SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug Coated Balloon Percutaneous Transluminal Angioplasty Catheter

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

Device Product code: ONU

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

Date(s) of Panel Recommendation: June 12, 2014

Premarket Approval Application (PMA) Number: P130024

Date of FDA Notice of Approval: October 9, 2014

Priority Review: Granted priority review status on December 23, 2013 because it is a novel breakthrough design.

II. 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.

III. CONTRAINDICATIONS

1. Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
2. 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.
3. Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

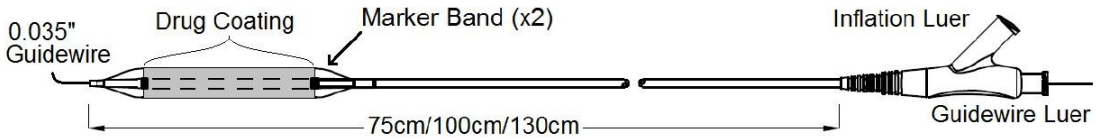
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Lutonix 035 Drug Coated Balloon PTA catheter instructions for use.

V. DEVICE DESCRIPTION

The Lutonix 035 Drug Coated Balloon PTA Catheter (Lutonix DCB) is a combination device/drug product incorporating an over-the-wire percutaneous transluminal angioplasty (PTA) catheter with paclitaxel drug coating on the surface of the balloon (see Figure 1).

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



PTA Catheter Component

The Lutonix DCB is compatible with a 0.035" guidewire and is available in 75 cm, 100 cm and 130 cm catheter lengths. Balloon sizes range from 4.0 mm - 6.0 mm in diameter and from 40 mm - 100 mm in length (see Table 1). Devices are compatible with 5F (for the 4.0-5.0 mm balloon diameters) and 6F (for the 6.0 mm balloon diameter) introducer sheaths. Note that all device sizes proposed for marketing were included in the clinical trials with exception of the 75 cm length catheter. The design of the Lutonix DCB catheter component is similar to standard PTA catheters.

Table 1: Available Balloon Sizes

Balloon Diameter (mm)	Balloon Length			
	40 mm	60 mm	80 mm	100 mm
4.0	✓	✓	✓	✓
5.0	✓	✓	✓	✓
6.0	✓	✓	✓	✓

Drug Components

The Lutonix DCB coating is a non-polymer based formulation, consisting of paclitaxel as the active pharmaceutical ingredient and excipients polysorbate and sorbitol. The paclitaxel coating is distributed evenly across the working length of the balloon with a dose density of 2 µg/mm^2 yielding variable total dosage depending on balloon size (see Table 2).

Table 2: Total Drug Dosage (Paclitaxel) by Balloon Size

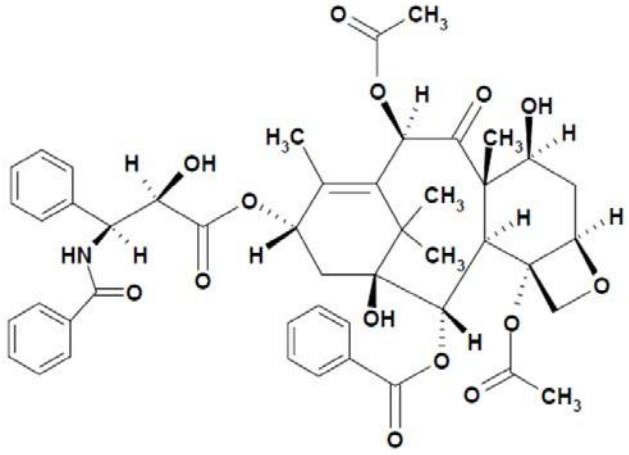
Balloon Size (Diameter x Length)	Total Dosage (mg)
4.0 x 40 mm	1.0
4.0 x 60 mm	1.5
4.0 x 80 mm	2.0
4.0 x 100 mm	2.5
5.0 x 40 mm	1.3
5.0 x 60 mm	1.9
5.0 x 80 mm	2.5
5.0 x 100 mm	3.1
6.0 x 40 mm	1.5
6.0 x 60 mm	2.3
6.0 x 80 mm	3.0
6.0 x 100 mm	3.8

Paclitaxel is a cytotoxic drug used for oncological indications and manufactured using a semi- synthetic process (see Table 3).

The excipients polysorbate and sorbitol utilized in the Lutonix drug coating are as described in the USP National Formulary. The key functional characteristic of the excipients polysorbate and sorbitol in the formulation is to allow for adequate release of the paclitaxel drug substance to the tissue of the vascular wall during the balloon inflation.

Table 3: Paclitaxel Drug Details

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
CAS Registry Number	33069-62-4

Compendial Name (USP)	Paclitaxel
Structure	
Molecular Formula	$C_{47}\ H_{51}\ NO_{14}$
Relative Molecular Mass	Mr : 854
Structural Formula	

Mechanism of Action

The primary mode of operation for the Lutonix DCB is the mechanical dilatation of the vessel, with the paclitaxel-based drug coating having an ancillary effect. The primary effect attributed to the device forms the basis for primary regulation under by the Center for Devices and Radiological Health (CDRH) with consultation from the Center for Drug Evaluation and Research (CDER). The mechanism by which neointimal growth is inhibited by the addition of the drug coating has not been established. In general, paclitaxel is a lipophilic, anti-mitotic agent that prevents microtubule destruction, which has been reported in prior studies to prevent migration/proliferation of smooth muscle cells, inflammatory cells and fibroblasts as well as inhibit the secretion of extracellular proteins. Several studies in animal models have also shown that paclitaxel applied locally reduces restenosis by inhibiting smooth muscle cell proliferation and neointimal hyperplasia.[1,2]

VI. 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),

1. Sollott SJ, Cheng L, Pauly RR, Jenkins GM, Monticone RE, Kuzuya M, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. J Clin Invest. 1995;95 (4):1869-76.
2. Axel DI, Kunert W, Göggelmann C et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation. 1997;96 (2):636-45.

- Minimally invasive treatment (plain old balloon angioplasty (POBA), endovascular stent, directional atherectomy), and
- Surgical treatment (surgical bypass).

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. 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; Twenty-one 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.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) which may be associated with the use of the device.

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

Potential adverse events 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

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

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 4 below.

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

Table 4: Catheter Bench Test Summary

Test	Description of Test	Acceptance Criteria	Test Results
Dimensional and Functional Attributes	The catheter is dimensionally measured and functionally tested with accessory devices to confirm their compatibility with the catheter.	FDA PTCA Guidance, Section B.1: 75, 100 and 130 cm in shaft length; 0.035" guidewire compatible and 5F sheath (4.0 and 5.0mm balloon size) and 6F sheath (6.0mm balloon size) compatible.	The device met the established acceptance criteria.
Minimum Balloon Burst Strength	Balloon is incrementally inflated until burst.	FDA PTCA Guidance, Section B.2: Rated burst pressure (RBP) of the balloon with 95% confidence and 99.9% reliability shall $\geq$ 12 atm.	The device met the established acceptance criteria.

Test	Description of Test	Acceptance Criteria	Test Results
Balloon Compliance	Balloon is incrementally inflated and measured to determine the balloon compliance curve.	FDA PTCA Guidance, Section B.3: Characterization only for development of the balloon compliance curve.	The device met the established acceptance criteria.
Balloon Inflation and Deflation Time	Time to inflate and deflate the balloon to and from RBP is measured.	FDA PTCA Guidance, Section B.4: Inflation time is ≤ 20 seconds. Deflation time is ≤ 40 seconds.	The device met the established acceptance criteria.
Balloon Fatigue	Balloon is inflated to RBP and deflated for total of 20 cycles.	FDA PTCA Guidance, Section B.5: With 95% confidence and 90% reliability, balloon shall not rupture when inflated and deflated to RBP for up to 20 cycles.	The device met the established acceptance criteria.
Tensile Strength	Testing is performed to confirm the tensile strength of the catheter.	FDA PTCA Guidance, Section B.6: Catheter tensile strength ≥ 10N.	The device met the established acceptance criteria.
Flexibility and Shaft Kink	Testing is performed on the catheter shaft to determine its bend radius before kink may occur.	FDA PTCA Guidance, Section B.8: Characterization only.	The device met the established acceptance criteria.
Torque Strength	Testing is performed in a simulated use tracking model to determine the rotation of the catheter before damage may occur.	FDA PTCA Guidance, Section B.9: Characterization only.	The device met the established acceptance criteria.
Balloon Preparation, Delivery and Retrieval	Catheter is prepared per the IFU and tracked and retrieved through a simulated use track model.	FDA PTCA Guidance, Section B.10: Catheter shall not be damaged after preparation, track and retrieval through a simulated use track model.	The device met the established acceptance criteria.
Radiopacity	The radiopacity of the catheter markers are confirmed to be acceptably visible under fluoroscopic imaging.	FDA PTCA Guidance, Section B.11: Marker bands shall be visible under fluoroscopy imaging.	The device met the established acceptance criteria.
Particulate Matter	Testing was performed to evaluate the number of particles ≥ 10 µm, ≥ 25 µm and ≥ 50 µm in size associated with simulated use tracking and deploying.	This testing was performed for characterization only	Characterization of the amount of particulate matter generated under conditions described in the test description was performed.

Biocompatibility

Biocompatibility testing for the Lutonix DCB was conducted separately on (1) the balloon with drug coating, and (2) the Lutonix balloon catheter without the drug coating. In addition, chemical characterization testing was conducted on the LUTONIX balloon catheter with drug coating to support the overall biocompatibility of the drug-coated balloon. The balloon with drug coating was categorized as an implant device with permanent blood contact (>30 days), and the Lutonix balloon catheter without the drug coating was categorized as an externally communicating device with limited contact duration (< 24 hours) with circulating blood. Tests were conducted on ethylene oxide sterilized products.

All biocompatibility testing was conducted in accordance with:

- Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters (September 8, 2010)
- Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery systems Document (April 18, 2010)
- Draft Guidance for Industry: Coronary Drug-Eluting Stents- Nonclinical and Clinical Studies Companion Document (March 2008)
- Draft Guidance for Industry: Coronary Drug-Eluting Stents- Nonclinical and Clinical Studies (March 2008)
- Good Laboratory Practices Regulations (21 CFR § 58)
- ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and testing within a risk management framework (2009)

A summary of the biocompatibility data provided to support this PMA can be found in Table 5, below.

Table 5: Biocompatibility Data

Test Name	Test Description	Balloon and Coating only	Balloon Catheter w/o Drug Coating	Lutonix DCB w/Drug Coating	Results
Cytotoxicity	ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells	x	x		Non-toxic
Sensitization	ISO Guinea Pig Maximization	x	x		Non-sensitizing
Irritation	ISO Intracutaneous Reactivity	x	x		Non-irritating
Acute Systemic Toxicity	ISO Systemic Toxicity Study	x	x		Non-toxic

Test Name	Test Description	Balloon and Coating only	Balloon Catheter w/o Drug Coating	Lutonix DCB w/Drug Coating	Results
Pyrogenicity	USP Material Mediated Pyrogenicity	x	x		Non-pyrogenic
Hemocompatibility	ASTM Hemolysis Study (Direct and Indirect Contact)	x	x		Non-hemolytic
	Complement Activation Assay C3a and SC5b-9	x	x		Not a complement activator
Supportive Analytical Chemistry Tests					
Chemical Characterization*	Gas Chromatography - Mass Spectroscopy (GC/MS) for volatile and semi-volatile, organic compounds		x	x	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
	Inductively Coupled Plasma (ICP) Spectroscopy for metallic compounds		x	x	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
	Liquid Chromatography - Mass Spectroscopy (LC/MS) for semi-volatile and non-volatile organic compounds		x	x	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns

*FTIR and USP Physicochemical data were also provided, but were not used to support the biocompatibility of this device.

The sponsor did not conduct the following traditional biocompatibility studies on the Lutonix DCB: a venous unheparinized *in vivo* thrombogenicity study, sub-chronic toxicity, chronic toxicity, and muscle implantation. The potential for thrombogenicity, sub-chronic toxicity, chronic toxicity and implantation were evaluated as part of other *in vivo* studies conducted to evaluate the safety and effectiveness of the product in a vascular location, as described in Section X, below. These additional animal studies demonstrated a lack of significant thrombus formation, inflammation and toxicity when the product was used in a clinically-relevant vascular location.

The omission of genotoxicity and carcinogenicity testing were supported by information regarding the starting materials and processing of the finished drug-

coated balloon in conjunction with chemical characterization data and toxicity information from the literature.

The information provided demonstrates that the Lutonix DCB is biocompatible for its intended use.

B. 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 6 below.

The animal pharmacokinetic study indicated that paclitaxel was rapidly transferred to the target arterial tissue and slowly eliminated over time. The peak tissue concentration occurred within one hour (C_{max} = 58.8 ng/g ± 54.2 ng/mg), with detectable drug persisting through 180 days post treatment. The maximal systemic drug concentration was low (C_{max} = 2.88 ng/mL), with undetectable quantities in plasma after 24 hours. The treated arteries displayed minimal endothelial loss, fibrin deposition, and inflammation with long-term drug effect (medial smooth muscle cell loss) peaking at 90 days. In parallel, healing of the treated arteries was evident by significantly greater medial proteoglycan and collagen deposition at 180 days. To evaluate the safety of the Lutonix DCB formulation, clearance organs (liver, kidneys) and downstream muscular tissues (gastrocnemius, rectus femoris, semimembranosus, and semitendinosus muscles) were evaluated after a treatment with a 4x dose was performed in the SFA porcine model. No evidence of ischemia from downstream emboli or systemic toxicity was observed[3].

Table 6: Animal Study Overview

Description / Study #	Animal Model	Devices	Study Design	Time points	Endpoints
Safety Study	48 arteries of 22 Domestic Swine	Model 9003* 4, 5, and 6 x 80mm test devices using – 2ug/mm^2 Lutonix DCB Control-uncoated	Single balloon treatment in Femoral Arteries	28, 90, 180 Days	• Quantitative Angiography • Clinical Safety • Histopathology/ SEM • Device handling

3 Yazdani, S.K., et al., Vascular, Downstream, and Pharmacokinetic Responses to Treatment with a low dose drug-coated balloon in a swine femoral artery model. Catheter Cardiovasc Interv, 2013.

		balloon			
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

* Model 9003 for the preclinical safety study is identical to the 9004 model with the exception that the 9004 model was .035" guidewire compatible.

C. Additional Studies

Coating Testing

The drug coating tests for characterization and to confirm the specification requirement are summarized in Table 7.

Table 7: Drug Coating Tests

Test	Description of Test	Acceptance Criteria	Test Results
Coating Uniformity	Coated balloon is sectioned and the drug content of each section is measured.	Drug content along the balloon surface shall be within ± 10% of proportional content.	The device met the established acceptance criteria.
Coating Durability	Drug coated balloon is inflated and deflated to RBP and drug loss is measured. Drug coated balloon is passed through a hemostasis valve and drug loss is measured.	Drug loss after inflation/deflation cycle and after passage through hemostasis valve shall be ≤ 0.1% of labeled content.	The device met the established acceptance criteria.
Coating thickness	Cross section of the drug coating is measured for characterization.	Characterization Only	The device met the established acceptance criteria.
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.	Characterization Only	The device met the established acceptance criteria.

Test	Description of Test	Acceptance Criteria	Test Results
Particulate Matter	Testing was performed to evaluate the number of particles ≥ 10 µm, ≥ 25 µm and ≥ 50 µm in size associated with simulated use tracking and deploying.	This testing was performed for characterization only	Characterization of the amount of particulate matter generated under conditions described in the test description was performed.

Chemistry, Manufacturing and Controls (CMC) Testing

The following analytical testing was performed on the Lutonix DCB as part of CMC testing. Each batch of finished devices underwent CMC release testing summarized in Table 8.

Table 8: CMC Release Tests

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

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.

Stability/Shelf-Life

Coating stability studies were conducted according to ICH guidelines to establish an expiration date/shelf-life for the paclitaxel drug coating on the Lutonix DCB. Stability test evaluation of the coating included appearance, assay, impurities/degradants, dissolution and *in-vitro* particulate matter. Appropriate engineering tests were performed on aged product to ensure that the Lutonix DCB meets the acceptance criteria established for the non-aged devices throughout their shelf 1ife. Packaging tests were also performed on packaging subjected to the worst case shipping simulation and then aged to ensure that the packaging would remain acceptable for the shelf life of the Lutonix DCB. The data supports a 24 month shelf life for the Lutonix DCB.

X. SUMMARY OF PRIMARY CLINICAL STUDY

LEVANT II - Pivotal, single blind, multi-center study

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of percutaneous balloon angioplasty, after predilatation, of de novo and restenotic lesions in native superficial femoral and popliteal arteries with the Lutonix DCB in the US and Europe under IDE # G100255. Data from this pivotal IDE study were the basis for the PMA approval decision. A summary of the pivotal IDE study is presented below.

A. Study Design

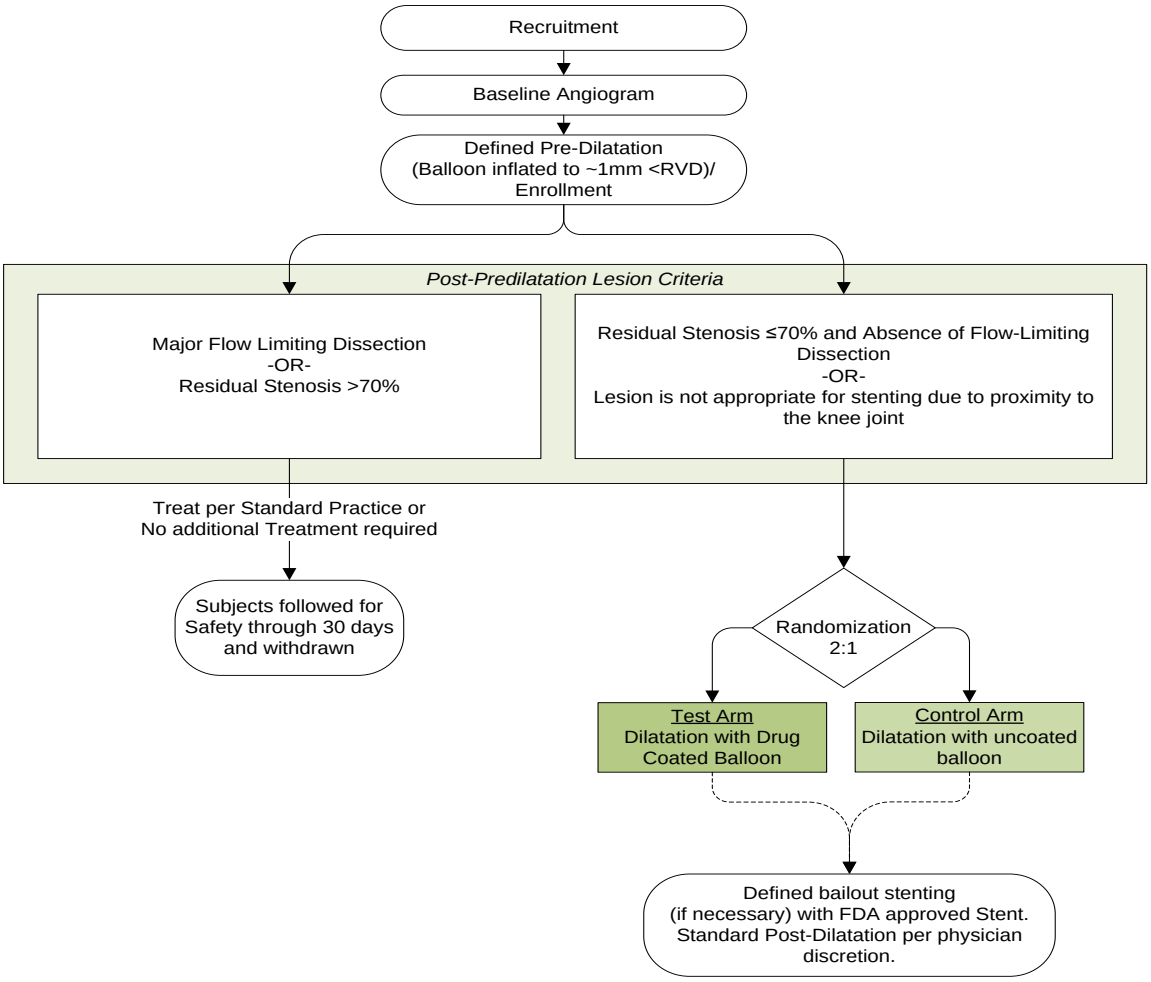
Patients were treated between July 2011 and July 2012. The database for this PMA P130024 reflected data collected through February 2014 and included 476 patients. There were 54 investigational sites across the US and Europe.

The study was a prospective, multi-center, single blind, 2:1 (test:control) randomized trial for treatment of femoropopliteal arteries. The study compared the Lutonix DCB to an active alternative control treatment with a standard uncoated PTA catheter, a legally marketed alternative with similar indications for use.

The 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. After informed consent, 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. See below Study Flow Chart, Figure 2.

Roll-in and randomized subjects were followed for safety and effectiveness at intervals of 30 days, 6 months, and 12 months and will continue to be followed annually through 5 years.

Figure 2: Study Flow Chart



While the study is considered to be single-blind, extensive efforts were made to ensure an unbiased evaluation of all clinical measures. Both the subjects as well as the investigator conducting the follow-up visits were to be blinded to treatment until the completion of the 12 month visit. In addition, the clinical status of the subject was to be established prior to review of the follow-up duplex ultrasound evaluating target vessel patency. All DUS operators, core lab evaluators, and members of the Clinical Events Committee (CEC) were blinded to the subject's treatment assignment. Since the coated device both looks and feels different than uncoated devices, it was not possible to blind the interventionalist conducting the procedure. Blinding

procedures were reviewed at the time of each site initiation by a sponsor representative.

The study was overseen by an independent data monitoring committee (DMC) for the oversight and safety monitoring of the study and comprised of physicians and a biostatistician. An independent CEC comprised of at minimum three clinicians adjudicated all serious adverse events, including all patient deaths. Independent core laboratories provided uniform imaging and duplex ultrasound analysis.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the LEVANT 2 randomized study was limited to patients who met the following inclusion criteria:

   - Patient with symptoms of peripheral artery disease classified as Rutherford Category 2 to 4.
   - Patient has de novo or restenotic lesion in native superficial femoral or popliteal artery that 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.
   - Patient has a single lesion or multiple lesions segment that is ≤15 cm in length in a reference vessel 4.0 to 6.0 mm in diameter.

   Patients were not permitted to enroll in the LEVANT 2 randomized study if they met any of the following exclusion criteria:

   - Patient has history of hemorrhagic stroke within 3 months prior to the study procedure;
   - Patient has previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the study procedure;
   - Patient has 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 study procedure or treated with dialysis);
   - Patient has significant inflow disease which cannot be treated prior to the target lesion treatment.
   - Patient has 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;
   - Patient has severe calcification that renders the lesion undilatable;
   - Patient has lesion that requires the use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1, 6, 12 and 24 months postoperatively. Subgroup of patients was subjected to a pharmacokinetics substudy for collection of blood sample at post-procedure and 1 month follow-up.

Table below details the preoperative evaluations and postoperative objective parameters measured during the study. Adverse events and complications were recorded at all visits.

Table 9: Follow-Up Schedule and Testing Requirements

Event	Visit									
	Pre-Procedure	Procedure	Post-Procedure	1 Month[1]	6 Month	12 Month	24 Month	36 Month[1]	48 Month[1]	60 Month[1]
Physical Exam[2]	√		√	√[3]	√	√	√			
Medication Compliance	√			√	√	√	√	√	√	√
Resting ABI	√[4]		√[4]	√[4]	√	√	√			
Rutherford Classification	√				√	√	√			
Blood Analysis (CBC with differential; CMP, pregnancy[6])	√[5]		√	√[3]	√	√				
Six minute Walk Test[7]	√				√	√	√			
WIQ, EQ5D and SF36-v2 Questionnaires	√				√	√	√			
Angiogram		√								
Adverse Event Monitoring		√	√	√	√	√	√	√	√	√
Duplex Ultrasound (after clinical assessment)			√[8]		√	√	√			
PK Study[9]	√		√	√						

telephone or clinical visit, depending on timing of duplex ultrasound (if required)

[2] *Physical Exam must be performed by and MD, PA, or NP*

[3] *Required if clinical visit occurs*

[4] *Resting ABI is required within 90 days of index procedure. Resting ABI is not required post procedure or at 1-month, but investigator encouraged to capture if possible*

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

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

[7] *Unless physical condition precludes from testing*

[8] *Baseline duplex is only required once (anytime post-procedure through the 1-month visit)*

[9] *A subset of approximately 30 subjects at select USA sites*

3. Clinical Endpoints

With regards to safety, the primary endpoint was 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.

Secondary endpoints for safety included:

- 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 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

With regards to effectiveness, the primary effectiveness endpoint is primary patency at 12 months. Primary patency is defined as the absence of binary restenosis (as adjudicated by the blinded core-lab) and freedom from target lesion revascularization (TLR, adjudicated by the CEC).

Secondary effectiveness endpoints included the following to be 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

4. Methods

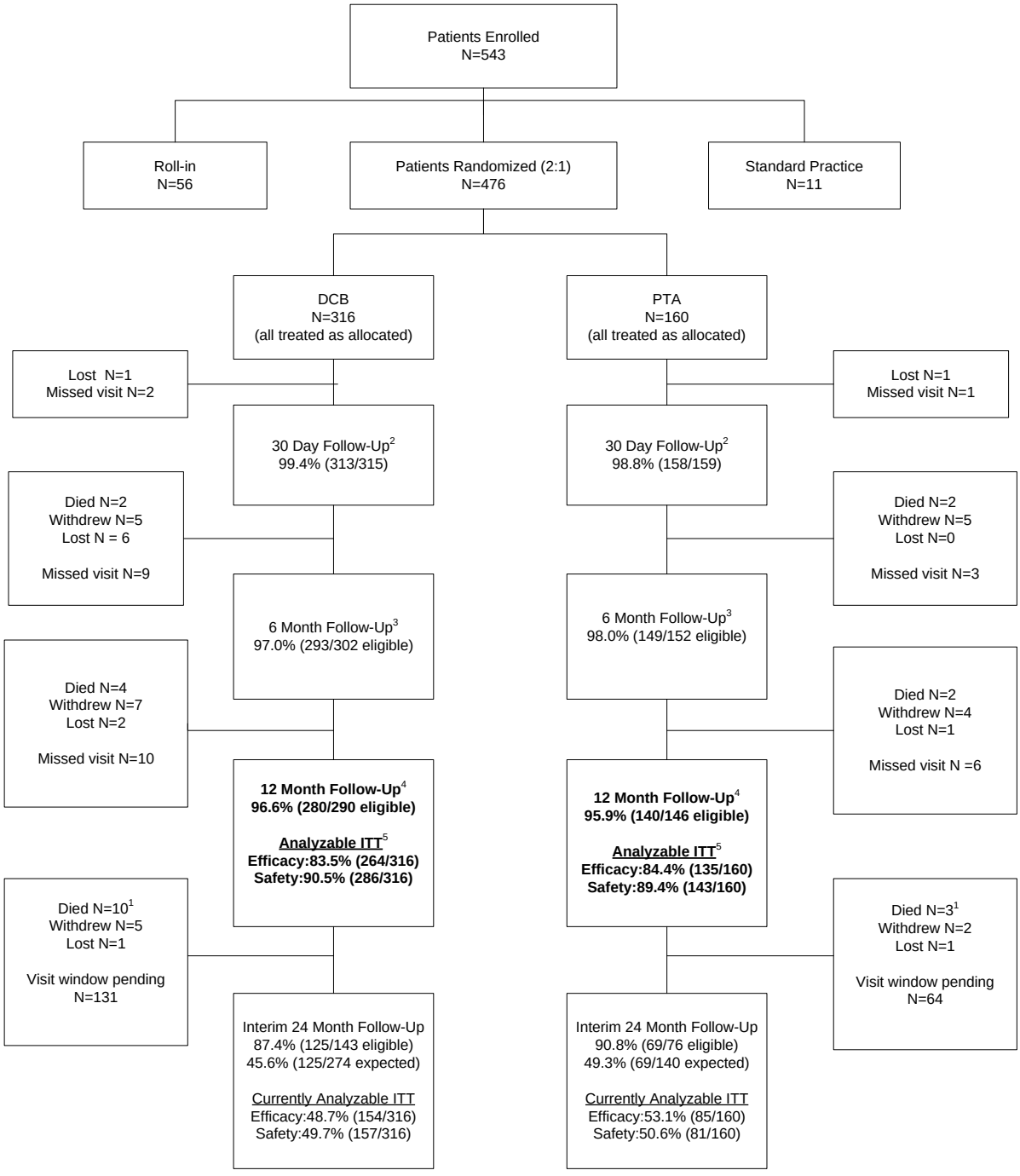
Subjects presenting with claudication or ischemic rest pain and an angiographically significant lesion in the superficial femoral or popliteal artery and a patent outflow artery to the foot were enrolled. Study subjects received a baseline angiogram to confirm an angiographically significant lesion in 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 were assessed by quantitative analysis at a designated (blinded) core laboratory. All suspected SAEs and device failures/malfunctions were adjudicated an independent (blinded) Clinical Events Committee. Intent-to-treat population (ITT), which includes all those who were enrolled and randomized, was pre-specified as the primary analysis population. 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.

B. Accountability of PMA Cohort

At the time of database lock, of the 476 randomized patients in the pivotal IDE study, 90% (429) patients are available for safety analysis and 88% (399) are available for effectiveness analysis for the 12 month primary endpoint analysis. The complete patient flow is shown in the study consort flow diagram below.

Figure 3: LEVANT 2 Cohort Flow Diagram



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral vascular disease study performed in the US and Europe. Overall, comorbidities at baseline was well-matched and representative of the patient population with peripheral vascular disease. Table 10 presents baseline patient demographics for the LEVANT 2 subjects.

Table 10: Demographics

Variable	Test DCB	Control PTA	P-value[1]
Age (years), Mean ± SD (n) median (min, max)	67.8 ± 10.0 (316) 68.2 (44.5, 91.4)	69.0 ± 9.0 (160) 69.0 (41.5, 89.4)	0.209
Gender, % (n/N)			0.216
Female	38.9% (123/316)	33.1% (53/160)	
Male	61.1% (193/316)	66.9% (107/160)	
Ethnicity, % (n/N)			0.741
Hispanic or Latino	7.9% (25/316)	8.8% (14/160)	
Not Hispanic or Latino	91.8% (290/316)	91.3% (146/160)	
Patient chose not to respond	0.3% (1/316)	0.0% (0/160)	
Race, % (n/N)			0.160
Asian	1.3% (4/316)	2.5% (4/160)	
Black or African American	3.8% (12/316)	8.1% (13/160)	
Patient chose not to respond	4.1% (13/316)	4.4% (7/160)	
White	90.8% (287/316)	85.0% (136/160)	
Height (cm), Mean ± SD (n) median (min, max)	169.3 ± 10.3 (316) 170.0 (135.0, 194.0)	170.3 ± 10.1 (160) 171.5 (142.0, 190.0)	0.335
Weight (kg), Mean ± SD (n) median (min, max)	83.1 ± 17.0 (316) 82.0 (42.0, 146.0)	82.5 ± 17.1 (160) 80.0 (48.0, 133.0)	0.709
BMI (kg/m^2), Mean ± SD (n) median (min, max)	29.0 ± 5.3 (316) 28.5 (15.8, 52.7)	28.3 ± 4.8 (160) 27.9 (18.1, 48.5)	0.221
BMI>=30, % (n/N)	34.8% (110/316)	30.6% (49/160)	0.360
Smoking, % (n/N)			0.548
Current smoker	35.1% (111/316)	33.8% (54/160)	
Never smoked	20.9% (66/316)	17.5% (28/160)	
Previously smoked	44.0% (139/316)	48.8% (78/160)	
Dyslipidemia/Hypercholesterolemia, % (n/N)	89.6% (283/316)	86.3% (138/160)	0.286
Diabetes Mellitus, % (n/N)	43.4% (137/316)	41.9% (67/160)	0.758
Type			0.034
Type I	9.5% (13/137)	1.5% (1/67)	

Variable	Test DCB	Control PTA	P-value[1]
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 11.

Table 11: Baseline Angiographic Data

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

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

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

D. Safety and Effectiveness Results

A total of 476 patients (316 Lutonix DCB and 160 control PTA) were enrolled and randomized from 54 clinical sites. Among these, 25 patients from the Lutonix DCB group and 38 patients from the Control PTA group had major protocol violation and were excluded from per-protocol population (7.9% Lutonix DCB vs. 23.8% Control PTA). All but four patients were excluded from the per-protocol population due to geographic miss, i.e. Core-lab identified that target lesion was missed when treated. The higher incidence of geographic miss in the control arm may be driven by an operator's tendency to revert to standard of care treatment.

Results for the primary safety and effectiveness endpoints of the LEVANT 2 clinical study are described and summarized below. 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.

1. Safety Results

   The analysis of safety was based on the randomized cohort of 429 patients with evaluable primary safety data at 12 months. The key safety outcomes for this study are presented below in Table 12 thru Table 14. Adverse effects are reported in Table 15.

   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.

Overall, 90.5% (286/316) test DCB subjects and 89.4% (143/160) control PTA subjects were evaluable for primary safety endpoint testing. Missing subjects included 7.3% (23) test 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) test 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 free from any safety event in the test group was 83.9% compared to 79.0% in the control group at 12 months, and noninferior safety was demonstrated (p = 0.005) with a noninferiority margin of 5%.

Table 12: Primary Safety Endpoint Success Rateat 1 year (ITT completers)

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%.

The primary safety endpoint was also analyzed using time-to-event Kaplan-Meier survival analysis to address the issue of missing data, reference Figure 4. At 365 days, 86.7% of Lutonix DCB subjects and 81.5% of control PTA subjects were free from safety events.

Figure 4: Primary Safety Rate 12 Months by Kaplan-Meier

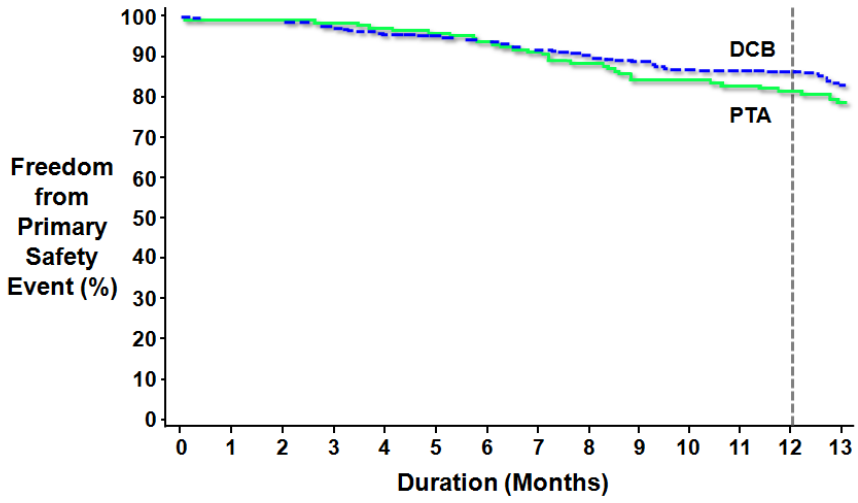


Table 13. Primary Safety Rate 12 Months by Kaplan-Meier

	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.

Table 14 describes results from the first three (ordered) secondary endpoints. Following the hierarchical method, no pre-specified secondary endpoint met its objective since the first hypothesis tested (Total TLR at 12 months) failed to show that the Lutonix DCB was superior to PTA (p=0.208). The results for the next two secondary endpoints are presented for informational purpose only.

Table 14. 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[2])	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.
[2] One patient exited after a non-TVR safety event

Adverse effects that occurred in the PMA clinical study:
Table 15 provides a summary of the Serious Adverse Events (SAE) observed in the LEVANT 2 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 body structure or a body function. Overall, individual events occurred with similar frequencies in the two treatment groups.

Table 15. Serious Adverse Events at 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.

2. Effectiveness Results

The analysis of effectiveness was based on the 264 patients with evaluable primary effectiveness endpoint at the 12 month time point. Key effectiveness outcomes are presented in Table 16 thru **Error! Reference source not found.**.

The primary effectiveness endpoint is primary patency at 12 months. Primary patency is defined as the absence of binary restenosis (as adjudicated by the blinded core-lab) and freedom from target lesion revascularization (TLR, adjudicated by the CEC).

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

The proportion of subjects with primary patency at 12 months was 65.2% in the Lutonix DCB group and 52.6% in the control PTA group, and superior effectiveness ($p = 0.015$) of Lutonix DCB over control PTA was demonstrated.

Table 16: Primary Effectiveness Endpoint at 1 Year (ITT completers)

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.

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.

The percentage of binary restenoses (primary patency failures) leading to a reintervention (TLR) was similar for both groups, see Table 17.

Table 17: Reason for Primary Patency Failure (ITT completers)

Effectiveness Event	Test DCB %(n/N Failures)	Control PTA %(n/N Failures)	Difference %
TLR	38.0% (35/92)	37.5% (24/64)	0.5%
Adjudicated Restenosis without TLR	62.0% (57/92)	62.5% (40/64)	-0.5%

Primary patency has also been analyzed using time-to-event Kaplan-Meier survival analysis to address missing data, reference Figure 5. At 365 days, the

primary patency rate was 73.4% for the Lutonix DCB group compared to 56.7% for the control PTA group.

Figure 5: Primary Patency Rate 12 Months by Kaplan-Meier

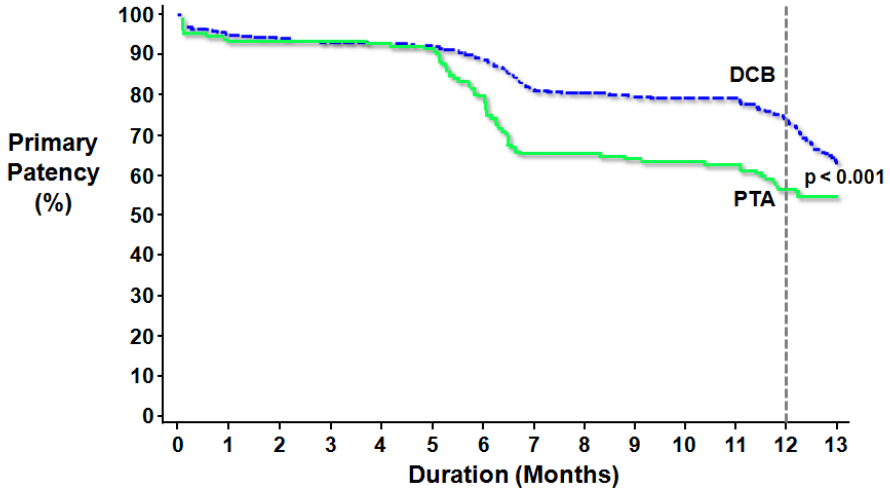


Table 18. Primary Patency Rate 12 Months by Kaplan-Meier

	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).

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 improved 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) was 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).

3. Subgroup Analyses

Pediatric Populations

Peripheral artery disease is not typically found in pediatric populations excepting rare homozygous lipid disorders. Accordingly, the safety and effectiveness of the Lutonix 035 Drug Coated Balloon in pediatric populations was not studied in the LEVANT II study.

Sex/Gender Analysis

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. Please refer to Table 25.

Further assessment regarding outcomes in the female subgroup is planned in a US Post Market Approval study.

Table 19: Primary Endpoints at 1 Year by Gender

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

Pharmacokinetic Substudy

Pharmacokinetics analysis was performed in a subset of patients randomized to the LUTONIX DCB catheter arm in the LEVANT 2 clinical study (n=22 subjects) who received varied doses in the 1.3 mg – 5 mg range. 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 LUTONIX DCB treatment generally exhibited a bi-exponential decay; characterized by a rapid distribution phase followed by a log-linear elimination phase. Following LUTONIX DCB catheter treatment, the 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, respectively.

4. Results Summary

The results of the LEVANT 2 pivotal IDE study provide the clinical evidence supporting the safety and effectiveness of Lutonix DCB. The pivotal IDE study successfully met both primary (safety and effectiveness) endpoints at 12 months by direct comparison to conventional balloon angioplasty. These results demonstrate that treatment of native femoropopliteal lesions with Lutonix DCB provides more durable patency than standard PTA through 12 months with comparable safety and provides a reasonable assurance of safety and effectiveness. 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.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 155 investigators and 5 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Significant payment of other sorts: 5

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

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 the Lutonix Catheter for treatment of femoropopliteal lesions.

With respect to safety, the Lutonix catheter performed comparably to conventional POBA in the LEVANT 1 Trail. 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.

LEVANT 2 Safety Registry

Objective

The primary objective of the LEVANT 2 Safety Registry was to collect additional safety on the Lutonix DCB in a large population. Effectiveness data were also collected.

Study Design

The primary endpoint of the LEVANT 2 Safety Registry is 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)4, all-cause death, amputation, AFS, target vessel revascularization (TVR), thrombosis, major vascular complications, and readmission for cardiovascular events.

Demographics

Following informed consent, 657 subjects were enrolled at 63 clinical sites across the US and Europe. Baseline characteristics and treated lesions were comparable to the randomized LEVANT 2cohort. Presents selected demographics for the LEVANT 2 Randomized and LEVANT 2 Safety Registry cohorts. Note: Data on the 56 LEVANT 2 Roll-in subjects are also included.

4 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.

Table 20: Selected Demographics

Variable	LEVANT 2 Roll-in DCB	LEVANT 2 Randomized DCB	LEVANT 2 Safety Registry DCB	All DCB
Age (years), Mean ± SD (n) median (min, max)	69.2 ± 9.6 (56) 68.2 (46.9, 89.3)	67.8 ± 10.0 (316) 68.2 (44.5, 91.4)	68.7 ± 9.5 (657) 68.8 (41.6, 93.8)	68.4 ± 9.7 (1029) 68.6 (41.6, 93.8)
Gender, % (n/N)				
Female	39.3% (22/56)	38.9% (123/316)	36.2% (238/657)	37.2% (383/1029)
Male	60.7% (34/56)	61.1% (193/316)	63.8% (419/657)	62.8% (646/1029)
Ethnicity, % (n/N)				
Hispanic or Latino	3.6% (2/56)	7.9% (25/316)	1.8% (12/657)	3.8% (39/1029)
Not Hispanic or Latino	94.6% (53/56)	91.8% (290/316)	98.2% (645/657)	96.0% (988/1029)
Patient chose not to respond	1.8% (1/56)	0.3% (1/316)	0.0% (0/657)	0.2% (2/1029)
Race, % (n/N)				
American Indian or Alaska native	0.0% (0/56)	0.0% (0/316)	0.2% (1/657)	0.1% (1/1029)
Asian	0.0% (0/56)	1.3% (4/316)	0.3% (2/657)	0.6% (6/1029)
Black or African American	5.4% (3/56)	3.8% (12/316)	5.0% (33/657)	4.7% (48/1029)
Native 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 21: 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)
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)

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

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.

Results

As this study is on-going, safety data are presented at this time and include data from the LEVANT 2 (including Roll-in subjects) and the LEVANT Safety Registry. There were 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.

Composite safety endpoint results are summarized in Table 22 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 22: Composite Safety Endpoint Success Rate by Time point (All DCB Population)

Freedom from Safety Event[1]	Roll-in DCB %(n/N)	Randomized DCB %(n/N)	Registry DCB %(n/N)	All DCB %(n/N)
1 Month	100.0% (54/54)	99.4% (306/308)	99.4% (643/647)	99.4% (1003/1009)
6 Months	96.1% (49/51)	92.0% (275/299)	98.0% (582/594)	96.0% (906/944)
12 Months	91.7% (44/48)	84.0% (241/287)	94.6% (423/447)	90.5% (708/782)

[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

Secondary endpoints are tabulated in Table 23 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 23: 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)
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)

Outcome Measure (CEC Adjudicated)	Visit	Roll-in DCB %(n/N)	Randomized DCB %(n/N)	Registry DCB %(n/N)	All DCB %(n/N)
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.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on June 12, 2014, the Circulatory System Devices Panel voted 9-0 that there is reasonable assurance the device is safe, 9-0 that there is reasonable assurance that the device is effective, and 9-0 that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

A panel meeting summary is provided in the following website link:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm395638.htm

B. FDA's Post-Panel Action

The panel indicated that a warning may be needed in the Instructions for Use regarding the treatment effect in women. Instead, a statement was made in the Special Populations section of the Instructions for Use. All other panel recommendations were followed. There were no major outstanding issues to be resolved after the panel meeting.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness data drawn from the LEVANT 2 randomized clinical study 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. Patients that met the following inclusion criteria were entered into this study.

- Patient with symptoms of peripheral artery disease classified as Rutherford Category 2 to 4.
- Patient with a de novo or restenotic lesion in native superficial femoral or popliteal artery that 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.
- Patient with a single lesion or multiple lesions segment that is ≤15 cm in length in a reference vessel 4.0 to 6.0 mm in diameter.

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 superficial femoral and popliteal arteries.

Note that there were disparate findings from the gender analyses in that US females had comparatively reduced patency with the DCB. This issue is the subject of a planned Post Approval Study.

B. 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 superficial femoral and popliteal arteries.

C. 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 enrolled in single-arm studies also performed in United States and Europe.

- Although the pooled data suggest improved patency with the DCB these results were not replicated for the US female subgroup. This issue will be the subject of further assessment in a Post Approval Study.

- 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 effective than percutaneous transluminal angioplasty alone with regard to patency. This treatment is valued by patients and preferred to the alternatives because it improves their quality of life with expected 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 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.

D. 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 after predilatation is 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 group, indicating that percutaneous transluminal angioplasty with the Lutonix Drug Coated Balloon after predilatation is non-inferior for safety compared to the current standard of care, PTA.

XIV. CDRH DECISION

CDRH issued an approval order on October 9, 2014. The final conditions of approval cited in the approval order are described below.

1. *PAS 1 (Extended Follow-Up Study):* This study will be conducted as per protocol dated September 26, 2014. This study will follow the premarket cohort through 5 years post-procedure to evaluate the long-term performance of the Lutonix DCB versus PTA in the treatment of stenosis or occlusion of the femoropopliteal arteries.

   The study will be a continued follow-up of participants from the LEVANT 2 Safety Registry (n=657), the LEVANT 2 DCB (n=316), and the LEVANT 2 roll-in (n=56), compared against results from the LEVANT 2 control group (PTA) (n=160). The primary safety endpoint will be composite freedom from: all-cause perioperative (30 days) death, index limb amputation at 2 years, index limb reintervention at 2 years, and index limb-related death at 2 years. The primary effectiveness endpoint will be primary patency of the target lesion at 2 years. Secondary endpoints will be assessed at 5 years and include the primary safety endpoint and its components, anticipated and unanticipated adverse events, all-cause death, major vascular complications, and target lesion revascularization.

2. *PAS 2 (New Enrollment of Female Patients Study):* This study will be conducted as per protocol dated September 26, 2014. This will be a randomized, multicenter study of newly enrolled female patients treated with Lutonix DCB, compared against PTA patients for the treatment of stenosis or occlusion of the femoropopliteal arteries.

   A sample size of 570 de novo patients will be enrolled and randomized to a Lutonix DCB group or a PTA control group. The primary safety endpoint will be composite freedom from: all-cause perioperative (30 days) death, index limb amputation at 1 year, index limb reintervention at 1 year, and index limb-related death at 1 year. The primary effectiveness endpoint will be primary patency of the target lesion at 1 year. Secondary endpoints will be assessed at 5 years and include the primary safety endpoint and its components, anticipated and unanticipated adverse events, all-cause death, major vascular complications, and target lesion revascularization.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. 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.

XVI. REFERENCES