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: None

Premarket Approval Application (PMA) Number: P130024/S009

Date of FDA Notice of Approval: February 7, 2017

The original PMA P130024 was approved on October 9, 2014 and is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo or restenotic lesions up to 150mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Lutonix® 035 Drug Coated Balloon PTA Catheter.

II. INDICATIONS FOR USE

The Lutonix® 035 Drug Coated Balloon PTA Catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic or in-stent restenotic lesions up to 300mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm.

III. CONTRAINDICATIONS

This device is contraindicated for use in:

- Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be excreted in

human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The Lutonix® 035 Drug Coated Balloon PTA Catheter (hereafter referred to as 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**).

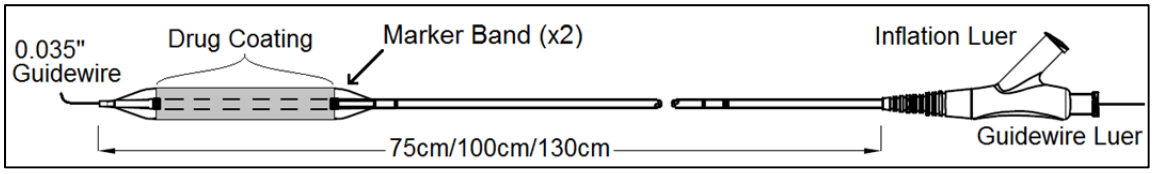


Figure 1: Lutonix® 035 Drug Coated Balloon PTA Catheter, Model 9004

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 - 7.0 mm in diameter and from 40 mm - 150 mm in length (see **Table 1**). Non-radiopaque GeoAlign® Marker Bands are designated on the catheter shaft by 1cm increment bands (see **Figure 2** & **Figure 3**). Devices are compatible with 5F introducer sheaths. 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	120 mm	150 mm
4.0	✓	✓	✓	✓	✓	✓
5.0	✓	✓	✓	✓	✓	✓
6.0	✓	✓	✓	✓	✓	✓
7.0	✓	✓				

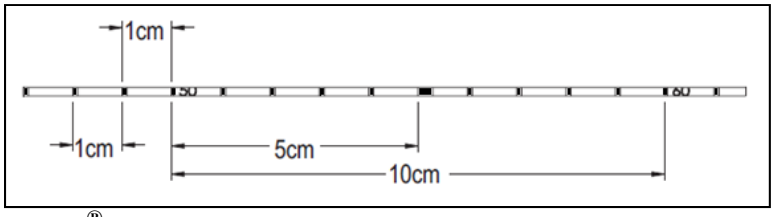


Figure 2: GeoAlign® Marker Bands are non-radiopaque and designed to be utilized outside the introducer sheath

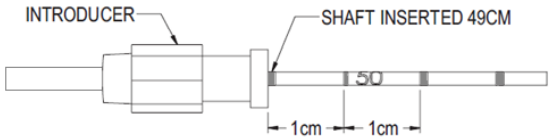


Figure 3: GeoAlign® Marker Band number in relation to the introducer sheath (example)

Drug Components

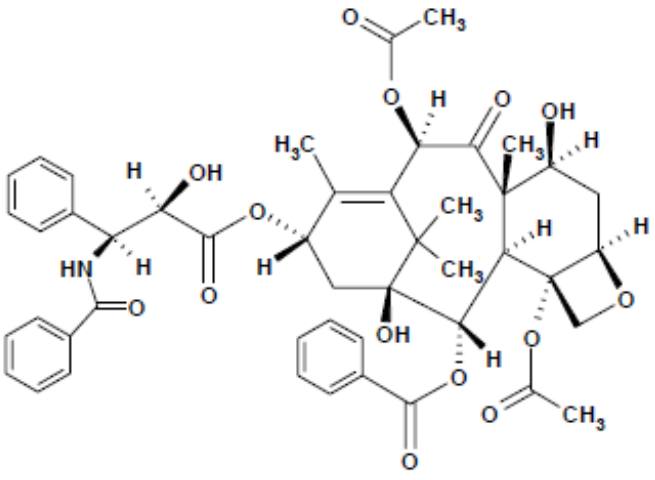
The Lutonix DCB coating is a non-polymer based formulation, consisting of paclitaxel as the active pharmaceutical ingredient and excipients polysorbate and sorbitol. The paclitaxel coating is distributed evenly across the working length of the balloon with a dose density of 2 µg/mm^2, yielding variable total dosages 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
4.0 x 120 mm	3.0
4.0 x 150 mm	3.8
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
5.0 x 120 mm	3.8
5.0 x 150 mm	4.7
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
6.0 x 120 mm	4.5
6.0 x 150 mm	5.7
7.0 x 40 mm	1.8
7.0 x 60 mm	2.6

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 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),
- 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 DCB has been commercially available outside of the U.S. since 2012 and in the U.S. since 2014. **Table 4** includes a list of countries in which the Lutonix DCB is currently marketed in. No recall has occurred since the initial pre-market approval in October 2014.

Table 4: Marketed Countries for the Lutonix DCB

AUSTRALIA	**EU**	**LATIN AMERICA**
CANADA	AUSTRIA	ARGENTINA
EEMEA	BELGIUM	BRAZIL
ALGERIA	DENMARK	CHILE
CZECH REPUBLIC	FINLAND	BOLIVIA
EGYPT	FRANCE	COLOMBIA
IRAN	GERMANY	MEXICO
ISRAEL	GREECE	**REST OF WORLD**
POLAND	HOLLAND	INDIA
RUSSIA	ITALY	KOREA
SAUDI ARABIA	NORWAY	MALAYSIA

SLOVENIA	PORTUGAL	PAKISTAN
TURKEY	SPAIN	SINGAPORE
UAE	SWEDEN	SOUTH AFRICA
	SWITZERLAND	TAIWAN
	UNITED KINGDOM	THAILAND
		USA

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
- Arrhythmias
- Embolization
- Hematoma
- Hemorrhage, including bleeding at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness
- Pneumothorax or hemothorax
- Sepsis/infection
- Shock
- Stroke
- Thrombosis
- Vessel dissection, perforation, rupture, or spasm

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 NONCLINICAL STUDIES

As no changes have been made to the product design or specifications since approval of P130024 and subsequent supplements, all of the catheter bench testing and animal studies previously performed and provided in P130024 and supplements are applicable to and support the use of the Lutonix DCB for treatment of in-stent restenosis (ISR) in the superficial femoral (SFA) and the popliteal arteries. The SSED containing the previous catheter bench testing and animal studies to support the de novo and restenotic lesions in the native arteries are available in the CDRH website. To support the new indication for treatment of in-stent restenosis and lesion lengths up to 300 mm, additional in-stent bench performance testing and an animal safety margin study were performed.

A. Laboratory Studies

In-Stent Catheter Bench Testing

The Lutonix DCB was subjected to the mechanical bench testing at both baseline and aged conditions per the FDA Guidance on percutaneous transluminal coronary angioplasty (PTCA) catheters and Lutonix's internal requirements to support the additional indications for treatment of in-stent restenosis. Summary of the results is provided in **Table 5** below.

Table 5: In-Stent Catheter Bench Test Summary

Test	Description of Test	Acceptance Criteria	Test Results
Minimum Balloon Burst Strength (in-stent)	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 ≥ 12 atm.	The device met the established acceptance criteria.
Balloon Fatigue (in-stent)	Balloon is inflated to RBP and deflated for total of 10 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 10 cycles.	The device met the established acceptance criteria.

Test	Description of Test	Acceptance Criteria	Test Results
Particulate Matter (in-stent)	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.	Acceptance criteria are established for each device size based on the correlation to animal testing.	The device met the established acceptance criteria and the results were similar to testing without a stent.

The results confirm that the Lutonix DCB meets all the requirements of the in-stent catheter bench testing. The data from testing of aged product supports the 36 month shelf life of the Lutonix DCB.

B. Safety Margin Animal Study

To support treatment of longer lesion lengths using the Lutonix DCB, an additional 3X safety margin animal study was performed; reference **Table 6** below. The study was conducted in accordance with FDA 21 CFR Part 58, the GLP Regulations.

Porcine femoral arteries were treated with excess paclitaxel dosing (an average of 37.2 mg) using the Lutonix PTA Balloon, providing a 3X safety margin for lesion lengths up to 330 mm. The animals were then survived for 28 or 90 days following treatment, and safety endpoints were examined. No safety concerns were noted based on overall animal health, organ function, target tissue histopathology, downstream histopathology, or plasma pharmacokinetics (PK) assessment at either 28 or 90 days. Low levels of particulates were observed microscopically in downstream tissue beds which resulted in fibrinoid vascular necrosis of small vessels, although not at a clinically significant level. Overall, *in vivo* vascular safety of the device at a 3X safety margin dose was supported.

Table 6: Animal Study Overview

Description / Study #	Animal Model	Devices	Study Design	Time points	Endpoints
Safety Margin Study	9 Domestic Swine	Test – 3x Dose Lutonix DCB (36.0-40.5 mg/pig)	Multiple balloons (3x Dose) in Femoral Arteries	28, 90 Days	• Histopathology • Clinical Safety • Plasma PK levels • Organ function assessment

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed three clinical studies (Global SFA registry (including Long Lesion and ISR Subgroups), SFA ISR study, and the Lutonix Long Lesion SFA study) to establish a reasonable assurance of safety and effectiveness of the Lutonix DCB for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic or in-stent restenotic lesions up to 300mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm. The SFA ISR study was conducted in the U.S. and the Global SFA registry and Lutonix Long Lesion SFA study were conducted outside of the United States (OUS), in countries including

Austria, Belgium, England, France, Germany, Greece, Italy, Poland, Spain, and Switzerland. Data from these clinical studies were the basis for the PMA supplement approval decision. Summaries of these clinical studies are presented below.

Global SFA Registry

A. Study Design

Patients were treated between December 2012 and July 2013. The database for this Panel Track Supplement reflected data collected through December 2015 and included 691 patients. There were 38 investigational sites.

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

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

All required clinical data were collected on a web-based standardized electronic case report forms. Monitoring was performed to ensure compliance. All serious adverse events (SAEs), including deaths and index limb reinterventions, were adjudicated by an independent Clinical Events Committee (CEC).

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Global SFA real-world registry was limited to patients who met the following inclusion criteria:

   - Patients with stenotic or obstructive lesion of the femoropopliteal artery with Rutherford Category ≤ 4.
   - Patient has at least one patent native outflow artery to the angle as confirmed by angiography.

   Patients were not permitted to enroll in the Global SFA real-world registry if they met any of the following exclusion criteria:

   - Patient has known inadequate distal outflow or planned future treatment of vascular disease distal to the target lesion;

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations in accordance with the schedule listed in **Table 7** below. All of the exams and tests were considered standard of care. The only difference from routine practice was that all adverse events were to be reported within each follow-up window at 1, 6, 12, and 24 months after the index procedure. Contact could be made either by telephone or by a clinical visit.

The key time-points are shown below in the tables summarizing safety and effectiveness.

Table 7: Follow-Up Schedule and Testing Requirements

Event	Pre-Procedure	Procedure	Post-Procedure	1 Month	6 Month	12 Month	24 Month	Revascularization
Inclusion/Exclusion Criteria	√	√						
Pregnancy Test (If applicable)	√							
Rutherford Scale	√			√[1]	√[1]	√[1]	√[1]	√
Informed Consent	√							
Medical History	√							
Medication Compliance	√			√	√	√	√	√
Angiogram		√						
Adverse Event Monitoring		√	√	√	√	√	√	√

[1] If physical visit at site

3. Clinical Endpoints

With regards to safety, composite of freedom at 30 days from target vessel revascularization (TVR), major index limb amputation, and device- and procedure-related death was the primary endpoint (referred to as the Vascular Interventional Advances (VIVA) safety endpoint). Secondary endpoints for safety included:

- Composite of freedom from all-cause perioperative (≤30 day) death and freedom from the following at 6, 12 and 24 months: index limb amputation, index limb re-intervention, and index-limb-related death.
- The following endpoints assessed at 6, 12, and 24 months:
  - All-cause death
  - Device- and procedure-related mortality
  - Unexpected device or drug-related adverse events
  - Index limb amputation (major and minor reported separately)
  - Reintervention for treatment of thrombosis of the target vessel
  - Reintervention for treatment of embolization to its distal vasculature

- Target Lesion Revascularization (TLR)
- Target Vessel Revascularization (TVR)
- Composite of any amputation or target limb reintervention within 30 days of the procedure.

With regards to effectiveness, freedom from TLR at 12 months was the primary endpoint. Secondary effectiveness endpoints included acute device success, procedural success, and primary patency at 6, 12, and 24 months.

This study was a real-world registry to assess the safety and effectiveness in a heterogeneous population and did not have pre-defined hypothesis testing for determination of success/failure.

B. Accountability of PMA Cohort

At the time of database lock, following informed consent, 691 subjects were enrolled at 38 clinical sites across 10 European countries in this clinical study. Patient follow-up compliance through 12 months is 89.9% and follow-up through 24 months is 83.9%, as depicted in **Table 8** below.

Table 8: Subject Disposition

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

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral vascular disease study performed in Europe. **Table 9 – Table 11** present patient demographics and baseline information for the Global SFA registry subjects. Pre-dilatation using a standard PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 64.9% of subjects and final procedure bailout spot stenting occurred in 25.2% of the subjects.

Table 9: Demographics

Summary	Global SFA Registry (N=691)
Age (Years), Mean ± SD (n)	68.2 ± 9.86 (691)
Gender - Male, % (n/N)	67.9% (469/691)
BMI (kg/m2), Mean ± SD (n)	27.2 ± 4.23 (665)

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

Table 10: Baseline Angiographic Data

Summary	Global SFA Registry (N=691)
Number of Treated Lesions, % (n/N)	
1	84.4% (583/691)
2	13.9% (96/691)
3	1.6% (11/691)
4	0.1% (1/691)
Total Target Lesion (mm, Site), Mean ± SD (n)	101.2 ± 84.2 (685)
Treated Length (mm, Site), Mean ± SD (n)	136.6 ± 89.7 (689)
Stenosis (%DS, Site), Mean ± SD (n)	90.0 ± 11.0 (686)
CTO, % (n/N)	31.2% (214/686)
Average RVD (mm, Site), Mean ± SD (n)	5.2 ± 0.67 (681)
Calcification, % (n/N)	50.2% (238/474)
TASC II Lesion Class, % (n/N)	
A	46.8% (231/494)
B	33.4% (165/494)
C	13.2% (65/494)
D	6.7% (33/494)
Number of Patent Runoff Vessels, Mean ± SD (n)	2.3 ± 0.78 (691)

Table 11: Procedural Data

Summary	Global SFA Registry (N=691)
Contralateral Access, % (n/N)	52.2% (361/691)
Vessel Preparation	

Summary	Global SFA Registry (N=691)
Predilation Performed, % (n/N)	64.9% (448/690)
%DS Post Predilation, Mean ± SD (n)	39.2 ± 23.32 (425)
Dissection During Pre-DCB Dilatation, % (n/N)	30.1% (135/448)
Dissection Grade During Pre-DCB Dilatation, % (n/N)	
A	21.6% (29/134)
B	35.1% (47/134)
C	26.9% (36/134)
D	10.4% (14/134)
E	5.2% (7/134)
F	0.7% (1/134)
Atherectomy, % (n/N)	1.3% (9/691)
Others, % (n/N)	0.1% (1/691)
Study Device Treatment	
Inflation Time per Balloon (sec), Mean ± SD (n)	108.4 ± 39.54 (676)
Balloon Pressure (atm), Mean ± SD (n)	9.5 ± 2.16 (674)
Balloon to Vessel Ratio (Inflated Diameter/RVD), Mean ± SD (n)	1.00 ± 0.09 (681)
%DS Post-DCB, Mean ± SD (n)	17.8 ± 20.51 (678)
Dissection Post-Study Treatment, % (n/N)	38.0% (262/689)
Dissection Post-Study Treatment Grade, % (n/N)	
A	39.5% (103/261)
B	30.3% (79/261)
C	19.5% (51/261)
D	6.1% (16/261)
E	3.4% (9/261)
F	1.1% (3/261)
Final Procedure Outcome	
Additional Lesion Treatments, % (n/N)	23.8% (164/690)
%DS Post Procedure, Mean ± SD (n)	14.6 ± 18.69 (680)
Dissection Post-Study Treatment, % (n/N)	18.4% (127/690)
Dissection Post-Study Treatment Grade, % (n/N)	
A	67.7% (86/127)
B	18.9% (24/127)
C	3.9% (5/127)
D	5.5% (7/127)
E	2.4% (3/127)
F	1.6% (2/127)
Bailout Spot Stenting, % (n/N)	25.2% (174/690)
Total Lesion Length of Bailout Spot Stent Patients[1] (mm), Mean ± SD (n)	131.0 ± 97.8 (161)
Total Bailout Spot Stent Length (mm), Mean ± SD (n)	128.5 ± 110.3 (166)

[1]Excludes lesion lengths < 10 mm

D. Safety and Effectiveness Results

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

1. Safety Results

The analysis of safety was based on the cohort of 685 evaluable subjects at the 30 day time point. The key safety outcomes are presented in **Table 12** below.

Table 12: Primary Safety Endpoint

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

[1] Exact binomial confidence interval

Secondary Safety Endpoint

An additional analysis was performed to determine the percent of subjects who were free from composite safety events of all-cause perioperative (≤30 day) death and index limb amputation, index limb re-intervention, and index limb related death at 12 months, which was the primary safety endpoint from LEVANT 2, the supporting pivotal study for the original PMA and allows for analysis of longer term safety. A total of 652 subjects were evaluable for the secondary safety endpoint analysis. The success rate from the composite safety events by subject count was 86.8% for all subjects at 12 months and was 80.2% at 24 months, as described in **Table 13** below.

Table 13: Secondary Safety Endpoint

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

[1] Exact binomial confidence interval

Adverse events are reported in **Table 14** below.

Table 14: Serious Adverse Event at 12 Months (CEC Adjudicated)

AE Category	Event Description	SFA Global Registry (N=688) % (n)
Access site complication	Arterial embolization	0.3% (2)
	Arterial occlusion puncture site	1.0% (7)
	Hematoma/ bleeding puncture site - major	0.6% (4)
	Hematoma/ bleeding puncture site - minor	0.1% (1)
	Pseudo aneurysm	0.9% (6)
	Puncture site infection	0.3% (2)
Cardiovascular	Acute coronary syndrome	0.6% (4)
	Angina, stable	1.0% (7)
	Angina, unstable	0.4% (3)
	Arrhythmia - Bradycardia	0.1% (1)

AE Category	Event Description	SFA Global Registry (N=688) % (n)
	Arrhythmia - Tachycardia	0.3% (2)
	Arrhythmia - Other	0.1% (1)
	Cardiogenic shock	0.1% (1)
	Chronic heart failure	0.1% (1)
	Death	0.6% (4)
	Endocarditis	0.1% (1)
	Hypertension	0.1% (1)
	Myocardial infarction	0.6% (4)
	Cardiac Decompensation	1.0% (7)
	Aortic valve insufficiency	0.1% (1)
Endocrine system	Diabetes Mellitus, Type I	0.1% (1)
	Diabetes Mellitus, Type II	0.3% (2)
Gastrointestinal	Cholecystitis	0.3% (2)
	Diarrhea	0.4% (3)
	Gastritis	0.1% (1)
	Gastrointestinal bleeding	0.6% (4)
	Other infectious/ inflammatory	0.7% (5)
	Constipation	0.1% (1)
Infectious	Local infection	0.4% (3)
	Septicemia/ bacteremia	0.1% (1)
	Influenza	0.1% (1)
Neurological / nervous system	Dizziness/ vertigo	0.3% (2)
	Fainting/ Syncope/ vasovagal reaction	0.1% (1)
	Peripheral nervous system complication	0.3% (2)
	Stroke – hemorrhagic	0.1% (1)
	Stroke – ischemic	0.4% (3)
	Transient Ischemic Attack	0.6% (4)
	Paraplegia/ paraperesis	0.3% (2)
	Stroke - Unknown	0.1% (1)
	Carpal tunnel syndrome	0.1% (1)
Respiratory	Bronchitis	0.1% (1)
	Carcinoma	0.6% (4)
	Chronic obstructive pulmonary disease	0.1% (1)
	Cough	0.1% (1)
	Dyspnea	0.3% (2)
	Pneumonia	0.9% (6)
	Pulmonary edema	0.3% (2)
	Sleep apnea	0.3% (2)
Skeletal, spine and muscular system	Arthralgia	0.3% (2)
	Arthritis	0.4% (3)
	Back pain	0.1% (1)
	Fracture (bone)	0.9% (6)
	Hernia	0.1% (1)
	Osteomyelitis	0.1% (1)
Target lesion	Aneurysm	0.1% (1)
	Occlusion/ closure	2.3% (16)
	Restenosis	3.1% (21)
	Thrombus – in - lesion	0.3% (2)
Target vessel	Aneurysm	0.1% (1)
	Occlusion/ closure	0.9% (6)
	Restenosis	2.2% (15)

AE Category	Event Description	SFA Global Registry (N=688) % (n)
	Thrombus – distal of lesion	0.1% (1)
	Lower limb pain left	0.1% (1)
Genito-urinary system	Renal failure/ insufficiency	0.4% (3)
Various	Amputation	0.4% (3)
	Carcinoma (not specified elsewhere)	0.6% (4)
	Death (non - cardiac or neurological)	0.1% (1)
	Headache	0.1% (1)
	Other	3.3% (23)
	Claudication	1.3% (9)
	Edema	0.3% (2)
	Anemia	0.4% (3)
	Contusion/ bruise	0.3% (2)
	Anemia	0.1% (1)
Vessel specific complications (not puncture site or target vessel)	Arterial occlusion	1.5% (10)
	Arterial thrombosis	0.6% (4)
	Atherosclerosis	0.4% (3)
	Dissection	0.4% (3)
	Embolism	0.3% (2)
	(Re)stenosis	4.1% (28)
	Gangrene	0.3% (2)

2. Effectiveness Results

The analysis of effectiveness was based on the cohort of 648 evaluable subjects at the 12 month time point. The key effectiveness outcomes are presented in **Table 15** below**.**

Table 15: Primary Effectiveness Endpoint – All Subjects

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

[1] Exact binomial confidence interval

Secondary Effectiveness Endpoint

Primary Patency of the target lesion was determined by investigator assessment based on presenting symptoms and clinical exam and by absence of CEC adjudicated TLR event. A total of 614 subjects were evaluable for primary patency at 12 months and 532 subjects at 24 months. The primary patency success rate at 12 months as determined by subject counts was 83.1% and was 71.8% at 24 months, as described in **Table 16** below.

Table 16: Secondary Endpoint Primary Patency at 12 Months

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

[1] Exact binomial confidence interval

3. Subgroup Analysis

The following preoperative characteristics were evaluated for potential association with outcomes: gender, long lesions, and ISR. Descriptive statistics of the outcomes are provided in **Table 17** below. Outcomes for the Long Lesion Subgroup by lesion length are provided in **Table 18** and **Table 19** below.

Table 17: Subgroup Analysis

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

Table 18: Primary Effectiveness Endpoint – Long Lesion Subgroup

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

[1] Exact binomial confidence interval

Table 19: Primary Safety Endpoint – Long Lesion Subgroup

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

[1] Exact binomial confidence interval

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 clinical study included 144 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

Lutonix SFA ISR Study

A. Study Design

Patients were treated between March 2014 and November 2015. The database for this Panel Track Supplement reflected data collected through April 2016 and included 82 randomized patients. There were 20 investigational sites.

The SFA ISR study was initially designed as a prospective, multicenter, single-blind, randomized, controlled trial comparing the Lutonix DCB to standard balloon angioplasty for treatment of femoropopliteal in-stent restenosis. Due to difficulties enrolling, the study was amended to a single-arm study design using a performance goal. No subjects have been enrolled under the single arm study design and the results presented below are for the randomized cohort.

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

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

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the SFA ISR 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 restenosis of previous bare or drug-eluting stents in the femoropopliteal artery that is between 4 and 22 cm in length in a reference vessel 4.0 to 6.0 mm in diameter.

Patients were <u>not</u> permitted to enroll in the SFA ISR study if they met any of the following exclusion criteria:

- Patient has history of stroke within 3 months prior to the study procedure;
- 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 lesion that requires the use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, stents, etc.).

2. <u>Follow-up Schedule</u>

All patients were scheduled to return for follow-up examinations in accordance with the schedule listed in **Table 20** below. All of the exams and tests were considered standard of care. The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 20: Follow-Up Schedule and Testing Requirements

EVENT	Pre-Procedure	Procedure	Post-Procedure	1 Month[1]	6 Month	12 Month	24 Month	36, 48, & 60 months[1]	Repeat Angio/Revasc
Inc/Exc Criteria	√	√							
Inf. Consent	√								
Med Hx	√								
Pregnancy Test[2]	√								
Physical Exam	√		√	√[3]	√	√	√		√[5]
Medication Compliance	√			√	√	√	√	√	√
Resting ABI	√[4]		√[5]	√[3]	√	√	√		√[5]
Rutherford Classification	√				√	√	√		√[5]
WIQ & EQ5D Questionnaires	√				√	√	√		
Angiogram		√							√
Adverse Event Monitoring		√	√	√	√	√	√	√	√
Duplex Ultrasound[6]			√[7]		√	√	√		√

[1] Follow-up can be by telephone or clinical visit
[2] For females of childbearing potential

[3]Required only if clinical visit occurs
[4]Resting ABI is required within 90 days prior to index procedure.
[5] Not required, but encouraged to capture if possible
[6]DUS to be performed after Clinical Assessment
[7]DUS may be capture anytime 0-6 weeks post procedure

3. Clinical Endpoints

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

Secondary endpoints for safety included major vascular complications to 30 days and the following reported at 1, 6, 12, 24, 36, 48, and 60 months:

- Composite Safety
- Death
- Amputation (minor and major separately) as determined by the CEC
- TVR
- Target Limb Revascularization

With regards to effectiveness, primary patency at 12 months was the primary effectiveness endpoint. Primary patency is defined as freedom from CEC-adjudicated clinically-driven TLR and from core laboratory-adjudicated binary restenosis.

Secondary effectiveness endpoints included acute device, technical and procedural success and the following endpoints at 6, 12, and 24 months:

- Primary and Secondary Patency
- TLR, both clinically driven and total TLR
- Sustained clinical benefit
- Change in Rutherford classification from baseline
- Change in Walking Impairment Questionnaire (WIQ)
- Change in quality of life from baseline as measured by the EQ-5D

Success criteria included demonstrating that 12-month primary patency rate of the DCB ISR Cohort was greater than or equal to the meta-analytic rate of 45% based on PTA treatment in ISR. Success also included the demonstration that the safety endpoint for the DCB ISR Cohort was greater than the rate determined from the PTA arm of the LEVANT 2 pivotal IDE study, which was determined to be 69%.

B. Accountability of PMA Cohort

At the time of database lock, 82 subjects were enrolled at 20 investigational sites in the U.S. Patient follow-up compliance through 12-month is 86.6%, as depicted in **Table 21** below.

Table 21: Subject Disposition

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Intent-to-Treat Subjects (ITT), n	53	29
Follow-up by Visit, % (n/N)		
Month 1	96.2%, (51/53)	96.6%, (28/29)
Month 6	94.3%, (50/53)	75.9%, (22/29)
Month 12	92.5%, (49/53)	75.9%, (22/29)
Duration of Follow-up (Days), Mean ± SD (n)	527.6 ± 195.1 (53)	453.8 ± 230.1 (29)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. **Table 22 – Table 24** present selected demographics and baseline angiographic data. Pre-dilatation using a standard PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 100% of subjects. No subjects required bailout spot stenting in this study.

Table 22: Demographics

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Age (Years), Mean ± SD (n)	68.9 ± 9.35 (53)	67.0 ± 8.64 (29)
Gender - Male, % (n/N)	56.6% (30/53)	41.4% (12/29)
BMI (kg/m^2), Mean ± SD (n)	28.6 ± 5.38 (53)	29.5 ± 5.65 (28)
Smoker, % (n/N)		
Current Smoker	37.7% (20/53)	13.8% (4/29)
Former Smoker	54.7% (29/53)	75.9% (22/29)
Hypertension, % (n/N)	96.2% (51/53)	93.1% (27/29)
Dyslipidemia/Hypercholesterolemia, % (n/N)	98.1% (52/53)	96.6% (28/29)
Diabetes, % (n/N)	37.7% (20/53)	55.2% (16/29)
Previous lower extremity artery revascularization, % (n/N)	100% (53/53)	100.0% (29/29)
Ischemic Heart Disease, % (n/N)	16.0% (8/50)	24.1% (7/29)
Renal Insufficiency/Failure or on Dialysis, % (n/N)	5.7% (3/53)	6.9% (2/29)
Baseline Target Limb Rutherford Grade, % (n/N)		
2	17.0% (9/53)	13.8% (4/29)
3	77.4% (41/53)	75.9% (22/29)
4	5.7% (3/53)	10.3% (3/29)
Baseline ABI of Target Limb, Mean ± SD (n)	0.77 ± 0.15 (46)	0.78 ± 0.20 (24)

Table 23: Baseline Angiographic Data

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

Table 24: Procedural Data

Summary	Lutonix DCB Subjects (N=53)	Standard PTA Subjects (N=29)
Contralateral Access, % (n/N)	92.5% (49/53)	96.6% (28/29)
Vessel Preparation		
Pre-dilatation Performed, % (n/N)	100.0% (53/53)	100.0% (29/29)
%DS Post Pre-dilatation, Mean ± SD (n)	34.6 ± 12.1 (47)	34.2 ± 13.2 (26)
Dissection During Pre-dilatation, % (n/N)	12.8% (6/47)	7.7% (2/26)
Study Device Treatment		
Inflation Time per Balloon (sec), Mean ± SD (n)	139.8 ± 89.5 (53)	181.8 ± 188 (28)
Balloon Pressure (atm), Mean ± SD (n)	8.8 ± 2.24 (53)	10.5 ± 3.43 (28)
Treated Length (mm), Mean ± SD (n)	152.4 ± 62.5 (50)	142.0 ± 74.7 (27)
%DS Post-Study Treatment, Mean ± SD (n)	22.2 ± 13.3 (50)	23.3 ± 6.97 (27)
Dissection Post-Study Treatment, % (n/N)	28.0% (14/50)	25.9% (7/27)
Bailout Stent Post Study Device, % (n/N)	0.0% (0/53)	0.0% (0/29)
Final Procedure Outcome		
Post-Study Balloon Dilatation Performed, % (n/N)	13.2% (7/53)	3.4% (1/29)
%DS after Post-Dilatation, Mean ± SD (n)	28.9 ± 5.55 (7)	26.0 (1)
Dissection after Post-Dilatation, % (n/N)	28.6% (2/7)	0.0% (0/1)
Bailout Stent used Post-Dilatation, % (n/N)	0.0% (0/6)	0.0% (0/1)
Final %DS, Mean ± SD (n)	20.7 ± 11.3 (50)	23.4 ± 6.98 (27)

D. Safety and Effectiveness Results

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

1. Safety Results

The analysis of safety takes into account the entire patient experience of 82 subjects evaluable for the primary safety endpoint survival analysis. The primary safety

endpoint by Kaplan-Meier estimates is 72.6% for the DCB subjects and 61.0% for the PTA subjects. There were no procedure or device related deaths and no unanticipated adverse events reported. The key safety outcomes for this study are presented below in **Table 25**. Adverse events are reported in **Table 26.**

Table 25: Primary Safety Endpoint

Group	Time	N[1]	Survival % [95% CI]	Cumulative Information at Visit Day		
				Subjects with Events	Subjects Censored	Subjects at Risk
LTX DCB	Month 1 (30 Days)	52	96.2% [85.7%, 99.0%]	2	1	50
	Month 6 (183 Days)	47	88.5% [76.2%, 94.7%]	6	1	46
	Month 12 (365 Days)	40	72.6% [58.2%, 82.8%]	14	11	28
PTA	Month 1 (30 Days)	28	100.0% [NA, NA]	0	1	28
	Month 6 (183 Days)	25	92.4% [73.0%, 98.1%]	2	3	24
	Month 12 (365 Days)	14	61.0% [37.9%, 77.7%]	9	10	10

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

Table 26: Serious Adverse Events at 12 Months (Site Reported)

AE Category	Event Description	Lutonix DCB (N=53) % (n)	Standard PTA (N=29) % (n)
Blood and lymphatic system disorders	Anemia	0% (0)	3.4% (1)
Cardiac disorders	Acute myocardial infarction	0% (0)	3.4% (1)
	Angina pectoris	1.9% (1)	3.4% (1)
	Atrial fibrillation	1.9% (1)	3.4% (1)
	Cardiac arrest	1.9% (1)	0% (0)
	Cardiac failure congestive	5.7% (3)	6.9% (2)
	Coronary artery disease	1.9% (1)	0% (0)
	Myocardial infarction	3.8% (2)	0% (0)
Gastrointestinal disorders	Constipation	1.9% (1)	0% (0)
	Gastrointestinal hemorrhage	1.9% (1)	0% (0)
	Gastrointestinal ulcer hemorrhage	0% (0)	3.4% (1)
	Intestinal polyp	0% (0)	3.4% (1)
	Lower gastrointestinal hemorrhage	0% (0)	3.4% (1)
	Umbilical hernia	1.9% (1)	0% (0)
General disorders and Administration site conditions	Catheter site hematoma	0% (0)	3.4% (1)
	Non-cardiac chest pain	1.9% (1)	0% (0)
	Thrombosis in device	3.8% (2)	0% (0)
Hepatobiliary disorders	Hepatic cirrhosis	1.9% (1)	0% (0)
Infections and infestations	Cellulitis	1.9% (1)	3.4% (1)
	Cystitis escherichia	0% (0)	3.4% (1)
	Gangrene	1.9% (1)	0% (0)
	Klebsiella infection	1.9% (1)	0% (0)
	Osteomyelitis	1.9% (1)	0% (0)
	Pneumonia	1.9% (1)	0% (0)
	Respiratory tract infection	1.9% (1)	0% (0)
	Sepsis	1.9% (1)	3.4% (1)

AE Category	Event Description	Lutonix DCB (N=53) % (n)	Standard PTA (N=29) % (n)
Injury, poisoning and procedural complications	Ankle fracture	1.9% (1)	0% (0)
	Craniocerebral injury	1.9% (1)	0% (0)
	Femur fracture	1.9% (1)	0% (0)
	Meniscus injury	0% (0)	3.4% (1)
	Peripheral artery restenosis	15.1% (8)	20.7% (6)
	Vascular pseudo aneurysm	0% (0)	3.4% (1)
Metabolism and nutrition disorders	Diabetes mellitus inadequate control	0% (0)	3.4% (1)
Musculoskeletal and connective tissue disorders	Muscle spasms	1.9% (1)	0% (0)
	Osteoarthritis	0% (0)	3.4% (1)
Neoplasms benign, malignant and unspecified (inclcysts and polyps)	Intraductal papilloma of breast	1.9% (1)	0% (0)
	Lung neoplasm malignant	1.9% (1)	3.4% (1)
	Uterine leiomyoma	0% (0)	3.4% (1)
Nervous system disorders	Carotid artery stenosis	0% (0)	3.4% (1)
	Cervicobrachial syndrome	0% (0)	3.4% (1)
	Encephalomalacia	0% (0)	3.4% (1)
Renal and urinary disorders	Hydronephrosis	0% (0)	3.4% (1)
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	1.9% (1)	3.4% (1)
	Epistaxis	1.9% (1)	0% (0)
	Pleural effusion	1.9% (1)	0% (0)
Skin and subcutaneous tissue disorders	Skin ulcer	1.9% (1)	3.4% (1)
Uncoded	Total occlusion of SFA	1.9% (1)	0% (0)
Vascular disorders	Hypertension	0% (0)	3.4% (1)
	Hypotension	1.9% (1)	0% (0)
	Intermittent claudication	13.2% (7)	20.7% (6)
	Peripheral arterial occlusive disease	1.9% (1)	0% (0)
	Peripheral artery dissection	1.9% (1)	0% (0)
	Peripheral artery stenosis	13.2% (7)	6.9% (2)
	Peripheral embolism	0% (0)	3.4% (1)
	Peripheral ischemia	0% (0)	3.4% (1)
	Peripheral vascular disorder	1.9% (1)	0% (0)

2. Effectiveness Results

The analysis of effectiveness takes into account the entire patient experience of 78 subjects evaluable for the primary patency survival analysis. The 12 month primary patency rate by Kaplan-Meier estimates is 66.2% for the DCB subjects compared to 49.6% for the PTA subjects. The key effectiveness outcomes for this study are presented below in **Table 27.**

Table 27: Primary Effectiveness Endpoint

Group	Time	N[1]	Survival % [95% CI]	Cumulative Information at Visit Day		
				Subjects with Events	Subjects Censored	Subjects at Risk
LTX DCB	Month 1 (30 Days)	49	94.0% [82.6%, 98.0%]	3	2	46
	Month 6 (183 Days)	42	91.9% [79.9%, 96.9%]	4	9	38
	Month 12 (365 Days)	31	66.2% [49.4%, 78.5%]	14	19	18
PTA	Month 1 (30 Days)	26	96.3% [76.5%, 99.5%]	1	2	24
	Month 6 (183 Days)	19	77.2% [53.4%, 89.9%]	5	6	16
	Month 12 (365 Days)	8	49.6% [26.3%, 69.3%]	10	11	6

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

3. Secondary Effectiveness Endpoint

The secondary effectiveness endpoint of freedom from clinically driven TLR success rate by Kaplan-Meier estimate at 12 months (Day 365) was 78.4% for Lutonix DCB and 61.0% for control PTA, as depicted in **Table 28** below.

Table 28: Clinically-Driven TLR-Free at 12 Months

Group	Time	N[1]	Survival % [95% CI]	Cumulative Information at Visit Day		
				Subjects with Events	Subjects Censored	Subjects at Risk
LTX DCB	Month 1 (30 Days)	52	96.2% [85.7%, 99.0%]	2	1	50
	Month 6 (183 Days)	50	94.3% [83.4%, 98.1%]	3	1	49
	Month 12 (365 Days)	43	78.4% [64.4%, 87.4%]	11	11	31
PTA	Month 1 (30 Days)	28	100.0% [NA, NA]	0	1	28
	Month 6 (183 Days)	25	92.4% [73.0%, 98.1%]	2	3	24
	Month 12 (365 Days)	14	61.0% [37.9%, 77.7%]	9	10	10

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

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 SFA ISR study included 77 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f).

Lutonix Long Lesion SFA Study

A. Study Design

Patients were treated between December 2013 and May 2015. The database for this Panel Track Supplement reflected data collected through December 2015 and included 118 Lutonix DCB patients. There were 14 investigational sites.

This study was a prospective, global multi-center, single arm registry study for treatment of long lesions in the femoropopliteal arteries.

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

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

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

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Long Lesion SFA study was limited to patients who met the following inclusion criteria:

   - Patients with stenotic or obstructive lesion of the femoropopliteal artery with Rutherford Category 2- 4.
   - TASC II Class C or D Lesions with intended target lesion treatment segment(s) cumulatively ≥ 14 cm in length and vessel diameter between 4 – 7mm.
   - Patient has at least one patent native outflow artery to the angle as confirmed by angiography.

   Patients were not permitted to enroll in the Long Lesion SFA study if they met any of the following exclusion criteria:

   - Patient has history of stroke within 3 months prior to the study procedure;
   - 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;

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations in accordance with the schedule listed in **Table 29** below. All of the exams and tests were

considered standard of care. The only difference from routine practice was that all adverse events were to be reported within each follow-up window at 1, 6, 12, 24, and 36 months after the index procedure.

Table 29: Follow-Up Schedule and Testing Requirements

EVENT	Pre-Procedure (Baseline)	Procedure	Post-Procedure	1 Month[1]	6 Month	12 Month	24 Month	36 Months[1]	Repeat Angio/Revasc
Inclusion/Exclusion Criteria	√	√							
Informed Consent	√								
Medical History	√								
Physical Exam (pregnancy test[2])	√		√	√[3]	√	√	√		√
Medication Compliance	√			√[3]	√	√	√	√	√
Resting ABI	√[4]		√[6]	√[3,5]	√	√	√		√
Rutherford Classification	√				√	√	√		√
WIQ & EQ5D Questionnaires	√				√	√	√		
Angiogram		√							√
Adverse Event Monitoring		√	√	√	√	√	√	√	√
Duplex Ultrasound			√[7]		√	√	√		

[1] Follow-up can be by telephone or clinical visit
[2] Pregnancy test required for females of childbearing potential at baseline only
[3] Required only if clinical visit occurs
[4] Resting ABI is required within 90 days prior to index procedure.
[5] Not required, but encouraged to capture if possible
[6] Resting ABI to be performed after the Clinical Assessment
[7] DUS may be captured anytime 0-6 weeks post procedure

3. Clinical Endpoints

The primary safety endpoint was a composite of freedom from all-cause peri-procedural (≤30 day) death and freedom at 1 year from the following: index limb amputation (above and below the ankle) and index limb re-intervention.

Secondary endpoints for safety included major vascular complications to 30 days and the following reported at 1, 6, 12, 24, and 36 months:

- Composite Safety
- All-cause Death
- Amputation (minor and major separately) as determined by the CEC
- TVR
- Target Limb Revascularization

The primary effectiveness endpoint was primary patency at 12 months as defined as freedom from CEC-adjudicated clinically-driven TLR and from core laboratory-adjudicated binary restenosis.

Secondary effectiveness endpoints included acute device, technical and procedural success and the following endpoints at 6, 12, and 24 months:

- Primary and Secondary Patency
- Target Lesion Revascularization (TLR) both clinically driven and total TLR
- Change in Rutherford classification from baseline
- Change of resting Ankle Brachial Index (ABI) from baseline
- Change in Walking Impairment Questionnaire
- Change in quality of life from baseline as measured by the EQ-5D

This study was a single-arm prospective registry to assess the safety and effectiveness in long (≥ 140 mm) SFA diseased lesions and did not have pre-defined hypothesis testing for determination of success/failure.

B. Accountability of PMA Cohort

At the time of database lock, following informed consent, 118 DCB subjects were enrolled at 14 clinical sites across 5 European countries. Patient follow-up compliance through 12-month is 89%, as depicted in **Table 30** below.

Table 30: Subject Disposition

Summary	DCB Subjects
ITT Subjects (Enrolled Subjects), n	118
Follow-up by Visit, % (n/N) Month 1, % (n/N) Month 6, % (n/N) Month 12, % (n/N)	 98.3% (116/118) 89.0% (105/118) 89.0% (105/118)
Duration of Follow-up (Days), Mean ± SD (n)	392.5 ± 125.94 (118)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral vascular disease study performed in Europe. **Table 31 – Table 33** presents selected demographics and baseline angiographic data. Pre-dilatation using a standard PTA catheter was required as part of the clinical study to prepare the vessel and occurred in 98.3% of subjects and post-study device bailout spot stenting occurred in 39.8% of the subjects.

Table 31: Demographics

Summary	DCB Subjects (N=118)
Age (Years), Mean ± SD (n)	67.6 ± 9.23 (118)
Gender - Male, % (n/N)	73.7% (87/118)
BMI (kg/m^2), Mean ± SD (n)	27.1 ± 4.48 (114)
Smoking Current Smoker Past Smoker	 41.5% (49/118) 28.8% (34/118)
Hypertension	85.6% (101/118)
Hyperlipidemia	30.5% (36/118)
Diabetes	36.4% (43/118)

Summary	DCB Subjects (N=118)
History of Vascular Disease, % (n/N)	86.4% (102/118)
History of Cardiac Disease, % (n/N)	53.4% (63/118)
History of Renal Disease, % (n/N)	27.1% (32/118)
Baseline Target Limb Rutherford Grade, % (n/N) 0 2 3 4 5	 0.9% (1/116) 24.1% (28/116) 69.0% (80/116) 5.2% (6/116) 0.9% (1/116)
Baseline ABI of Target Limb, Mean ± SD (n)	0.69 ± 0.26 (111)

Table 32: Baseline Angiographic Data

Summary	DCB Subjects (N=118)
Number of Treated Lesions, % (n/N) 1 2	 92.4% (109/118) 7.6% (9/118)
Total Lesion Length (mm), Mean ± SD (n)	212.5 ± 68.32 (117)
Stenosis (%DS), Mean ± SD (n)	89.5 ± 14.00 (117)
CTO, % (n/N)	52.1% (61/117)
RVD (mm), Mean ± SD (n)	4.7 ± 0.76 (117)
Any Calcification, % (n/N)	88.1% (104/118)
Highest Severity of Calcification, % (n/N) Mild Moderate Severe	 21.2% (22/104) 57.7% (60/104) 21.2% (22/104)
Highest TASC Classification, % (n/N) B C D	 0.8% (1/118) 77.1% (91/118) 22.0% (26/118)
Treated Lesion Locations, % (n/N) SFA, Proximal SFA, Mid SFA, Distal Popliteal, Proximal Popliteal, Mid Popliteal, Distal	 51.3% (60/117) 35.9% (42/117) 14.5% (17/117) 4.3% (5/117) 0.9% (1/117) 0.0% (0/117)
Number of Patent Run-off Vessels 2 3 4	 31.6% (37/117) 34.2% (40/117) 34.2% (40/117)

Table 33: Procedural Data

Summary	DCB Subjects (N=118)
Contralateral Access, % (n/N)	55.6% (65/117)
Vessel Preparation	
Predilation Performed, % (n/N)	98.3% (116/118)
%DS Post Predilation, Mean ± SD (n)	45.6 ± 13.8 (101)
Dissection During Pre-DCB Dilatation, % (n/N)	81.2% (82/101)

Summary	DCB Subjects (N=118)
Dissection Grade During Pre-DCB Dilatation, % (n/N)	
A	56.1% (46/82)
B	30.5% (25/82)
C	12.2% (10/82)
D	1.2% (1/82)
Bailout Spot Stenting Performed, % (n/N)	6.9% (8/116)
Study Device Treatment	
Inflation Time per Balloon (sec), Mean ± SD (n)	137.4 ± 47.99 (118)
Transit Time per Balloon (sec), Mean ± SD (n)	30.5 ± 23.04 (112)
Balloon Pressure (atm), Mean ± SD (n)	8.6 ± 2.03 (117)
Treatment Overstretch (Inflated Diameter/RVD), Mean ± SD (n)	1.13 ± 0.19 (117)
Total Length of DCB Balloons (mm, Site), Mean ± SD (n)	248.0 ± 70.48 (118)
%DS Post-DCB, Mean ± SD (n)	37.4 ± 13.95 (116)
Dissection Post-Study Treatment, % (n/N)	81.9% (95/116)
Dissection Grade Post-Study Treatment, % (n/N)	
A	50.5% (48/95)
B	40.0% (38/95)
C	7.4% (7/95)
D	2.1% (2/95)
Bailout Spot Stenting Post Study Device, % (n/N)	39.8% (47/118)
Final Procedure Outcome	
Post-DCB Dilation Performed, % (n/N)	58.5% (69/118)
%DS after Post-DCB Dilatation, Mean ± SD (n)	28.7 ± 14.83 (67)
Dissection after Post-DCB Treatment, % (n/N)	64.6% (42/65)
Dissection Grade after Post-DCB Treatment, % (n/N)	
A	59.5% (25/42)
B	38.1% (16/42)
D	2.4% (1/42)
Bailout Spot Stent used Post-DCB Dilatation, % (n/N)	65.2% (45/69)
Final %DS, Mean ± SD (n)	29.1 ± 12.54 (117)

D. Safety and Effectiveness Results

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

1. Primary Safety Endpoint

The analysis of safety was based on 107 subjects evaluable at the 12 month evaluation. The key outcomes for this study are presented in **Table 34** and **Table 35** (by lesion length). Adverse events are reported in **Table 36.**

Table 34: Primary Safety Endpoint

Measure	Success % (n/N)	95% CI[1]
Primary Safety Endpoint	79.4% (85/107)	70.5%, 86.6%

[1] Exact binomial confidence interval

Table 35: Primary Safety Endpoint by Lesion Length

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

[1] Exact binomial confidence interval

Table 36: Serious Adverse Event at 12 Months (Site Reported)

AE Category	Event Description	Lutonix Long Lesion Study (N=118) % (n)
Blood and lymphatic system disorders	Anemia	1.7% (2/118)
Cardiac disorders	Acute myocardial infarction	1.7% (2/118)
	Angina pectoris	1.7% (2/118)
	Angina unstable	1.7% (2/118)
	Aortic valve stenosis	0.8% (1/118)
	Atrial fibrillation	0.8% (1/118)
	Cardiac failure	0.8% (1/118)
	Coronary artery disease	4.2% (5/118)
Gastrointestinal disorders	Colitis	1.7% (2/118)
	Diarrhea	0.8% (1/118)
	Duodenal perforation	0.8% (1/118)
	Gastritis	0.8% (1/118)
	Gastrointestinal hemorrhage	0.8% (1/118)
General disorders and administration site conditions	Device occlusion	2.5% (3/118)
Hepatobiliary disorders	Cholecystitis acute	0.8% (1/118)
Infections and infestations	Bronchiolitis	0.8% (1/118)
	Diverticulitis	0.8% (1/118)
	Gangrene	0.8% (1/118)
	Herpes zoster	0.8% (1/118)
	Infected skin ulcer	0.8% (1/118)
	Muscle abscess	0.8% (1/118)
	Pneumonia	0.8% (1/118)
	Septic shock	0.8% (1/118)
Injury, poisoning and procedural complications	Acetabulum fracture	0.8% (1/118)
	Contusion	0.8% (1/118)
	Peripheral arterial reocclusion	6.8% (8/118)
	Peripheral artery restenosis	10.2% (12/118)
	Post procedural hematoma	0.8% (1/118)
	Post procedural hemorrhage	0.8% (1/118)
	Pubis fracture	0.8% (1/118)
	Traumatic hematoma	0.8% (1/118)
	Vascular graft complication	0.8% (1/118)
	Vascular graft occlusion	0.8% (1/118)
	Vascular pseudoaneurysm	2.5% (3/118)
Metabolism and nutrition disorders	Dehydration	0.8% (1/118)

AE Category	Event Description	Lutonix Long Lesion Study (N=118) % (n)
Musculoskeletal and connective tissue disorders	Gouty arthritis	0.8% (1/118)
	Intervertebral disc protrusion	0.8% (1/118)
	Osteoarthritis	0.8% (1/118)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	0.8% (1/118)
	Eyelid tumor	0.8% (1/118)
	Squamous cell carcinoma of skin	0.8% (1/118)
Nervous system disorders	Carotid artery stenosis	0.8% (1/118)
	Cerebral infarction	0.8% (1/118)
	Intracranial hematoma	0.8% (1/118)
	Ischemic stroke	0.8% (1/118)
Psychiatric disorders	Depression	0.8% (1/118)
Renal and urinary disorders		0.8% (1/118)
	Renal failure	0.8% (1/118)
Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	0.8% (1/118)
	Pulmonary embolism	0.8% (1/118)
Skin and subcutaneous tissue disorders	Diabetic foot	0.8% (1/118)
Vascular disorders	Arterial occlusive disease	0.8% (1/118)
	Circulatory collapse	0.8% (1/118)
	Deep vein thrombosis	0.8% (1/118)
	Extremity necrosis	0.8% (1/118)
	Femoral artery occlusion	4.2% (5/118)
	Hypertensive crisis	0.8% (1/118)
	Peripheral arterial occlusive disease	3.4% (4/118)
	Peripheral artery stenosis	5.9% (7/118)
	Peripheral artery thrombosis	0.8% (1/118)
	Peripheral embolism	0.8% (1/118)

2. Primary Effectiveness Endpoint

The analysis of effectiveness was based on 102 subjects evaluable at the 12 month evaluation. The key outcomes for this study are presented in **Table 37** and **Table 38** (by lesion length).

Table 37: Primary Effectiveness Endpoint

Measure	Success % (n/N)	95% CI[1]
Primary Patency at 12 Months	57.8% (59/102)	47.7%, 67.6%

[1] Exact binomial confidence interval

Table 38: Primary Effectiveness Endpoint by Lesion Length

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

[1] Exact binomial confidence interval

3. Secondary Effectiveness Endpoint

The freedom from clinically-driven TLR success rate at 12 months as determined by subject counts was 85.8%, as depicted in **Table 39** below.

Table 39: Clinically-Driven TLR-Free at 12 Months

Measure	Success % (n/N)	95% CI[1]
Clinically-Driven TLR-Free at 12 Months	85.8% (91/106)	77.7%, 91.9%

[1] Exact binomial confidence interval

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 Long Lesion study included 18 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f).

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness data are drawn from the Global SFA Real-World registry, SFA ISR study, and the Lutonix Long Lesion SFA study to demonstrate a reasonable assurance of effectiveness for treatment of in-stent restenosis and long lesions up to 300 mm in length with the Lutonix DCB. No hypothesis testing was performed, and this assessment is based primarily on clinical interpretation of descriptive statistics and the totality of the data submitted. A summary of the effectiveness results used to support a reasonable assurance of effectiveness is summarized below:

ISR:

Global SFA Real-World Registry ISR Cohort:

- Primary effectiveness endpoint of freedom from TLR at 12 months was 90.7%.

- Secondary effectiveness endpoint of primary patency at 12 months was 80.7%.

SFA ISR Study Interim Results:

- KM estimate of primary patency at 12 months (day 365) of 66.2% for DCB vs. 49.6% for standard PTA.
- KM estimate of freedom from clinically-driven TLR at 12 months (day 365) of 78.4% for DCB vs. 61.0% for standard PTA.

It should be noted that follow ups for the ISR subset of the Global SFA registry were performed per standard of care at clinical visits or by telephone, rather than by the more stringent clinical visits and Doppler ultrasound (DUS) evaluations used in the LEVANT 2 trial, which was used to support the original PMA, P130024. This protocol difference likely accounts for the higher effectiveness results as compared to the non-ISR lesions of the LEVANT 2 trial. Additionally, interim results from the Lutonix SFA ISR study demonstrated a trend toward increased effectiveness of the DCB arm as compared to the PTA arm. Differences of approximately 15% were seen for both primary patency and TLR between treatment groups. Collectively, the results from the ISR Subset of the Global SFA Real-World Registry, as well as the interim study results from the SFA ISR study, demonstrate with reasonable assurance that the Lutonix DCB can be used effectively in patients with ISR lesions.

Long Lesions:

Global SFA Real-World Registry Long Lesion Subset:

- Primary effectiveness endpoint of freedom from TLR at 12 months was 93.2%.
- Secondary effectiveness endpoint of primary patency at 12 months was 74.6%.

Long Lesion SFA Study Interim Results:

- Primary patency at 12 months of 57.8%.
- Clinically driven TLR-free rate at 12 months of 85.8%.

As noted above, the Long Lesion Subset of the Global SFA registry evaluated subjects according to standard-of-care and allowed for clinical assessment by the physicians during clinical visit or by telephone, rather than the more rigorous assessments in the LEVANT 2 trial. The data from the Global SFA registry represent real-world clinical results as the patient evaluation and treatment were performed per the clinically-driven symptoms per the standard of care practices. This protocol differences likely accounts for higher effectiveness results in the global registry.

The Lutonix Long Lesion SFA study, with exception of lesion length, enrolled similar patients and used similar evaluation methodologies and follow-up protocol as the LEVANT 2 pivotal study. Clinical comparisons of the DCB subjects in the Long Lesion study as compared to the DCB subjects in the LEVANT 2 study demonstrated a lower primary patency rate of 57.8% as compared to 65.2% for the DCB arm of the LEVANT 2 study, which is to be expected given the lesion lengths studied were on average greater than 3 times as long. The clinically-driven TLR rate was similar

between both of these groups. Collectively, the results from the Global SFA Real-World Registry and the Long Lesion SFA study demonstrate with reasonable assurance that the Lutonix DCB can be used effectively in patients with ISR lesions and long lesions.

B. Safety Conclusions

The safety for treatment of in-stent restenosis and long lesion is supported by the clinical studies, the additional in-stent bench testing, and the pre-clinical animal study performed to support a 3X margin of safety for treatment of up to 12.4mg of drug dose per patients. The clinical safety outcomes are drawn from the Global SFA Real-World registry, the Lutonix SFA ISR study, and the Lutonix Long Lesion SFA study support reasonable assurance of safety for treatment of in-stent restenosis and long lesions. No hypothesis testing was performed and this assessment is based on clinical interpretation of descriptive statistics and the totality of the data. A summary of the safety results is included below:

ISR:

Global SFA Real-World Registry ISR Subset:

- Primary safety endpoint of freedom from target vessel revascularization (TVR), major index limb amputation, and device- and procedure-related death at 30 days was 100%.
- Secondary safety endpoint at 12 months was 86%.

SFA ISR Study:

- Primary safety endpoint of freedom from composite safety events at 12 month (day 365) of 72.6% for DCB vs. 61% for standard PTA.

The global registry results are similar to those reports in from LEVANT 2 of 99.7% and 83.9% at 30 days and 12 months, respectively. Interim results from the SFA ISR study demonstrated a trend toward increased safety of the DCB arm as compared to the PTA arm with differences of approximately 10% between treatment groups for the primary safety assessment. Collectively, the results from the ISR Subset of the Global SFA Real-World Registry, as well as the interim study results from the SFA ISR study, demonstrate with reasonable assurance that the Lutonix DCB can be used safely in patients with ISR lesions.

Long Lesions:

Global SFA Real-World Registry Long Lesion Subset:

- Primary safety endpoint of freedom from target vessel revascularization (TVR), major index limb amputation, and device- and procedure-related death at 30 days was 99.3%.
- Secondary safety endpoint (LEVANT 2 primary safety) of 84.2%.

Long Lesion SFA Study:

- Primary safety endpoint of freedom from composite safety at 12 month (day 365) of 79.4%

The results from the Long Lesion Subset of the Global SFA are similar to those demonstrated in LEVANT 2 of 99.7% and 83.9% at 30 days and 12 months, respectively. The Lutonix Long Lesion SFA study, with exception of lesion length, enrolled similar patients and used similar evaluation methodologies and follow-up protocol as LEVANT 2 study, and the results are also comparable (79.4% as compared to 83.9% for the DCB arm of the LEVANT study). Collectively, the results from the Long Lesion Subset of the Global SFA Real-World Registry and the Long Lesion SFA study demonstrate with reasonable assurance that the Lutonix DCB can be used safely in patients with ISR lesions.

C. Benefit-Risk Conclusions

The probable benefits of the Lutonix DCB for treatment of ISR and long lesions up to 300 mm in length are based on combination of bench testing, a safety margin animal study, and the data collected in the clinical studies, as described above. The probable benefit of the Lutonix DCB 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 DCB included:

- In a global registry, the primary patency and freedom from TLR rates in ISR and long lesion subgroups are within reasonable clinical range and reflect real-world outcomes.
- The SFA ISR study presented interim randomized results comparing DCB to standard PTA for treatment of in-stent restenosis which showed meaningful benefit of DCB as compared to standard PTA.
- The Long Lesion SFA study presented 12 month results for treatment of long lesions (average lesion length of 212.5 mm) that is significantly longer than treated in the LEVANT 2 pivotal study. Clinical comparison to shorter lesions did not suggest unexpected trends with regard to safety and effectiveness.
- Patient risk is minimized by limiting use to operators who have the necessary training to use the device safely and effectively and adhere to recommended peri-procedural medication regimens.

This submission did not include specific information on patient perspectives for this device.

The data available support that the probable benefits outweigh the probable risks for using the Lutonix DCB for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic or in-stent restenotic lesions up to 300mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7mm.

D. Overall Conclusions

The clinical and non-clinical data in this application support reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results from the three clinical studies demonstrate a benefit for the use the Lutonix DCB in treatment of ISR lesions and long lesion with limited risks. Therefore, it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use.

XIII. CDRH DECISION

CDRH issued an approval order on February 7, 2017. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – *ISR and LL Cohorts of the Global SFA Registry Continued Follow-Up Study*: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The ISR and LL Cohorts of the Global SFA Registry Continued Follow-Up Study must be conducted per Protocol CL0004-01, Version 1.0, dated October 12, 2012. This study is a multi-center, single arm, prospective continued follow-up of the ISR and LL Cohorts of the Global SFA Registry. It will evaluate the long-term safety and effectiveness of the Lutonix Drug Coated Balloon in In-Stent Restenotic and Long Lesions. The safety and effectiveness endpoints to be assessed through 24 months post-procedure are: (1) the composite of freedom from all-cause peri-procedural (≤30 day) death and freedom at 1 year and 2 years from: index limb amputation, index limb re-intervention, and index limb death and (2) freedom from TLR at 1 year and 2 years, as defined in the protocol.

2. ODE Lead PMA Post-Approval Study – *SFA ISR IDE Continued Follow-Up Study*: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The SFA ISR IDE Continued Follow-Up Study must be conducted per Protocol CL0018-01, Version 4.0, dated July 6, 2016. This study is a multi-center, single arm, prospective continued follow-up of the SFA ISR Study (IDE G130244). It will evaluate the long-term safety and effectiveness of the Lutonix Drug Coated Balloon in In-Stent Restenotic Lesions. The safety and effectiveness endpoints to be assessed through 36 months post-procedure are: (1) the composite of freedom from all-cause peri-procedural (≤30 day) death and freedom at 1 year, 2 years, and 3 years from index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death and (2) primary patency at 1 year and 2 years, as defined in the protocol. Target Lesion Revascularization will also be reported at 3 years.

3. ODE Lead PMA Post-Approval Study – *Lutonix Long Lesion SFA Continued Follow-Up Study*: The Office of Device Evaluation (ODE) will have the lead for this clinical

study, which was initiated prior to device approval. The Lutonix Long Lesion SFA Continued Follow-Up Study must be conducted per Protocol CL0017-01, Version 2.0, dated March 31, 2014. This study is a multi-center, single arm, prospective continued follow-up of the EU Long Lesion Trial. It will evaluate the long-term safety and effectiveness of the Lutonix Drug Coated Balloon in Long Lesions. The safety and effectiveness endpoints to be assessed through 36 months post-procedure are: (1) the composite of freedom from all-cause peri-procedural (≤30 day) death and freedom at 1 year, 2 years, and 3 years from the following: index limb amputation and (above or below the ankle) and index limb re-intervention and (2) primary patency at 1 year and 2 years, as defined in the protocol. Target Lesion Revascularization will also be reported at 3 years.

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

XIV. 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.

XV. REFERENCES

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.