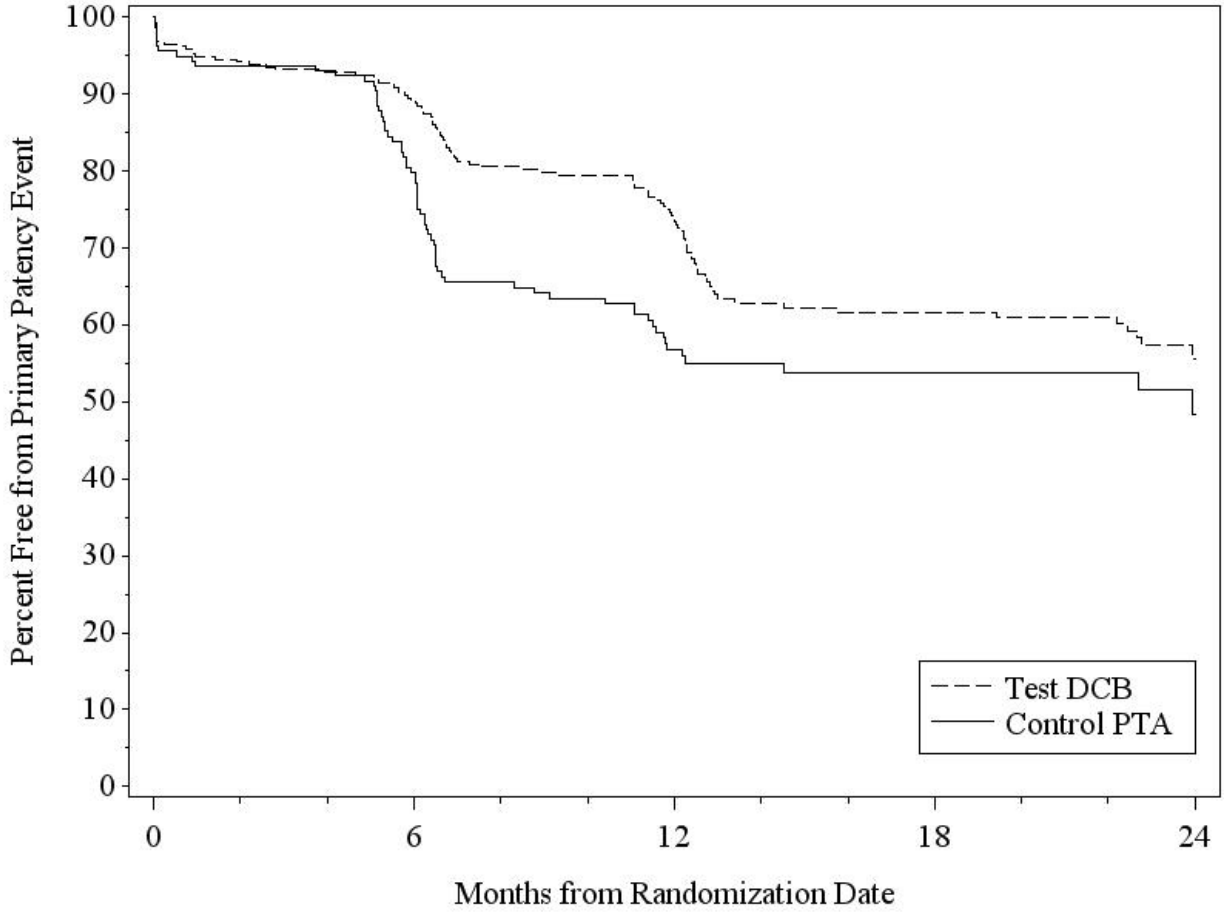


Table 21. Primary Patency by Kaplan-Meier Analysis (ITT Population)

	Test DCB				Control PTA			
Time[1]	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival %	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
730 days	53.7%	108	182	26	48.4%	69	77	14

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

1.10.1.7 TLR at 12 months

TLR rates at 12 month follow-up were similar for Lutonix DCB and control PTA groups, although trending favorable for Lutonix DCB.

Table 22. TLR rate at 12 Months

Measure	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[1]
Total TLR at 12 Months	12.3% (35/285) [8.5, 16.1]	16.8% (24/143) [10.7, 22.9]	-4.5% [-11.7, 2.7]	0.208

[1] Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.

1.10.1.8 Pharmacokinetic Sub-Study

Pharmacokinetic testing for blood paclitaxel level was performed on a sub-set of 22 Lutonix DCB subjects from 7 different sites. Blood samples were collected several times prior to patient discharge and at 30-day follow-up.

Evidence of systemic paclitaxel amount was observed in all tested subjects before discharge, but no drug was detected in any of the 30-day follow-up samples. The pharmacokinetics of paclitaxel generally exhibited a bi-exponential decay; characterized by a rapid distribution phase followed by a log-linear elimination phase. Following Lutonix DCB treatment, group mean (SD) values for 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, respectively. The mean elimination half-life was estimated at 6.88 h for evaluable subjects; however, blood sampling was very limited in the study.

1.10.1.9 LEVANT 2 Study Conclusion

The Lutonix DCB is an angioplasty balloon coated with the drug paclitaxel. The Lutonix DCB is indicated for percutaneous transluminal angioplasty of obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries ≤ 150 mm in length and 4-6 mm in reference vessel diameter. Like all angioplasty balloons, the immediate result of treatment is the opening of the blocked artery by balloon dilatation, and procedural success of Lutonix DCB was comparable to that of control balloon angioplasty (88.9% vs. 86.8%). The ancillary benefit of the paclitaxel drug coating is to improve the durability of patency by reducing restenosis over time without leaving metal behind. The LEVANT 2 Randomized trial is a prospective, multicenter, single blind, randomized, controlled trial of 476 randomized subjects that successfully met both co-primary (safety and efficacy) endpoints at 12 months by direct comparison to conventional balloon angioplasty (control PTA).

At 12 months, primary patency of the Lutonix DCB group was superior to that of the standard PTA group (65.2% vs. 52.6%, p = 0.015). Primary safety (freedom from 30-day all cause perioperative death and 12-month index limb-related death, amputation, and revascularization) of DCB was non-inferior to control PTA (83.9% vs. 79.0%, p = 0.005). Use of paclitaxel-coated balloons provided better efficacy with a similar safety profile to control PTA balloons.

No safety risks were observed that might counterbalance the demonstrated efficacy benefit. Treatment of native femoropopliteal lesions with Lutonix DCB provides more durable patency than PTA without increasing safety risk.

1.10.2 LEVANT I Randomized European Study

1.10.2.1 Study Design

The Lutonix LEVANT I trial was a prospective, multicenter, single blind, randomized trial comparing the Lutonix DCB (Model 9003, 0.018" guidewire compatible version) vs. standard PTA catheter (POBA – plain old balloon angioplasty) for treatment of femoropopliteal arteries with and without stenting. The LEVANT I trial enrolled subjects presenting with clinical evidence of claudication or critical limb ischemia (CLI) and an angiographically significant lesion in the femoropopliteal arteries. After pre-dilatation of the lesion, subjects were stratified based on pre-defined criteria to undergo PTA only (Balloon Group, with provisional bail-out stenting only if necessary) or stenting with post-dilatation (Stent Group). Subjects in each stratification group were then randomized to treatment with either the Lutonix DCB (test arm) or standard uncoated balloon angioplasty (POBA control arm). See **Figure 6** for a schematic of the treatment flow and **Table 23** for the study design overview.

Figure 6: Flowchart of Subject Randomization

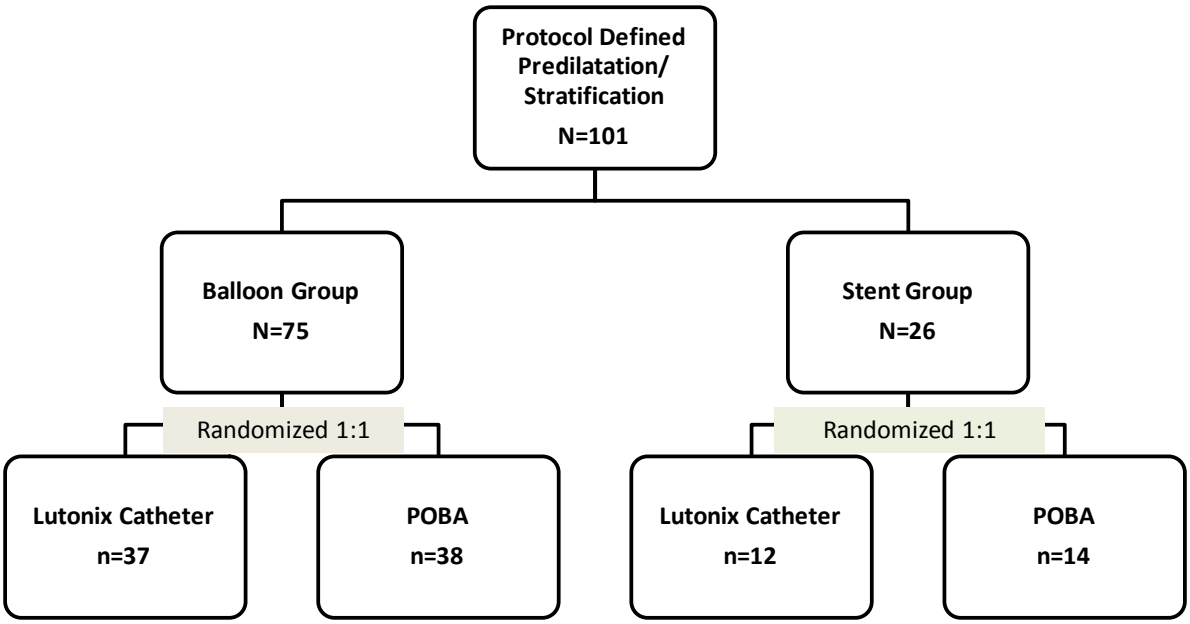


Table 23. LEVANT I Randomized Trial Study Design

Item	Description
Study Type/Design	Prospective, Multicenter, Single Blind, Randomized, Safety and Efficacy
Study Objective	The objective of the LEVANT I Clinical Study was to assess the safety and efficacy of the Lutonix DCB 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.
Number of Subjects Enrolled	101 patients (75 balloon group and 26 stent group), see **Figure 6** above.
Treatment Lesion	De novo or restenotic angiographically significant lesion in the superficial femoral or popliteal artery with lesion length of ≤ 15 cm in length and reference vessel of 4 mm – 6 mm in diameter.
Treatment Device	Test Arm: LUTONIX® Catheter (Model 9003, 0.018" guidewire compatible) Control Arm: Non-coated standard percutaneous transluminal angioplasty balloon catheter (standard PTA catheter)
Balloon Sizes	Balloon Diameters: 5 mm & 6 mm Balloon Lengths: 60 mm and 100 mm in length.
Post-procedure Antiplatelet Therapy	Appropriate antiplatelet therapy (clopidogrel) for at least 30-days (Balloon group) and 3 months (Stent group) and aspirin indefinitely.
Primary Endpoints	Angiographically assessed late lumen loss (LLL) at 6 months.
Randomized Subject Follow-Up Schedule	*Clinical*: 6, 12, and 24 Months *Duplex Ultrasound (DUS):* 6, 12, and 24 months
Status	24 month Final Report completed.

1.10.2.2 Dataset

The primary analysis dataset includes data for all subjects on an intent-to-treat (ITT) basis, and data for all subjects randomized to Lutonix DCB are compared to data for all subjects randomized to POBA.

All data reported in the body of this report reflect data reported by the CRO and were 100% monitored to the source data. Subset analyses and primary patency based on alternative censoring methods and alternative threshold PSVRs indicating restenosis were independently calculated by the Integra Group (statistical consultant) from data provided by the CRO.

1.10.2.3 Demographics and Baseline Lesion Characteristics

The mean age of enrolled subjects was 68±9 years, 63% were male, 35% were current smokers, 34% were previous smokers and 48% had Type II diabetes mellitus. At baseline examination, 71% of the subjects were rated a Rutherford Category 3, 22% were Rutherford Category 2, and the remaining 7% were Rutherford Category 4 and 5. More than 40% reported previous coronary artery disease, and other co-morbidities (renal disease, congestive heart failure,

cerebrovascular disease and structural heart disease) were common. There were no statistically significant differences between the groups for any demographic or medical history factor.

By quantitative vascular angiography (QVA), mean lesion length was 8.1±3.7 and 8.0±3.8cm and RVD was 4.1±0.6 and 4.2±0.7mm in the Lutonix DCB and control POBA arms, respectively. Eighty nine percent of treated lesions were de novo lesions, with the majority located in the mid and distal portions of the SFA. Popliteal lesions were treated in 4 (8.2%) test and 3 (5.8%) control cases.

The overall rate of concomitant stent implantation and procedural characteristics were similar in both randomized groups. In the Lutonix DCB arm, there were 8 (16%) device malfunctions due to a twisted balloon fold manufacturing defect that resulted in failure to completely inflate in target lesions.

1.10.2.4 Safety and Effectiveness Results

1.10.2.4.1 Primary Endpoint Results - Angiographic Late Lumen Loss at 6 Months

Angiographic data was evaluable for 74 subjects, including 39/49 (80%) of Lutonix DCB and 35/52 (67%) of POBA subjects.

The Primary Endpoint of mean late lumen loss in the analysis segment at 6 months was 0.46 ± 1.13 mm in the Lutonix DCB arm compared to 1.09 ± 1.07mm in the POBA arm ($p = 0.016$) in the ITT population.

In the balloon-only strata, mean late lumen loss was 0.45 ± 1.18mm in the Lutonix DCB arm vs. 1.19 ± 1.15 mm in the POBA arm ($p = 0.024$). 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 DCB and 17 of 35 (48.6%) for POBA at 6 months.

1.10.2.4.2 Safety and Efficacy Endpoints

Eighty-six (86) subjects had 12 month clinical follow-up, including 92% (45/49) Lutonix DCB and 79% (41/52) POBA subjects. Six (6) subjects died (2 Lutonix DCB, 4 POBA), 7 withdrew consent (2 Lutonix DCB, 5 POBA), and 2 were lost to follow-up (both POBA).

Twenty-four month information is available for 92% (45/49) Lutonix DCB and 82% (42/51) POBA subjects, including subjects that died. Seventy-nine (79) subjects had 24 month follow-up, including 84% (41/49) Lutonix DCB and 73% (38/52) POBA subjects. Since study commencement, 9 subjects died (4 Lutonix DCB, 5 POBA), 7 withdrew consent (2 Lutonix DCB, 5 POBA), and 6 were lost to follow-up (2 Lutonix DCB, 4 POBA).

At completion of the study, the percentage of enrolled subjects with any death, amputation, or target vessel thrombosis was 8% (4/49) for Lutonix DCB compared to 12% (6/52) for control POBA – reference **Table 24** below. Deaths in the Lutonix DCB arm were due to cancer (1), sepsis (1), and cardiac (2). Deaths in the control arm were due to cancer (1) and cardiac (4).

There were no target vessel thromboses and 1 amputation (subject later died) in the Lutonix DCB arm and one target vessel thrombosis (subject later withdrew) in the control arm. Composite major adverse events were 39% (19 of 49) for Lutonix DCB, including 15 TLRs, 1 amputation, and 4 deaths vs. 46% (24 of 52) for uncoated POBA control, with 20 TLRs, 1 thrombosis, and 5 deaths. Note: a given subject may have more than one event.

Through study completion at 24 months follow-up, a total of 35 subjects in the ITT population had a CEC-adjudicated TLR, including 36% (15/42) in the Lutonix DCB arm and 49% (20/41) in the control POBA arm – reference **Table 25**. Only one subject had a TVR without having a TLR, for a TVR rate of 36% (15/42) in the Lutonix DCB arm compared to 51% (21/41) in the control POBA arm.

Primary patency (PSVR < 2.5) was 57.1% (24/42) for Lutonix DCB compared to 39.5% (17/43) for control POBA – reference **Table 26** below.

Table 24: Cumulative Adverse Events as Adjudicated by CEC

Adverse event type through Designated Follow Up *(number of subjects having any events and total number of events)*	**Through 12 Months**		**Through 24 Months**	
	Lutonix Catheter N=49 n (total events)	**POBA N=52 n (total events)**	**Lutonix Catheter N=49 n (total events)**	**POBA N=52 n (total events)**
Non-serious AE[1]	23 (32)	29 (51)	28 (50)	31 (74)
SAE[1]	33 (66)	34 (80)	39 (90)	39 (110)
Thrombosis (target vessel)	0 (0)	1 (1)	0 (0)	1 (1)
Amputation	1 (1)	0 (0)	1 (1)	0 (0)
Death	3 (3)	4 (4)	4 (4)	5 (5)
TLR	13 (17)	14 (14)	15 (20)	20 (21)
TVR	13 (17)	15 (19)	15 (20)	21 (26)

[1] Any given subject may have more than one reported AE or SAE. SAEs reported at 24 Months follow-up that occurred within the 12 Month follow-up time window (395 days) are included at 12 Months.

Table 25: Target lesion revascularization, 12 and 24 months

Subgroup	**12 Months**		**24Months**	
	Lutonix % (n/N)	**POBA % (n/N)**	**Lutonix % (n/N)**	**POBA % (n/N)**
ITT	28.9% (13/45)	33.3% (14/42)	35.7% (15/42)	48.8% (20/41)
Balloon-only Strata	35.3% (12/34)	34.5% (10/29)	43.8% (14/32)	50.0% (14/28)
Stent Strata	9.1% (1/11)	30.8% (4/13)	10.0% (1/10)	46.2% (6/13)

Table 26: Primary Patency at 12 and 24 months (Failure must be proven by DUS) - ITT

Threshold for Restenosis Subgroup	12 Months		24 Months	
	Lutonix % (n/N)	**POBA % (n/N)**	**Lutonix % (n/N)**	**POBA % (n/N)**
DUS PSVR ≥ 2.5	**66.7% (30/45)**	**54.8% (23/42)**	**57.1% (24/42)**	**39.5% (17/43)**
Balloon-only Strata	61.8% (21/34)	51.7% (15/29)	50.0% (16/32)	40.0% (12/30)
Stent Strata	81.8% (9/11)	61.5% (8/13)	80.0% (8/10)	38.5% (5/13)

1.10.2.5 LEVANT I Study Conclusions

In LEVANT I randomized, controlled clinical study, the Lutonix DCB met the primary objective and demonstrated significantly less late lumen loss at 6 months and similar safety through 24 months by direct comparison to conventional balloon angioplasty.

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

The Lutonix DCB demonstrated safety comparable to conventional angioplasty (POBA) in the LEVANT I Trial, with similar ITT AE and SAE rates through 24 months. There were no unanticipated adverse device effects in the drug-coated balloon arm, and overall adverse event rates were similar to conventional uncoated balloon angioplasty.

1.11 Panel Meeting Recommendation and FDA's Post-Panel Action

[FDA TBD]

1.12 Conclusions Drawn from Pre-clinical and Clinical Studies

1.12.1 Effectiveness Conclusions

The primary effectiveness data drawn from the LEVANT 2 randomized and single arm clinical studies demonstrated a reasonable assurance of effectiveness for the Lutonix Drug Coated Balloon when used in accordance with the inclusion and exclusion criteria for the intended patient population. Primary patency at 12 months from the LEVANT 2 randomized trial was 65.2% in the Lutonix DCB treatment group and 52.6% in the standard PTA control group (p=0.015). In conclusion, the primary effectiveness hypothesis of the study was met, indicating that the Lutonix Drug Coated Balloon provides a significantly higher rate of primary patency compared to standard PTA. These results support the effectiveness of the Lutonix DCB for the treatment of symptomatic vascular disease of the above-the-knee femoropopliteal arteries.

1.12.2 Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in the clinical studies conducted to support PMA approval as described above. The primary safety data drawn from the LEVANT 2 randomized and single arm clinical studies demonstrated a reasonable assurance of safety for the Lutonix Drug Coated Balloon when used in accordance to its intended use. The event-free survival at 12 months from the LEVANT 2 randomized trial was 83.9% in the Lutonix DCB treatment group and 79.0% in the standard PTA control group. In conclusion, the primary safety hypothesis of the study was met, indicating that treatment with the Lutonix Drug Coated Balloon is as safe as treatment with standard PTA ($p < 0.005$). These results support the safety of the Lutonix DCB for the treatment of symptomatic vascular disease of the femoropopliteal arteries.

1.12.3 Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefit of the Lutonix Drug Coated Balloon of improving the patient symptoms and quality of life outweigh the probable risks associated with use of the device. Additional factors to be considered in determining probable risks and benefits for the Lutonix Drug Coated Balloon included:

- Patient follow-up was satisfactory and with limited missing data. The study results are superior to the results of standard angioplasty alone. Follow-up for the PMA was 12 months, but follow-up will continue for 5 years to evaluate the longer term device performance, such as the duration of the benefit and long term adverse event rates.

- The pivotal study was a multi-center study conducted in the United States and Europe. Additional patients were also enrolled in registry studies also performed in United States and Europe.

- Most patients with the disease have symptoms only, but some patients may have more extensive disease involvement. The device treats the hemodynamic consequences of the disease to improve perfusion and function. The disease is chronic and affects the mobility of the patient and the quality of life. It is treatable but not curable.

- There are alternative treatments available, but this treatment is more durable and more effective than percutaneous transluminal angioplasty alone. This treatment is highly valued by patients and preferred to the alternatives because it improves their quality of life with lesser need for repeat procedures.

- Patient risk is minimized by limiting use to operators who have the necessary training to use the device safely and effectively and adherence to recommended peri-procedural medication regimens.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for using the device for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-

the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 6 mm and total lesion lengths up to 150 mm.

1.12.4 Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The primary patency rate for the Lutonix Drug Coated Balloon was superior to the primary patency rate for control PTA, demonstrating that percutaneous transluminal angioplasty with the Lutonix Drug Coated Balloon is significantly more effective than control PTA. In addition, the event-free survival rate for the Lutonix Drug Coated Balloon treatment group was non-inferior to the control PTA control group, indicating that percutaneous transluminal angioplasty with the Lutonix Drug Coated Balloon is as safe as the current standard care of control PTA. Results from the European randomized clinical study provide additional evidence supporting the safety and effectiveness of the Lutonix Drug Coated Balloon.

1.13 CDRH Decision

[FDA TBD]

1.14 Approval Specifications

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.