Lutonix™ 014 Drug Coated Balloon PTA Catheter

Product Features: GeoAlign™ Marker Bands, 4F Sheath

INSTRUCTIONS FOR USE

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

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ENGLISH

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INSTRUCTIONS FOR USE

1 DEVICE DESCRIPTION

1.1 PTA Catheter Description

The Lutonix™ 014 Drug Coated Balloon PTA Catheter (Lutonix™ Catheter) consists of an over the wire catheter with a drug coated balloon fixed at the distal tip (**Figure 1**). The balloon is coated with a specialized formulation that includes the drug, paclitaxel. The Lutonix™ Catheter is 0.014" guidewire compatible, with a low profile, semi-compliant balloon formed to a low profile tapered tip to facilitate advancement of the catheter to and through the stenotic region of the vessel. For all balloon lengths, radiopaque markers delineate the working length of the balloon and aid in balloon placement. For balloon lengths of 100 mm and greater, two radiopaque markers are positioned on the distal portion of the balloon and one radiopaque marker is positioned on the proximal portion of the balloon to differentiate between the distal and proximal ends of the balloon. Non-radiopaque GeoAlign™ Marker Bands are designated on the catheter shaft by 1cm increment bands. Each 10cm increment is labeled with the distance from the distal balloon tip (**Figure 2** & **Figure 3**). Thicker bands denote the midway point (5cm) between the labeled distances. GeoAlign™ Marker Bands are designed to be used as a location reference tool. The proximal portion of the catheter includes an inflation female luer lock hub and a guidewire female luer lock hub. Each product is packaged with a balloon protector that has been positioned over the balloon and a disposable wire lumen stylet, both of which are to be removed prior to use. See **Table 1** for additional details. The Lutonix™ Catheter is utilized in patients with stenotic lesions (see indication) who have critical limb ischemia (CLI).

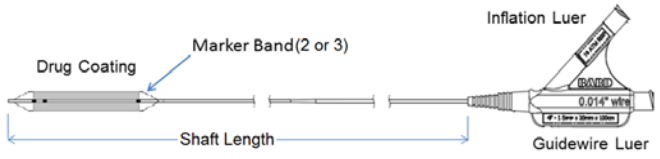


Figure 1. Lutonix™ 014 Drug Coated Balloon PTA Catheter

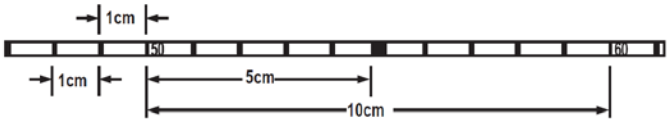


Figure 2. GeoAlign™ Marker Bands are non-radiopaque and designed to be utilized outside the introducer sheath

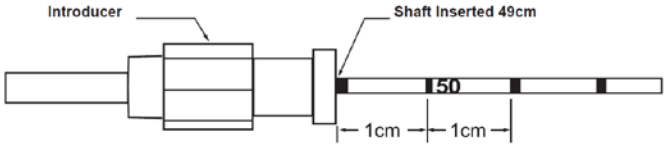


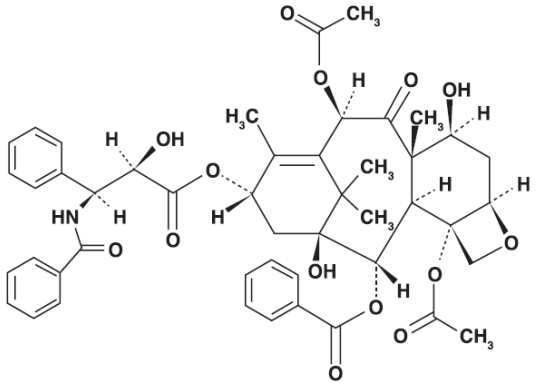
Figure 3. GeoAlign™ Marker Band number in relation to the introducer sheath (example)

Table 1. Lutonix™ 014 Drug Coated Balloon PTA Catheter Product Description (Reference to device specific product label)

Attribute	Peripheral (PTA)
Model Number	9005
Catheter Configuration	Over-the-Wire (OTW)
Available Balloon Diameters	2.0, 2.5, 3.0, 3.5, 4.0 mm
Available Balloon Lengths	40, 60, 80, 100, 120, 150 mm
Effective Catheter Length	100, 130, 150 cm
Radiopaque Marker Bands	2 or 3 (for ≥ 100m length balloons)
Nominal Balloon Pressure	6 atm
Balloon Rated Burst Pressure	15 atm
Maximum Guidewire	0.014"
Minimum Introducer Sheath	4F
Crossing Profile	3.0F – 2mm balloon 3.3F – 2.5mm balloon 3.7F – 3.0 – 3.5 mm balloon 4.0F – 4.0mm balloon
Coating Formulation	Active Pharmaceutical Ingredient: Paclitaxel Excipients: polysorbate, sorbitol

1.2 Drug Component Description

The active ingredient on the Lutonix™ 014 Drug Coated Balloon PTA Catheter is paclitaxel. Paclitaxel is a white powder, manufactured by a semi-synthetic process, with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 854. It is highly lipophilic, insoluble in water, and melts at approximately 216-217°C. The chemical name for paclitaxel is 5β,20-Epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate]. Paclitaxel CAS Registry number is 33069-62-4. Paclitaxel has the following chemical structure:



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

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

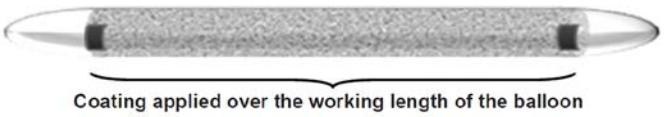


Figure 4. Drug Coating Distribution

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

Table 2. Balloon sizes and Paclitaxel dosage (mg)

Balloon Diameter (mm)	Total Dosage (mg) per Respective Balloon Length					
	40 mm	**60 mm**	**80 mm**	**100 mm**	**120 mm**	**150 mm**
2.0	0.5	0.8	1.0	1.3	1.5	1.9
2.5	0.6	0.9	1.3	1.6	1.9	2.4
3.0	0.8	1.1	1.5	1.9	2.3	2.8
3.5	0.9	1.3	1.8	2.2	2.6	3.3
4.0	1.0	1.5	2.0	2.5	3.0	3.8

2 INDICATIONS FOR USE

The **Lutonix™** 014 Drug Coated Balloon PTA catheter is indicated for patients with critical limb ischemia who have obstructive de novo or non-stented restenotic lesions in native popliteal, tibial, and peroneal arteries up to 320 mm in length and 2.0 to 4.0 mm in diameter.

3 CONTRAINDICATIONS

The Lutonix™ Catheter is contraindicated for use in:

- Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children over the next two years. It is unknown whether paclitaxel will be excreted in human milk and there is a potential for adverse reaction in nursing infants from paclitaxel exposure.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

4 WARNINGS

- **A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel device exposure.**

  Inadequate information is available to evaluate the potential mortality risk associated with the use of paclitaxel-coated devices for the treatment of other disease/conditions, including this device which is indicated for use below-the-knee.

  Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients.

- **Contents supplied STERILE using ethylene oxide (EO) process. Do not use if sterile barrier is damaged or opened prior to intended use.**
- **Do not use after 'use by' date.**
- **Do not use if product damage is evident.**
- **The Lutonix™ Catheter is for use in one patient only; do not reuse in another patient, reprocess or resterilize. Risks of reuse in another patient, reprocessing, or resterilization include:**
  - **o** Compromising the structural integrity of the device and/or device failure which, in turn, may result in patient injury, illness or death.
  - **o** Creating a risk of device contamination and/or patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to patient injury, illness, or death.
- **Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended.**
- **Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon, as this may cause air emboli in case of balloon burst.**
- **This product should not be used in patients with known hypersensitivity to paclitaxel or structurally related compounds, as this may cause allergic reaction difficulty in breathing, skin rash, or muscle pain.**
- **The safety and effectiveness of the Lutonix™ Catheter have not been established for treatment in cerebral, carotid, coronary, or renal vasculature.**
- **The safety and effectiveness of using more than maximum drug coating quantity of approximately 7.6mg paclitaxel in a patient has not been clinically evaluated.**

5 PRECAUTIONS

5.1 General Precautions

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

5.2 Use in Conjunction with Other Procedures

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

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

5.3 Device Handling Precautions

- Do not immerse the Lutonix™ Catheter in a saline bath. Replace any device where the balloon has come into contact with fluids prior to use.
- The coated balloon portion should be handled with dry sterile gloves whenever possible prior to use.
- The balloon protector should stay in place during preparation of the Lutonix™ Catheter and not be removed until just prior to placing over guidewire. If difficulty is encountered while removing the peel away balloon protector, a new Lutonix™ Catheter should be utilized. Removing the balloon protector by force can cause a kink in the catheter shaft and lumen constriction may occur, affecting inflation/deflation of the balloon.

5.4 Device Use/Procedure Precautions

- To ensure therapeutic drug delivery:
  - o Never inflate the Lutonix™ Catheter prior to reaching the target lesion.
  - o The Lutonix™ Catheter should be advanced to the target site as fast as possible and immediately inflated to appropriate pressure to ensure full wall apposition (balloon to artery ratio of 1:1). If the time to deployment of the Lutonix™ Catheter exceeds 3 minutes, the catheter requires replacement with a new unit.
- Maintain balloon inflation for a minimum of 2 minutes (120 seconds). The balloon may remain inflated as long as is required by the standard of care to achieve a good angioplasty outcome. For optimal results, the final % stenosis should be 0-20%.
-

- Vessel preparation of the target lesion, using the appropriate vessel preparation method as determined by the treating physician, is required prior to the use of the Lutonix™ Catheter.
- Vessel preparation using only PTA pre-dilatation was studied in the Lutonix BTK Trial.
- After insertion, do not over-tighten the hemostatic adaptor (if used) around the Lutonix™ Catheter shaft as lumen constriction may occur, affecting inflation/deflation of the balloon.
- Always advance and retrieve the Lutonix™ Catheter under negative pressure.
- The Lutonix™ Catheter should always be manipulated under adequate visualization when in the body.
- Do not continue to use the Lutonix™ Catheter if the shaft has been bent or kinked.
- Whenever possible, the Lutonix™ Catheter should be the final treatment of the vessel; however, post-dilatation is allowed with another PTA catheter or the previously used Lutonix™ Catheter.

5.5 Pre- and Post-Procedure Antiplatelet Regimen

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

6 USE IN SPECIAL POPULATIONS

- Pregnancy – Use in women who are breastfeeding, pregnant or intending to become pregnant or in men intending to father children over the next 2 years is contraindicated.
- Pediatric Use – The safety and effectiveness of the Lutonix™ Catheter in pediatric patients has not been established.
- Geriatric Use – Clinical studies of the Lutonix™ Catheter did not have an upper age limit.

7 DRUG INFORMATION

7.1 Mechanism of Action

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

7.2 Drug Interactions

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

7.3 Carcinogenicity, Genotoxicity, and Reproductive Toxicology

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

Studies performed in rats and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 18 and 55 times the dose provided by the Lutonix™ Catheter coated with 3.8 mg paclitaxel (4mm x 150mm balloon) adjusted for body weight). The drug resulted in increased resorptions and increased fetal deaths. No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (a daily dose of approximately 18 times the dose of the Lutonix™ Catheter (4mm x 150mm), adjusted for bodyweight).

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

8 POTENTIAL ADVERSE EVENTS

Potential adverse events which may be associated with a peripheral balloon dilatation procedure include:

- Additional intervention
- Allergic reaction to drugs, excipients or contrast medium
- Amputation/loss of limb
- Aneurysm or pseudoaneurysm
- Arrhythmias
- Embolization
- Hematoma
- Hemorrhage, including bleeding at the puncture site
- Hypotension/hypertension
- Inflammation
- Occlusion
- Pain or tenderness
- Pneumothorax or hemothorax
- Sepsis/infection
- Shock
- Stroke
- Thrombosis
- Vessel dissection, perforation, rupture, or spasm

Although systemic effects are not anticipated, refer to the Physicians' Desk Reference for more information on the potential adverse events observed with paclitaxel.

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

- Allergic/immunologic reaction to the drug coating (paclitaxel)
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/Arthralgia
- Myelosuppression
- Peripheral neuropathy

9 PATIENT COUNSELING INFORMATION

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

- Discuss the risks associated with a PTA procedure
- Discuss the risks associated with a paclitaxel coated PTA catheter
- Discuss the risks/benefits issues for this particular patient

- Post-procedure antithrombotic regimen
- Discuss alteration to current lifestyle immediately following the procedure and over the long term

10 SUMMARY OF CLINICAL STUDIES

10.1 Late Mortality Signal for Paclitaxel Coated Devices

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

The presence and magnitude of the late mortality risk should be interpreted with caution because of multiple limitations in the available data, including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.

Paclitaxel-coated balloons and stents improve blood flow to the legs and decrease the likelihood of repeat procedures to reopen blocked blood vessels compared to uncoated devices. The benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality).

Inadequate information is available to evaluate the potential mortality risk associated with the use of paclitaxel-coated devices for the treatment of other diseases/conditions including this device indicated for use in arteriovenous dialysis fistulae or below-the-knee.

In the Lutonix BTK randomized study (n=287 DCB and n=155 PTA) for treatment of below the knee disease, Kaplan Meier mortality estimates at 1 and 2 years are 8.3% (95% confidence interval (4.6% - 13.6%) and 16.2% (10.8%-23.0%), respectively, for the Lutonix DCB treatment device and 55.6% (1.8% - 12.6%) and 10.1% (4.5% -19.0%), respectively, for the PTA control device.

Additional information regarding long-term outcomes can be found in the sections below.

Clinical Data Overview

The safety and effectiveness of the Lutonix™ Catheter is derived from the pivotal IDE trial (Lutonix BTK Trial). The Lutonix BTK Real-World Registry provided additional supporting information but was not considered part of the primary data set supporting approval.

The 6 month and 12-month results from the Lutonix BTK Trial and the Lutonix BTK Real-World registry are presented below. Patient follow-up for the Lutonix BTK Trial is planned out to 5years and is ongoing. Patient follow-up for the Lutonix BTK Real-World Registry is planned out to 2 years.

10.2 Lutonix BTK Trial (Pivotal Study)

10.2.1 Objective

The primary objective of the Lutonix BTK Trial was to assess the safety and effectiveness of the Lutonix™ DCB for treatment of stenosis or occlusion of the infrapopliteal arteries.

10.2.2 Study Design

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

The primary safety endpoint was defined as freedom from the composite of all-cause death, above-ankle amputation or major reintervention of the index limb involving the infrapopliteal arteries through 30 days. The primary safety endpoint was tested using Farrington-Manning test for non-inferiority of proportions (a one-sided test at a significance level of 0.025).

H_0: The proportion of subjects with safety events in the Test group through 30-days post-index procedure is clinically inferior to that of the Control group.
H_1: The proportion of subjects with safety events in the Test group through 30-days post-index procedure is clinically non-inferior to that of the Control group.

$$\mathbf{H_0: P_{TEST} - P_{CONTROL} \geq 0.12 \quad vs. \quad H_1: P_{TEST} - P_{CONTROL} < 0.12}$$

Where *P.* is the rate of the primary safety endpoint at 30-days post-index procedure.

The primary effectiveness endpoint was composite of limb salvage and primary patency at 6 months. Limb salvage was defined as above-the-ankle amputation and primary patency defined as the absence of target lesion occlusion and freedom from clinically driven target lesion revascularization (CD-TLR). The primary effectiveness analysis was performed in a staged fashion by evaluating all vessels. The primary effectiveness endpoint was tested for superiority of Lutonix™ DCB compared to the standard PTA using log-rank test at a one-sided significance level of 0.0085 to control the overall error of the adaptive design and staged analysis.

H_0: The proportion of subjects with effectiveness events in the Control group through 6-months post-index procedure is equal to that of the Test group.
H_1: The proportion of subjects with effectiveness events in the Control group through 6-months post-index procedure is not equal to that of the Test group.

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

Where *P.* is the event-free rate from above the ankle amputation, target lesion occlusion and CD-TLR at 6 months post-index procedure.

Secondary endpoints were also studied and include the following:

Hypothesis Tested Secondary Endpoints:

The following secondary endpoints were prespecified for hypothesis testing if both primary objectives passed. The testing of the secondary objectives were performed in a hierarchical fashion in the order listed below to ensures that the study-wide Type 1 error rate is 0.025 single sided when all of the secondary endpoints are tested at α=0.025.

- Superiority of primary patency with exclusion of early mechanical recoil at 12 months
- Superiority of primary patency at 6 months
- Superiority of CD-TLR at 6 months
- Superiority of composite event-free rate from above-ankle amputation, unhealed wounds, ischemic rest pain, target vessel occlusion, and CD-TVR at 6 months

Secondary Endpoints:

- Device success, technical success and procedural success
- Change in Quality of Life by EQ-5D survey
- Death, any cause

- The following endpoints assessed at 30 days, 6 months, 12 months, 24 months, and 36 months:
  - Composite of Limb Salvage and Primary Patency
  - Wound healing including overall burden of incurred, new, and recurrent wounds
  - Change in Rutherford Class in target limb
  - Composite of freedom from the following index limb events: above ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically-driven TVR
  - Primary Patency
  - Primary Patency with exclusion of early mechanical recoil
  - Secondary Patency
  - Clinically-driven TLR
  - Clinically-driven TVR
  - Hemodynamic outcome
  - Change in Walking Impairment Questionnaire
  - Major amputation
  - All-Cause Death

10.2.3 Demographics

Following informed consent, 442 subjects were randomized 2:1 to the Lutonix™ DCB (n=287) and PTA (n=155) arms. **Table 3** presents baseline patient demographics and medical history for the Lutonix BTK trial subjects. None of the baseline characteristics were significantly different between treatment arms.

Table 3. Baseline Demographics and Medical History

	DCB Subjects (N=287)	PTA Subjects (N=155)	Total Subjects (N=442)	P-value[1]
Demographics				
Age (Years): N Mean (SD) Median Min, Max	 287 72.9 (9.65) 74.0 45.0, 96.0	 155 72.9 (9.62) 75.0 48.0, 91.0	 442 72.9 (9.63) 74.0 45.0, 96.0	0.9586
Gender, n (%) Male Female	 202 / 287 (70.4%) 85 / 287 (29.6%)	 104 / 155 (67.1%) 51 / 155 (32.9%)	 306 / 442 (69.2%) 136 / 442 (30.8%)	0.5173
Race, n (%) American Indian or Alaska Native Asian Black or African American White Other	 1 / 287 (0.3%) 25 / 287 (8.7%) 33 / 287 (11.5%) 226 / 287 (78.7%) 2 / 287 (0.7%)	 0 / 155 15 / 155 (9.7%) 12 / 155 (7.7%) 127 / 155 (81.9%) 1 / 155 (0.6%)	 1 / 442 (0.2%) 40 / 442 (9.0%) 45 / 442 (10.2%) 353 / 442 (79.9%) 3 / 442 (0.7%)	0.7468
BMI (kg/m²): N Mean (SD) Median Min, Max	 287 28.4 (6.31) 28.0 14.1, 69.9	 155 28.0 (5.65) 27.4 16.7, 51.6	 442 28.2 (6.08) 27.7 14.1, 69.9	0.6117
Rutherford Category, n (%) n 3 4 5	 287 26 (9.1%) 100 (34.8%) 161 (56.1%)	 155 16 (10.3%) 52 (33.5%) 87 (56.1%)	 442 42 (9.5%) 152 (34.4%) 248 (56.1)	0.9181
Medical History				
History of Risk Factors, n (%) Diabetes Dyslipidemia Hypertension Cigarette Smoking Current Former	285 / 287 (99.3%) 204 / 287 (71.1%) 225 / 287 (78.4%) 264 / 287 (92.0%) 170 / 287 (59.2%) 43 / 287 (15.0%) 127 / 287 (44.3%)	155 / 155 (100.0%) 106 / 155 (68.4%) 116 / 155 (74.8%) 148 / 155 (95.5%) 89 / 155 (57.4%) 19 / 155 (12.3%) 70 / 155 (45.2%)	440 / 442 (99.5%) 310 / 442 (70.1%) 341 / 442 (77.1%) 412 / 442 (93.2%) 259 / 442 (58.6%) 62 / 442 (14.0%) 197 / 442 (44.6%)	0.5436
Cardiac Disease, n (%) Angina Pectoris Arrhythmia (Other Than A-Fib) Atrial Fibrillation (A-Fib) Cardiomyopathy Coronary Artery Disease (CAD) Heart Failure Ischemic Heart Disease Myocardial Infarction (MI) Valvular Heart Disease Other	189 / 287 (65.9%) 31 / 287 (10.8%) 23 / 287 (8.0%) 59 / 287 (20.6%) 27 / 287 (9.4%) 135 / 287 (47.0%) 34 / 287 (11.8%) 12 / 287 (4.2%) 64 / 287 (22.3%) 28 / 287 (9.8%) 54 / 287 (18.8%)	110 / 155 (71.0%) 20 / 155 (12.9%) 13 / 155 (8.4%) 37 / 155 (23.9%) 21 / 155 (13.5%) 85 / 155 (54.8%) 16 / 155 (10.3%) 15 / 155 (9.7%) 31 / 155 (20.0%) 18 / 155 (11.6%) 27 / 155 (17.4%)	299 / 442 (67.6%) 51 / 442 (11.5%) 36 / 442 (8.1%) 96 / 442 (21.7%) 48 / 442 (10.9%) 220 / 442 (49.8%) 50 / 442 (11.3%) 27 / 442 (6.1%) 95 / 442 (21.5%) 46 / 442 (10.4%) 81 / 442 (18.3%)	0.2883

	DCB Subjects (N=287)	PTA Subjects (N=155)	Total Subjects (N=442)	P-value[1]
Respiratory Illness, n (%)	79 / 287 (27.5%)	53 / 155 (34.2%)	132 / 442 (29.9%)	0.1574
Asthma	14 / 287 (4.9%)	6 / 155 (3.9%)	20 / 442 (4.5%)	
Bronchitis	11 / 287 (3.8%)	5 / 155 (3.2%)	16 / 442 (3.6%)	
Chronic Obstructive Pulmonary Disease (COPD)	30 / 287 (10.5%)	27 / 155 (17.4%)	57 / 442 (12.9%)	
Other	45 / 287 (15.7%)	32 / 155 (20.6%)	77 / 442 (17.4%)	
Vascular Disease, n (%)	195 / 287 (67.9%)	112 / 155 (72.3%)	307 / 442 (69.5%)	0.3871
AAA	11 / 287 (3.8%)	11 / 155 (7.1%)	22 / 442 (5.0%)	
Aortic Disease	12 / 287 (4.2%)	4 / 155 (2.6%)	16 / 442 (3.6%)	
Aorto-Iliac Occlusive Disease	3 / 287 (1.0%)	0 / 155 (0.0%)	3 / 442 (0.7%)	
Deep Vein Thrombosis (DVT)	15 / 287 (5.2%)	8 / 155 (5.2%)	23 / 442 (5.2%)	
Iliac Artery Aneurysm	3 / 287 (1.0%)	2 / 155 (1.3%)	5 / 442 (1.1%)	
Stroke	35 / 287 (12.2%)	17 / 155 (11.0%)	52 / 442 (11.8%)	
Thrombolysis	1 / 287 (0.3%)	1 / 155 (0.6%)	2 / 442 (0.5%)	
Transient Ischemic Attack (TIA)	24 / 287 (8.4%)	10 / 155 (6.5%)	34 / 442 (7.7%)	
Vasculitis	0 / 287 (0.0%)	2 / 155 (1.3%)	2 / 442 (0.5%)	
Venous Insufficiency	20 / 287 (7.0%)	14 / 155 (9.0%)	34 / 442 (7.7%)	
Other	151 / 287 (52.6%)	85 / 155 (54.8%)	236 / 442 (53.4%)	
Other Disease, n (%)	255 / 287 (88.9%)	132 / 155 (85.2%)	388 / 442 (87.8%)	0.2260
Active Infection	16 / 287 (5.6%)	7 / 155 (4.5%)	23 / 442 (5.2%)	
Active Inflammatory Wounds	12 / 287 (4.2%)	8 / 155 (5.2%)	20 / 442 (4.5%)	
Bleeding Disorder	6 / 287 (2.1%)	2 / 155 (1.3%)	8 / 442 (1.8%)	
Cancer	50 / 287 (17.4%)	26 / 155 (16.8%)	76 / 442 (17.2%)	
Gastrointestinal Bleeding	12 / 287 (4.2%)	4 / 155 (2.6%)	16 / 442 (3.6%)	
Hepatic Insufficiency	0 / 287 (0.0%)	1 / 155 (0.6%)	1 / 442 (0.2%)	
Immunosuppressed	1 / 287 (0.3%)	0 / 155 (0.0%)	1 / 442 (0.2%)	
Liver Disease	6 / 287 (2.1%)	6 / 155 (3.9%)	12 / 442 (2.7%)	
Osteomyelitis	28 / 287 (9.8%)	6 / 155 (3.9%)	34 / 442 (7.7%)	
Renal Failure	68 / 287 (23.7%)	26 / 155 (16.8%)	94 / 442 (21.3%)	
Systemic Lupus Erythmetosus	1 / 287 (0.3%)	2 / 155 (1.3%)	3 / 442 (0.7%)	
Ulcers	136 / 287 (47.4%)	73 / 155 (47.1%)	210 / 442 (47.5%)	
Other	203 / 287 (70.7%)	115 / 155 (74.2%)	318 / 442 (71.9%)	
Previous and Planned Interventions				
Any intervention by subject[2], n/N (%)	209/287 (72.8%)	116/155 (74.8%)	325/442 (73.5%)	
Subject has undergone any coronary intervention, n/N (%)	121/287 (42.2%)	70/155 (45.2%)	191/442 (43.2%)	
Target limb has a previous stent, n/N (%)	42/287 (14.6%)	23/155 (14.8%)	65/442 (14.7%)	
Subject has undergone previous peripheral vascular interventions, n/N (%)	154/287 (53.7%)	84/155 (54.2%)	238/442 (53.8%)	
Subject planning to undergo planned surgical or vascular intervention within 30 days of procedures, n/N (%)	21/287 (7.3%)	9/155 (5.8%)	30/442 (6.8%)	
Total target limb interventions by subject, n/N (%)	170/287 (59.2%)	95/155 (61.3%)	265/442 (60.0%)	
0	54/287 (18.8%)	19/155 (12.3%)	73/442 (16.5%)	
1	27/287 (9.4%)	20/155 (12.9%)	47/442 (10.6%)	
2	14/287 (4.9%)	11/155 (7.1%)	25/442 (5.7%)	
3	11/287 (3.8%)	4/155 (2.6%)	15/442 (3.4%)	
4	3/287 (1.0%)	2/155 (1.3%)	5/442 (1.1%)	
5	2/287 (0.7%)	1/155 (0.6%)	3/442 (0.7%)	
6	4/287 (1.4%)	1/155 (0.6%)	5/442 (1.1%)	
7	1/287 (0.3%)	0/155 (0.0%)	1/442 (0.2%)	
9	1/287 (0.3%)	0/155 (0.0%)	1/442 (0.2%)	
10	0/287 (0.0%)	2/155 (1.3%)	2/442 (0.5%)	
>10				
Target limb interventions[3]				
Amputation	35 (12.2%)	16 (10.3%)	51 (11.5%)	
Atherectomy	20 (7.0%)	6 (3.9%)	26 (5.9%)	
Cutting/Scoring Balloon(s)	4 (1.4%)	2 (1.3%)	6 (1.4%)	
DCB	9 (3.1%)	6 (3.9%)	15 (3.4%)	
Other	25 (8.7%)	14 (9.0%)	39 (8.8%)	
Peripheral Bypass	1 (0.3%)	3 (1.9%)	4 (0.9%)	
Peripheral PTA	48 (16.7%)	32 (20.6%)	80 (18.1%)	
Stenting	29 (10.1%)	17 (11.0%)	46 (10.4%)	
Vascular Bypass	2 (0.7%)	0 (0.0%)	2 (0.5%)	

	DCB Subjects (N=287)	PTA Subjects (N=155)	Total Subjects (N=442)	P-value[1]
Total interventions by subject, n/N (%)				
0	76/287 (26.5%)	39/155 (25.2%)	115/442 (26.0%)	
1	62/287 (21.6%)	22/155 (14.2%)	84/442 (19.0%)	
2	49/287 (17.1%)	30/155 (19.4%)	79/442 (17.9%)	
3	29/287 (10.1%)	23/155 (14.8%)	52/442 (11.8%)	
4	18/287 (6.3%)	13/155 (8.4%)	31/442 (7.0%)	
5	20/287 (7.0%)	11/155 (7.1%)	31/442 (7.0%)	
6	7/287 (2.4%)	2/155 (1.3%)	9/442 (2.0%)	
7	4/287 (1.4%)	2/155 (1.3%)	6/442 (1.4%)	
8	6/287 (2.1%)	2/155 (1.3%)	8/442 (1.8%)	
9	8/287 (2.8%)	7/155 (4.5%)	15/442 (3.4%)	
10	2/287 (0.7%)	1/155 (0.6%)	3/442 (0.7%)	
11	1/287 (0.3%)	0/155 (0.0%)	1/442 (0.2%)	
12	2/287 (0.7%)	1/155 (0.6%)	3/442 (0.7%)	
13	2/287 (0.7%)	0/155 (0.0%)	2/442 (0.5%)	
18	0/287 (0.0%)	1/155 (0.6%)	1/442 (0.2%)	
22	0/287 (0.0%)	1/155 (0.6%)	1/442 (0.2%)	
25	1/287 (0.3%)	0/155 (0.0%)	1/442 (0.2%)	
All limb interventions[3]				
AAA Repair	2 (0.7%)	1 (0.6%)	3 (0.7%)	
Amputation	54 (18.8%)	26 (16.8%)	80 (18.1%)	
Atherectomy	32 (11.1%)	15 (9.7%)	47 (10.6%)	
Cardiac PTCA/Stent	50 (17.4%)	30 (19.4%)	80 (18.1%)	
Carotid Endarterectomy/Stent	7 (2.4%)	5 (3.2%)	12 (2.7%)	
Coronary Artery Bypass Graft (CABG)	57 (19.9%)	36 (23.2%)	93 (21.0%)	
Cryoplasty	1 (0.3%)	0 (0.0%)	1 (0.2%)	
Cutting/Scoring Balloon(s)	8 (2.8%)	2 (1.3%)	10 (2.3%)	
DCB	18 (6.3%)	7 (4.5%)	25 (5.7%)	
Other	52 (18.1%)	28 (18.1%)	80 (18.1%)	
Pacemaker Implantation	17 (5.9%)	11 (7.1%)	28 (6.3%)	
Peripheral Bypass	2 (0.7%)	5 (3.2%)	7 (1.6%)	
Peripheral PTA	84 (29.3%)	53 (34.2%)	137 (31.0%)	
Stenting	50 (17.4%)	31 (20.0%)	81 (18.3%)	
Valvuloplasty/Valve Replacement	8 (2.8%)	7 (4.5%)	15 (3.4%)	
Vascular Bypass	5 (1.7%)	2 (1.3%)	7 (1.6%)	
Vascular Iliac Graft	1 (0.3%)	0 (0.0%)	1 (0.2%)	

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, and other lesion-specific measures. See **Table 4**.

Table 4. Baseline Angiographic Data

	Treated Lesions	
	DCB	PTA
Angiographic Target Lesion Characteristics (by lesions) – Core Lab		
Target Lesion Length (mm), n Mean	349 111.8	206 94.7
Initial % Stenosis, n Mean	352 86.7	212 84.8
MLD (mm), n Mean	352 0.5	212 0.4
RVD (mm), n Mean	350 2.5	212 2.6
Run-off Present through Foot, n/N (%)	310/328 (94.5%)	192/202 (95.0%)
Run-off Vessels, n Anterior Tibial Posterior Tibial Peroneal	284 128 (45.1%) 102 (35.9%) 212 (74.6%)	181 88 (48.6%) 73 (40.3%) 135 (74.6%)
Pedal Arch, n/N (%), n Complete Incomplete	305 115 (37.7%) 190 (62.3%)	185 71 (38.4%) 114 (61.6%)
Any Calcification, n/N (%)	211/352 (59.9%)	115/212 (54.2%)
Severe Calcification, n/N (%)	53/352 (15.1%)	28/212 (13.2%)
TASC Lesion Type, n/N (%), n A B	351 182 (51.9%) 61 (17.4%)	209 131 (62.7%) 32 (15.3%)

	Treated Lesions	
	DCB	**PTA**
C D	62 (17.7%) 46 (13.1%)	28 (13.4%) 18 (8.6%)
Aneurysm, n/N (%)	0/351 (0.0%)	0/212 (0.0%)
Thrombus, n/N (%)	3/351 (0.9%)	1/212 (0.5%)
Eccentric Lesion, n/N (%)	6/351 (1.7%)	3/212 (1.4%)
Ulcerated Plaque, n/N (%)	1/351 (0.3%)	0/212 (0.0%)
AV Fistula, n/N (%)	2/351 (0.6%)	0/212 (0.0%)
Target Lesion Information (by Lesion) – Site Reported		
Lesion Type, n (%) Occlusion Re-occlusion Re-stenosis Stenosis Unknown	 137/380 (36.1%) 6/380 (1.6%) 8/380 (2.1%) 229/380 (60.3%) 0/380 (0.0%)	 75/225 (33.3%) 5/225 (2.2%) 2/225 (0.9%) 142/225 (63.1%) 1/225 (0.4%)
Lesion Locations, n (%) Popliteal Tibioperoneal Trunk Anterior Tibial Posterial Tibial Peroneal	 33 (8.7%) 91 (23.9%) 146 (38.4%) 90 (23.7%) 89 (23.4%)	 17 (7.6%) 57 (25.3%) 81 (36.0%) 58 (25.8%) 47 (20.9%)
Target Lesion Information (by Pathway) – Site Reported		
Number of Lesions by Flow Pathway, n (%) 1 2 3 6	 85.4% (275/322) 12.1% (39/322) 2.2% (7/322) 0.3% (1/322)	 79.2% (145/183) 18.6% (34/183) 2.2% (4/183) 0.0% (0/183)
Pathway Locations, n (%) Popliteal Tibioperoneal Trunk Anterior Tibial Posterial Tibial Peroneal	 33 / 322 (10.2%) 90 / 322 (28.0%) 132 / 322 (41.0%) 78 / 322 (24.2%) 76 / 322 (23.6%)	 17 / 183 (9.3%) 57 / 183 (31.1%) 65 / 183 (35.5%) 50 / 183 (27.3%) 45 / 183 (24.6%)

10.2.4 Methods

Subjects presenting with below-the-knee disease and an angiographically significant native artery lesion appropriate for angioplasty that is below the tibial plateau and above the tibiotalar joint were enrolled. After successful protocol-defined pre-dilatation with standard PTA catheter, subjects that continue to meet lesion and outflow angiographic criteria were randomized 2:1 to treatment with either the Lutonix DCB (test) or standard uncoated PTA catheter (control). All target lesions in up to two target vessels were treated with the as-randomized treatment device. Subjects with no target vessels that meet post-predilatation entry criteria were excluded (and treated per standard practice) and followed for safety for 30 days. Baseline clinical and angiographic data were collected on a web-based standardized electronic case report forms. Patients were blinded through the 6 month clinical visit and clinical and angiographic outcomes were assessed by quantitative analysis at a designated (blinded) core laboratory. All suspected SAEs and device failures/malfunctions were adjudicated by an independent Clinical Events Committee.

10.2.5 Results

A total of 442 patients (287 Lutonix™ DCB and 155 control PTA) were enrolled and randomized from 49 clinical sites in USA, Europe, Japan and Canada.

Results for the primary safety and effectiveness endpoints of the Lutonix BTK Trial are described and summarized in **Table 5**. For primary safety, 99.3% of the patients in the test DCB group were free from the primary safety events at 30 days compared to 99.4% in the of the Control PTA group and non-inferiority of the primary safety endpoint was met with p-value of <0.0001. For the primary effectiveness endpoint, 74.7% of the patients in the test DCB group were free from primary effectiveness events at 6 months compared to 64.2% in the Control PTA group. The primary effectiveness endpoint for superiority of DCB compared to PTA was not met with p = 0.0222.

Table 5. Summary of Primary Endpoints

Measure	Test DCB %(n/N)	Control PTA %(n/N)	Difference % [95% CI]	P-value
Freedom from Primary Safety Event[1]	284 / 286 (99.3%)	154 / 155 (99.4%)	-0.1% [-3.9%, 3.8%]	<0.0001
Primary Effectiveness Endpoint[2]	201 / 269 (74.7%)	88 / 137 (64.2%)	10.5% [0.3%, 18.8%]	0.0222

[1] Primary Safety is defined as a composite of freedom from all-cause death, above-ankle amputation or major reintervention of index limb below the knee through 30 days. 95% CI of the difference and the one sided p-value were calculated using non-inferiority Farrington-Manning Test, with margin of 12%

[2] Primary Effectiveness endpoint is defined as freedom from composite of above-ankle amputation, target lesion occlusion, and clinically driven target lesion revascularization through 6 months. 95% CI of the difference was based on the model estimated response rates in both groups and p-value was based on one-sided Wald Test based on model estimate of DCB treatment effect and subject as a random effect.

Figure 5 and **Table 6** provide the primary effectiveness rates through 6 months using a time-to-event Kaplan-Meier survival analysis.

Figure 5. Primary Effectiveness Rate by Kaplan-Meier

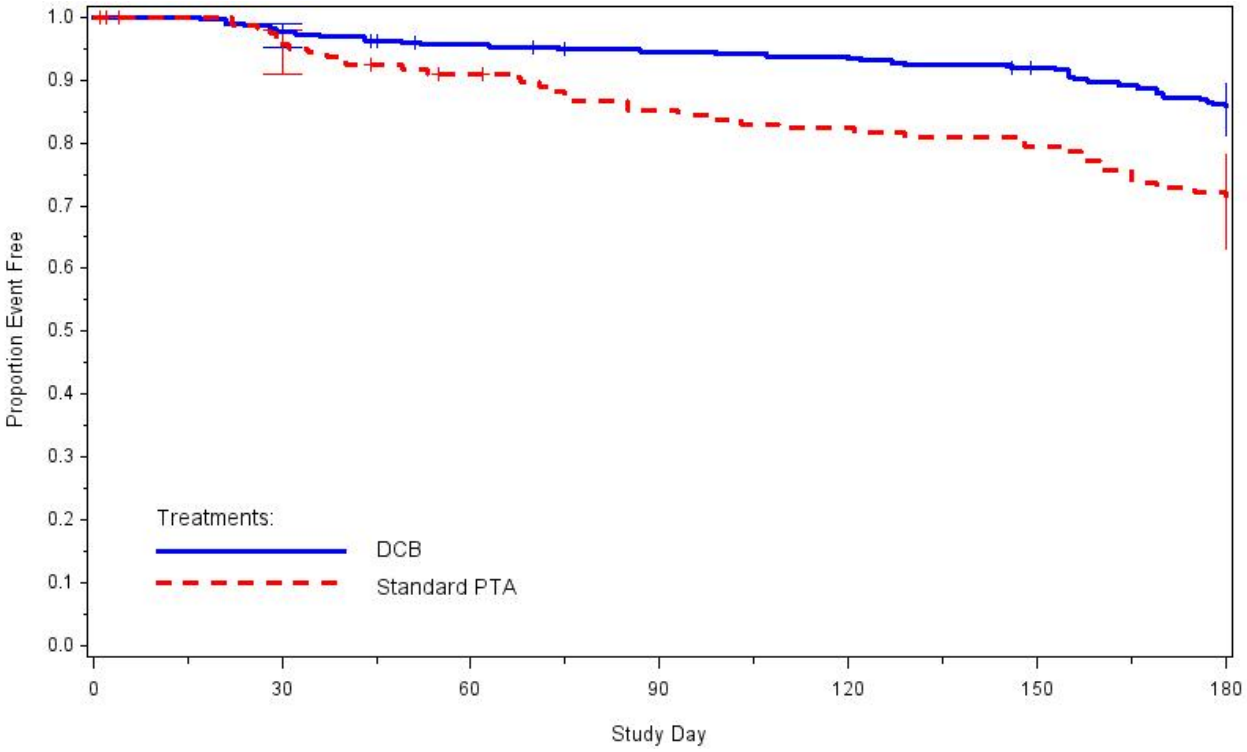


Table 6. Primary Effectiveness Rate by Kaplan-Meier

Time	Test DCB				Control PTA				Difference (95% CI)[2]
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	
30 days	97.7%	7	22	294	95.6%	7	24	153	2.0% (-1.4, 5.8%)
180 days	85.8%	40	48	235	71.4%	41	45	98	14.4% (5.4, 23.5%)

[1] Kaplan-Meier estimate of proportion of subjects without a composite failure event at the visit day.
[2] 95% CI for difference and p-value for one-sided test that DCB response is less than or equal to Standard PTA response obtained with bootstrap approach resampling individual subjects.

Secondary Endpoints

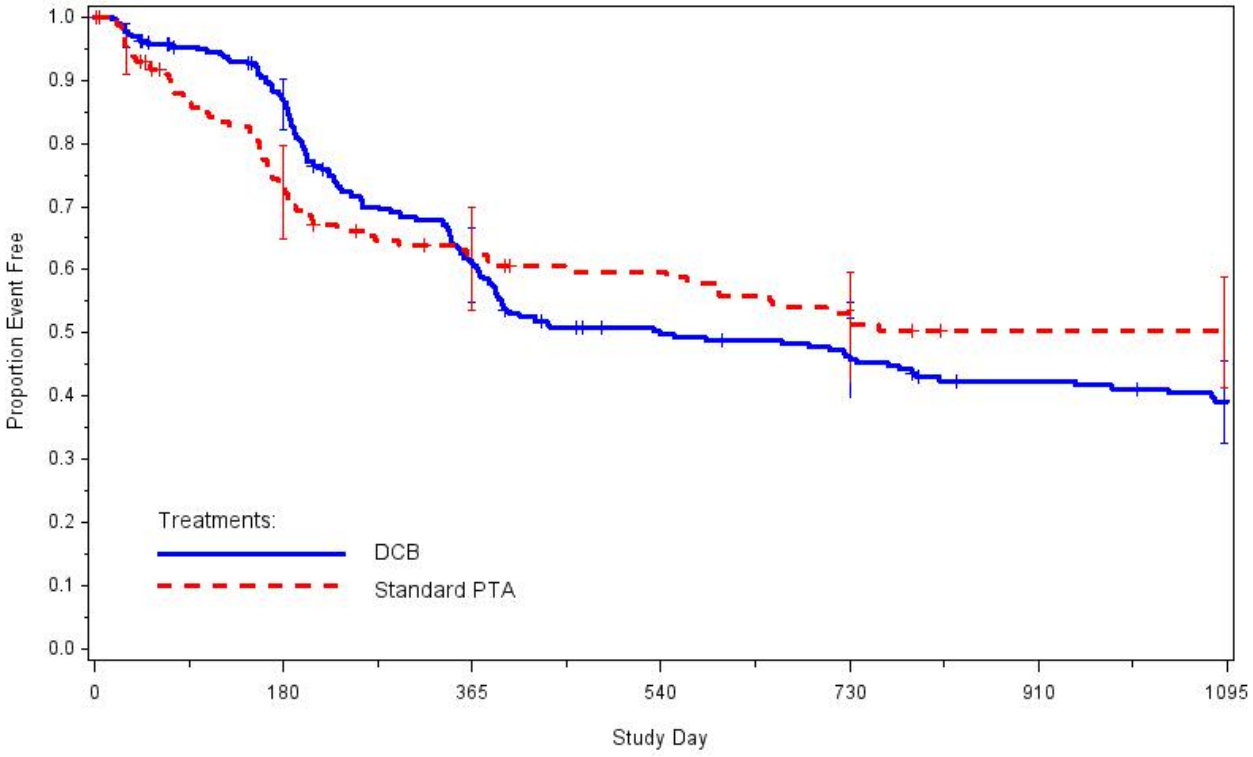
- Primary patency at 6 months by Kaplan-Meier
  As shown per Table 7 below, superiority of DCB for primary patency at 6 months with DCB benefit of 13.8%.

Table 7. Primary Patency

Time	Test DCB				Control PTA				Difference (95% CI)[2]
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	
30 days	97.7%	7	23	293	95.6%	7	25	152	2.1% (-1.4, 5.8%)
180 days	86.8%	37	51	235	73.0%	38	48	98	13.8% (4.9, 22.8%)
365 days	61.0%	103	70	150	62.2%	54	64	66	-1.2% (-12.0, 9.4%)
730 days	46.2%	136	96	91	51.3%	64	65	55	-5.1% (-16.6, 6.1%)
1095 days	39.1%	148	116	59	50.4%	65	89	30	--11.3% (-22.8, 0.3%)

[1] Kaplan-Meier estimate of proportion of subjects without primary patency failure at the visit day
[2] Subjects ongoing without an event at the visit day

Figure 6. Primary Patency by Kaplan-Meier

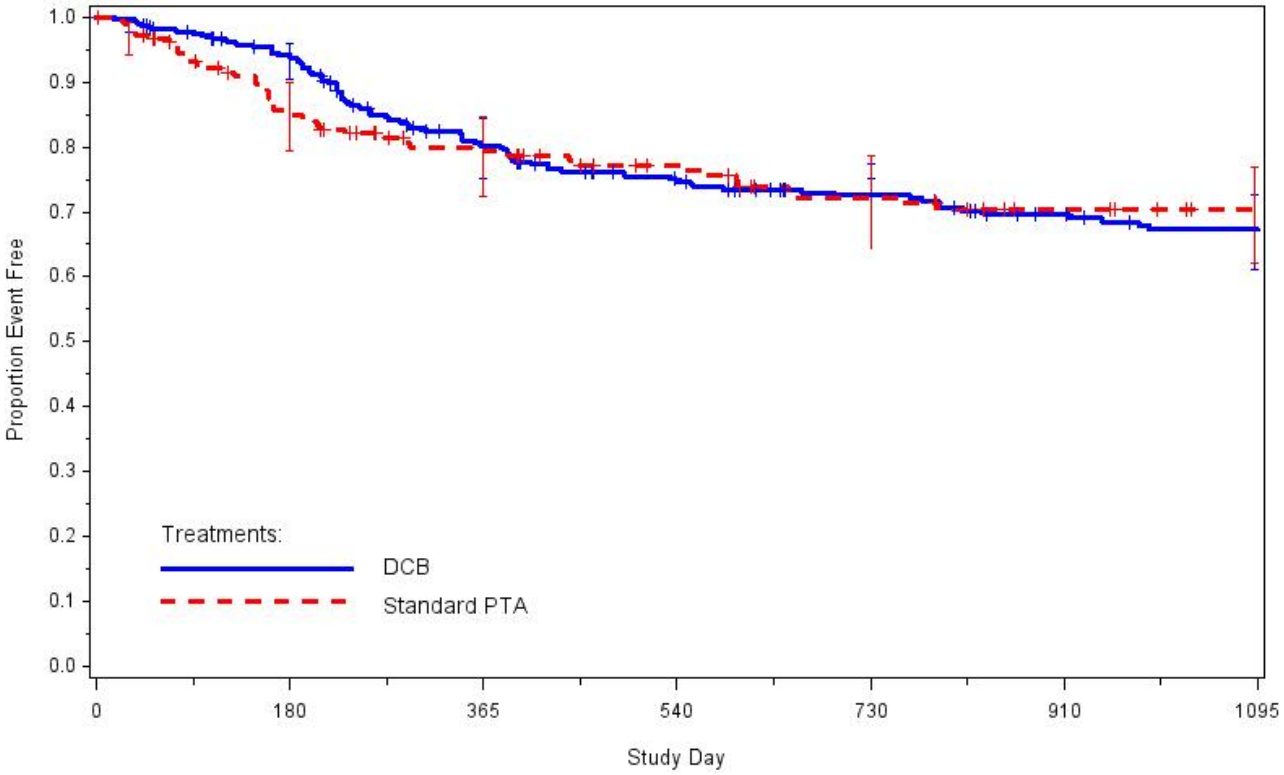


- Clinically-driven TLR at 6 months
  As shown per the Table 8 below, superiority of DCB for freedom from clinically driven TLR at 6 months with DCB benefit of 8.2% and p-value of 0.004.

Table 8. Clinically-Driven TLR

Time	Test DCB				Control PTA				Difference (95% CI)[2]
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	
30 days	99.7%	1	2	320	97.8%	4	1	179	1.9% (-0.1, 4.3%)
180 days	93.8%	19	20	284	85.6%	25	13	146	8.2% (2.1, 14.8%)
365 days	80.3%	58	42	223	79.4%	35	33	116	0.9% (-7.1, 9.0%)
730 days	72.6%	78	74	171	72.3%	44	54	86	0.3% (-9.2, 10.0%)
1095 days	67.3%	88	120	115	70.3%	46	85	53	-3.0% (-13.2, 7.4%)

Figure 7. Clinically-Driven TLR by Kaplan-Meier



Other secondary endpoints evaluated are the cumulative number of TLRS and time to TLR. The mean days to the first reintervention was 340±236 (95% CI 290, 390) in the DCB arm and 266±246 (95% CI 194, 339) in the PTA arm, accounting for a benefit of 74 days (95% CI -12, 159 days) for DCB (see **Table 10**).

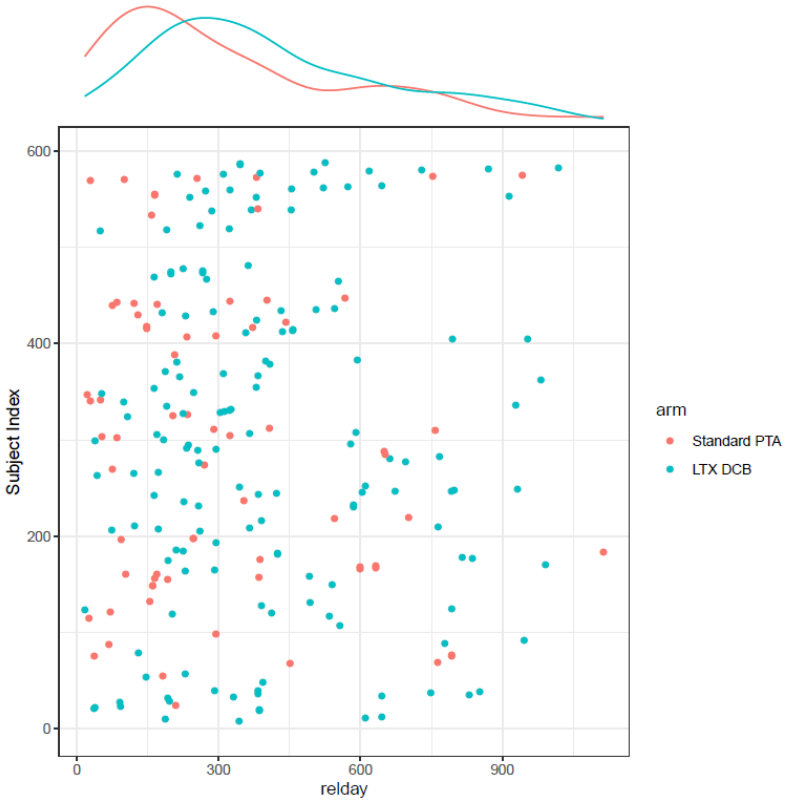
Table 9. Cumulative Number of TLRs per Subject by Visit

	Randomized Subjects	
Summary	**DCB (N=287)**	**PTA (N=155)**
Cumulative TLRs by 30-Day Visit Total Mean (SD) Min – Max	 5 0.0 (0.16) 0 - 2	 6 0.0 (0.22) 0 - 2
TLRs/Year by 30-Day Visit Mean (SD) Min – Max	 0.14 (1.29) 0.00 - 16.6	 0.32 (1.86) 0.00 - 16.6
Cumulative TLRs by 6-Month Visit Total Mean (SD) Min – Max	 36 0.1 (0.42) 0 - 3	 36 0.2 (0.56) 0 - 3
TLRs/Year by 6-Month Visit Mean (SD) Min – Max	 0.24 (0.83) 0.00 - 6.89	 0.42 (1.00) 0.00 - 5.21
Cumulative TLRs by 12-Month Visit Total Mean (SD) Min – Max	 101 0.4 (0.79) 0 - 5	 53 0.3 (0.74) 0 - 4
TLRs/Year by 12-Month Visit Mean (SD) Min – Max	 0.35 (0.84) 0.00 - 6.89	 0.35 (0.76) 0.00 - 3.70
Cumulative TLRs by 24-Month Visit Total Mean (SD) Min – Max	 151 0.5 (1.21) 0 - 11	 71 0.5 (0.92) 0 - 5
TLRs/Year by 24-Month Visit Mean (SD) Min – Max	 0.29 (0.74) 0.00 - 6.89	 0.26 (0.57) 0.00 - 3.48
Cumulative TLRs by 36-Month Visit Total Mean (SD) Min – Max	 170 0.6 (1.41) 0 - 15	 75 0.5 (0.98) 0 - 6
TLRs/Year by 36-Month Visit Mean (SD) Min – Max	 0.27 (0.70) 0.00 - 6.89	 0.23 (0.53) 0.00 - 3.48
Total TLRs Total Mean (SD) Min – Max	 170 0.6 (1.41) 0 - 15	 75 0.5 (0.98) 0 - 6
Total TLRs/Year Mean (SD) Min – Max	 0.26 (0.70) 0.00 - 6.89	 0.23 (0.53) 0.00 - 3.48

Table 10. Summary of Time to First TLR Events in Treatment Arms

	Flow Pathways		
	DCB Pathways (N=323)	**PTA Pathways (N=184)**	**Difference in Means 95% CI**
Subjects with a TLR at any time, n (%)	88 (27.2%)	47 (25.5%)	
Timing of all Events, n/N (%) Failure in Day 1 to Day 210 Failure in Day 211 to Day 395 Failure after Day 395 No Event	 28/323 (8.7%) 37/323 (11.5%) 23/323 (7.1%) 235/323 (72.8%)	 30/184 (16.3%) 6/184 (3.3%) 11/184 (6.0%) 137/184 (74.5%)	
Days to first TLR n Mean (SD) 95% CI	 88 339.9 (236.4) 289.9 - 390.0	 47 266.3 (246.0) 194.1 - 338.5	 73.7 -12.0 - 159.3
Days to TLR Events in First 210 Days n Mean (SD) 95% CI	 28 132.9 (61.74) 109.0 - 156.8	 30 117.3 (59.79) 94.9 - 139.6	 15.6 -16.3 - 47.6
Days to TLR from Day 210 through Day 395 n Mean (SD) 95% CI	 37 81.3 (64.05) 59.9 - 102.7	 6 94.5 (56.18) 35.5 - 153.5	 -13.2 -69.3 - 42.9
Days to TLR from Day 395 for Events after Day 395 n Mean (SD) 95% CI	 23 275.3 (192.3) 192.1 - 358.4	 11 256.8 (188.0) 130.5 - 383.1	 18.4 -124.2 - 161.0
Days to first 40 DCB and first 20 PTA Events n Mean (SD) 95% CI	 40 160.5 (66.88) 139.1 - 181.8	 20 85.5 (45.53) 64.2 - 106.8	 75.0 41.7 - 108.2
Days to first 80 DCB and first 40 PTA Events n Mean (SD) 95% CI	 80 285.6 (167.3) 248.3 - 322.8	 40 183.8 (139.1) 139.3 - 228.2	 101.8 41.0 - 162.6

Figure 8. Scatterplot of Time to First Target Lesion Revascularization by Treatment arm



Secondary Effectiveness Functional Outcomes
The Rutherford scores, walking impairment (WIQ) scores, ABI, TBI, and quality of life questionnaires each showed improvements from before treatment through 6 months in both treatment groups and were similar for both groups – see **Table 11** below.

Table 11. Secondary Endpoints – Functional Outcomes

Functional Outcome	Device	Scores, Mean (n)				
		Baseline	6 months	12 months	24 months	36 months
Rutherford Scores	Lutonix DCB	4.5 (287)	1.9 (243)	1.6 (220)	1.3 (175)	1.3 (131)
	Control PTA	4.5 (155)	1.5 (120)	1.5 (110)	1.3 (88)	1.1 (57)
Walking Impairment Scores	Lutonix DCB	30.0 (283)	33.8 (242)	33.3 (220)	33.1 (178)	30.5 (132)
	Control PTA	30.5 (153)	34.7 (122)	33.6 (111)	33.8 (90)	36.9 (60)
Ankle-Brachial Index	Lutonix DCB	0.81 (264)	0.97 (232)	0.92 (202)	0.94 (162)	0.94 (121)
	Control PTA	0.83 (146)	0.99 (117)	0.96 (107)	0.99 (85)	0.95 (53)
Toe-Brachial Index	Lutonix DCB	0.35 (149)	0.52 (147)	0.50 (127)	0.49 (101)	0.48 (82)
	Control PTA	0.39 (79)	0.49 (74)	0.43 (63)	0.50 (61)	0.52 (37)
Quality of Life (EQ-5D Index)	Lutonix DCB	0.66 (287)	0.74 (245)	0.76 (227)	0.76 (185)	0.74 (139)
	Control PTA	0.67 (155)	0.73 (125)	0.80 (114)	0.78 (93)	0.81 (62)

Secondary Safety Endpoints Descriptive
Primary safety endpoint (major adverse limb events and all cause death) was assessed through 12 months – see **Table 12** below. Similar results were observed at all time points through 12 months.

Table 12. Freedom from Primary Safety Events

Time Point	DCB (N=287)[1]	PTA (N=155)[1]	Difference (95% CI)[2]
30 Days	284 / 286 (99.3%)	154 / 155 (99.4%)	-0.1% (-1.6%, 1.5%)
6 Months	265 / 272 (97.4%)	139 / 146 (95.2%)	2.2% (-1.7%, 6.2%)
12 Months	242/ 253 (95.7%)	123 / 131 (93.9%)	1.8% (-3.1%, 6.6%)
24 Months	202 / 218 (92.7%)	100 / 110 (90.9%)	1.8% (-4.6%, 8.1%)
36 Months	146 / 162 (90.1%)	66 / 77 (85.7%)	4.4% (-4.7%, 13.5%)

[1] Response is freedom from BTK MALE + POD through each visit of interest
[2] 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance

Figure 9. Freedom from Primary Safety Events by Kaplan-Meier

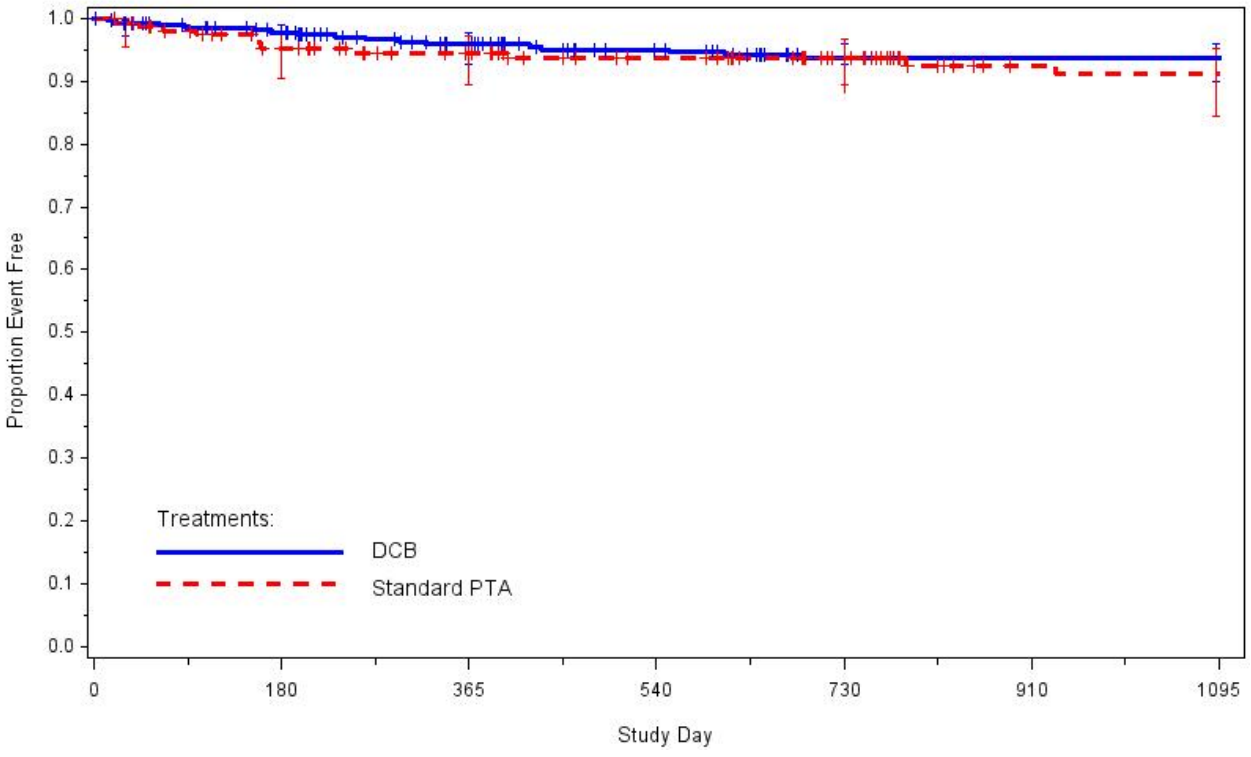


Table 7. Freedom from Primary Safety Events by Kaplan-Meier

Time	Test DCB				Control PTA				Difference (95% CI)[2]
	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	Survival[1] %	Subjects with Event	Censored Subjects	Subjects at Risk	
Day 30	99.3%	2	4	281	99.4%	1	1	153	-0.1%
Day 180	97.8%	6	17	264	95.3%	7	13	135	2.5%
Day 365	95.9%	11	37	239	94.6%	8	26	121	1.3%
Day 730	93.7%	16	84	187	93.7%	9	53	93	0.0%
Day 1095	93.7%	16	181	90	91.3%	11	100	44	2.4%

[1] Kaplan-Meier estimate of proportion of subjects without a composite failure event at the visit day.
[2] Subjects ongoing without an event at the visit day

Secondary safety endpoints were similar for both Lutonix™ DCB and control PTA – see **Table 14** through **17** below.

Table 8. Freedom from Major Amputation as Binary Endpoint through 36 Months

	DCB Subjects (N=287)		PTA Subjects (N=155)		
Visit	Response Rate[1]	95% CI[2]	Response Rate[1]	95% CI[2]	Difference 95% CI
30 Days	286/286 (100.0%)	(98.7%,100.0%)	154/155 (99.4%)	(96.5%,100.0%)	0.6% (-0.6%, 1.9%)
6 Months	267/271 (98.5%)	(96.3%, 99.6%)	142/145 (97.9%)	(94.1%, 99.6%)	0.6% (-2.1%, 3.3%)
12 Months	244/251 (97.2%)	(94.3%, 98.9%)	127/130 (97.7%)	(93.4%, 99.5%)	-0.5% (-3.8%, 2.8%)
24 Months	204/215 (94.9%)	(91.0%, 97.4%)	103/109 (94.5%)	(88.4%, 98.0%)	0.4% (-4.8%, 5.6%)
36 Months	148/159 (93.1%)	(88.0%, 96.5%)	67/ 74 (90.5%)	(81.5%, 96.1%)	2.5% (-5.2%, 10.3%)

[1] Major amputation is defined as amputation above the ankle of the index limb and is evaluated at 30 days, 6 months, and 12 months
[2] Exact binomial confidence intervals

Table 15. Freedom from Distal Embolization as Binary Endpoint to 36 Months

	DCB Subjects (N=287)		PTA Subjects (N=155)		
Visit	Response Rate	95% CI[1]	Response Rate	95% CI[1]	Difference (95% CI)[1]
30 Days	280 / 286 (97.9%)	(95.5%, 99.2%)	154 / 155 (99.4%)	(96.5%, 100.0%)	-1.5% (-3.5%, 0.6%)
6 Months	264 / 271 (97.4%)	(94.8%, 99.0%)	143 / 145 (98.6%)	(95.1%, 99.8%)	-1.2% (-3.9%, 1.5%)
12 Months	243 / 250 (97.2%)	(94.3%, 98.9%)	127 / 129 (98.4%)	(94.5%, 99.8%)	-1.2% (-4.2%, 1.7%)
24 Months	211 / 218 (96.8%)	(93.5%, 98.7%)	106 / 108 (98.1%)	(93.5%, 99.8%)	-1.4% (-4.8%, 2.1%)
36 Months	153 / 160 (95.6%)	(91.2%, 98.2%)	70 / 72 (97.2%)	(90.3%, 99.7%)	-1.6% (-6.5%, 3.3%)

[1] 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance

Table 16. Freedom from Thrombectomy/Thrombolysis as Binary Endpoint to 36 Months

	DCB Subjects (N=287)		PTA Subjects (N=155)		
Visit	Response Rate	95% CI[1]	Response Rate	95% CI[1]	Difference (95% CI)[1]
30 Days	285 / 286 (99.7%)	(98.1%, 100.0%)	155 / 155 (100.0%)	(97.6%, 100.0%)	-0.3% (-1.0%, 0.3%)
6 Months	267 / 271 (98.5%)	(96.3%, 99.6%)	142 / 145 (97.9%)	(94.1%, 99.6%)	0.6% (-2.1%, 3.3%)
12 Months	247 / 252 (98.0%)	(95.4%, 99.4%)	124 / 129 (96.1%)	(91.2%, 98.7%)	1.9% (-1.9%, 5.6%)
24 Months	206 / 218 (94.5%)	(90.6%, 97.1%)	103 / 108 (95.4%)	(89.5%, 98.5%)	-0.9% (-5.9%, 4.1%)
36 Months	150 / 163 (92.0%)	(86.7%, 95.7%)	67 / 73 (91.8%)	(83.0%, 96.9%)	0.2% (-7.3%, 7.8%)

[1] 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance

Table 17. All Cause Death[1]

	DCB Pathways (N=287)		PTA Pathways (N=155)		
Visit	Response Rate	95% CI[1]	Response Rate	95% CI[1]	Difference (95% CI)[1]
30 Days	3 / 286 (1.0%)	(0.2%, 3.0%)	1 / 155 (0.6%)	(0.0%, 3.5%)	0.4% (-1.3%, 2.1%)
6 Months	14 / 280 (5.0%)	(2.8%, 8.2%)	6 / 150 (4.0%)	(1.5%, 8.5%)	1.0% (-3.0%, 5.0%)
12 Months	23 / 270 (8.5%)	(5.5%, 12.5%)	11 / 139 (7.9%)	(4.0%, 13.7%)	0.6% (-5.0%, 6.2%)
24 Months	38 / 247 (15.4%)	(11.1%, 20.5%)	16 / 124 (12.9%)	(7.6%, 20.1%)	2.5% (-4.9%, 9.9%)
36 Months	47 / 200 (23.5%)	(17.8%, 30.0%)	23 / 94 (24.5%)	(16.2%, 34.4%)	-1.0% (-11.5%, 9.5%)

[1] 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance

Subgroup Analysis

Primary endpoints were analysed for gender and US Population subgroups and are provided in the tables below.

Similar primary effectiveness benefit for DCB (Δ12.0% for male and Δ10.4% for female) was observed in both males and females. For the US population, significant benefit in primary effectiveness was observed for DCB with Δ14.8% net benefit.

Table 9. Primary Endpoints – Gender

Primary Endpoint	Gender	Test DCB %(n/N)	Control PTA %(n/N)	Difference %
Primary Effectiveness	Female	80/103 (77.7%)	35/52 (67.3%)	10.4%
	Male	180/238 (75.6%)	77/121 (63.6%)	12.0%
Primary Safety	Female	85/85 (100.0%)	50/51 (98.0%)	2.0%
	Male	199/201 (99.0%)	104/104 (100.0%)	-1.0%

Table 10. Primary Endpoints – U.S. Population

Primary Endpoint	Test DCB %(n/N)	Control PTA %(n/N)	Difference %
Primary Effectiveness	165/211(78.2%)	71/112 (63.4%)	14.8%
Primary Safety	176/178 (98.9%)	96/97 (99.0%)	-0.1%

Adverse Events – Lutonix BTK Trial Clinical Experience

Table 20 provides a summary of the Serious Adverse Events (SAE) observed in the Lutonix BTK Trial 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 Stability-threatening illness or injury; resulted in a permanent impairment of a body structure or a body function; required in-subject hospitalization or prolongation of existing hospitalization; or resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function. Similar SAE rates were observed in both DCB and PTA subjects.

Table 20. Serious Adverse Events through 12 months

Body System Preferred Term	DCB Subjects (N=287) n (%)	PTA Subjects (N=155) n (%)
Subjects with at least one Serious Adverse Event	240 (83.6%)	126 (81.3%)
Blood And Lymphatic System Disorders	14 (4.9%)	3 (1.9%)
Anaemia	10 (3.5%)	3 (1.9%)
Anaemia Of Chronic Disease	1 (0.3%)	0
Heparin-Induced Thrombocytopenia	1 (0.3%)	0
Hypochromic Anaemia	1 (0.3%)	0
Leukocytosis	1 (0.3%)	0
Nephrogenic Anaemia	1 (0.3%)	0
Cardiac Disorders	81 (28.2%)	44 (28.4%)
Acute Coronary Syndrome	3 (1.0%)	1 (0.6%)
Acute Myocardial Infarction	14 (4.9%)	8 (5.2%)
Angina Pectoris	8 (2.8%)	6 (3.9%)
Angina Unstable	5 (1.7%)	0
Aortic Valve Disease	1 (0.3%)	0
Aortic Valve Stenosis	5 (1.7%)	2 (1.3%)
Arrhythmia Supraventricular	0	1 (0.6%)
Atrial Fibrillation	10 (3.5%)	6 (3.9%)
Atrial Flutter	0	2 (1.3%)
Atrial Tachycardia	0	1 (0.6%)
Atrioventricular Block	1 (0.3%)	1 (0.6%)
Atrioventricular Block Complete	0	1 (0.6%)
Atrioventricular Block Second Degree	2 (0.7%)	0
Bradyarrhythmia	1 (0.3%)	0

Body System Preferred Term	DCB Subjects (N=287) n (%)	PTA Subjects (N=155) n (%)
Bradycardia	1 (0.3%)	2 (1.3%)
Bundle Branch Block Left	1 (0.3%)	0
Cardiac Arrest	4 (1.4%)	2 (1.3%)
Cardiac Failure	11 (3.8%)	5 (3.2%)
Cardiac Failure Acute	5 (1.7%)	1 (0.6%)
Cardiac Failure Chronic	0	1 (0.6%)
Cardiac Failure Congestive	21 (7.3%)	12 (7.7%)
Cardio-Respiratory Arrest	0	1 (0.6%)
Cardiogenic Shock	1 (0.3%)	0
Cardiomegaly	1 (0.3%)	0
Cardiomyopathy	2 (0.7%)	1 (0.6%)
Cardiopulmonary Failure	1 (0.3%)	1 (0.6%)
Coronary Artery Disease	11 (3.8%)	5 (3.2%)
Coronary Artery Stenosis	3 (1.0%)	1 (0.6%)
Ischaemic Cardiomyopathy	6 (2.1%)	2 (1.3%)
Left Ventricular Failure	0	1 (0.6%)
Mitral Valve Incompetence	1 (0.3%)	2 (1.3%)
Myocardial Infarction	2 (0.7%)	2 (1.3%)
Myocardial Ischaemia	1 (0.3%)	0
Pericarditis	0	1 (0.6%)
Pulseless Electrical Activity	1 (0.3%)	0
Right Ventricular Failure	0	1 (0.6%)
Sick Sinus Syndrome	3 (1.0%)	2 (1.3%)
Tachycardia	0	1 (0.6%)
Tricuspid Valve Disease	1 (0.3%)	0
Tricuspid Valve Incompetence	0	1 (0.6%)
Ventricular Arrhythmia	1 (0.3%)	0
Ventricular Extrasystoles	1 (0.3%)	0
Ventricular Tachycardia	2 (0.7%)	0
Congenital, Familial And Genetic Disorders	2 (0.7%)	0
Buried Penis Syndrome	1 (0.3%)	0
Hydrocele	1 (0.3%)	0
Ear And Labyrinth Disorders	2 (0.7%)	0
Vertigo	2 (0.7%)	0
Eye Disorders	3 (1.0%)	3 (1.9%)
Angle Closure Glaucoma	0	1 (0.6%)
Cataract	2 (0.7%)	1 (0.6%)
Diabetic Retinopathy	1 (0.3%)	0
Eye Haemorrhage	0	1 (0.6%)
Gastrointestinal Disorders	23 (8.0%)	15 (9.7%)
Abdominal Hernia	1 (0.3%)	0
Abdominal Pain	0	2 (1.3%)
Abdominal Wall Haematoma	0	1 (0.6%)
Colitis Ischaemic	1 (0.3%)	1 (0.6%)
Constipation	0	1 (0.6%)
Dental Caries	0	1 (0.6%)
Diarrhoea	0	1 (0.6%)
Duodenal Ulcer	1 (0.3%)	0
Dyspepsia	1 (0.3%)	0
Dysphagia	1 (0.3%)	0
Faecal Incontinence	0	1 (0.6%)
Gastrointestinal Haemorrhage	7 (2.4%)	2 (1.3%)
Gastrointestinal Oedema	1 (0.3%)	0
Gastrooesophageal Reflux Disease	0	1 (0.6%)
Haemorrhoidal Haemorrhage	1 (0.3%)	0
Ileus Paralytic	1 (0.3%)	0
Inguinal Hernia	0	1 (0.6%)
Inguinal Hernia, Obstructive	1 (0.3%)	0
Intestinal Ischaemia	2 (0.7%)	0
Intestinal Mass	1 (0.3%)	0
Intestinal Obstruction	1 (0.3%)	0
Ischaemic Enteritis	0	1 (0.6%)
Large Intestine Polyp	1 (0.3%)	1 (0.6%)
Mesenteric Artery Stenosis	1 (0.3%)	0
Nausea	0	1 (0.6%)
Oesophagitis Ulcerative	0	1 (0.6%)
Retroperitoneal Haematoma	1 (0.3%)	0
Upper Gastrointestinal Haemorrhage	2 (0.7%)	0
Vomiting	0	2 (1.3%)
General Disorders And Administration Site Conditions	37 (12.9%)	9 (5.8%)
Adverse Drug Reaction	1 (0.3%)	0
Chest Pain	1 (0.3%)	1 (0.6%)

Body System Preferred Term	DCB Subjects (N=287) n (%)	PTA Subjects (N=155) n (%)
Death	8 (2.8%)	1 (0.6%)
Device Battery Issue	1 (0.3%)	0
Device Dislocation	0	2 (1.3%)
Device Occlusion	1 (0.3%)	1 (0.6%)
Disease Progression	4 (1.4%)	0
Impaired Healing	8 (2.8%)	3 (1.9%)
Local Swelling	1 (0.3%)	0
Non-Cardiac Chest Pain	2 (0.7%)	0
Oedema Peripheral	3 (1.0%)	0
Pyrexia	1 (0.3%)	1 (0.6%)
Systemic Inflammatory Response Syndrome	4 (1.4%)	0
Vessel Puncture Site Haematoma	1 (0.3%)	0
Vessel Puncture Site Haemorrhage	2 (0.7%)	0
Hepatobiliary Disorders	4 (1.4%)	3 (1.9%)
Bile Duct Stone	1 (0.3%)	0
Cholecystitis	1 (0.3%)	1 (0.6%)
Cholecystitis Acute	1 (0.3%)	1 (0.6%)
Cholelithiasis	1 (0.3%)	1 (0.6%)
Immune System Disorders	1 (0.3%)	0
Drug Hypersensitivity	1 (0.3%)	0
Infections And Infestations	93 (32.4%)	51 (32.9%)
Abscess	0	1 (0.6%)
Abscess Limb	1 (0.3%)	1 (0.6%)
Appendicitis	1 (0.3%)	1 (0.6%)
Arthritis Bacterial	2 (0.7%)	0
Atypical Pneumonia	1 (0.3%)	0
Bacteraemia	1 (0.3%)	1 (0.6%)
Bronchitis	5 (1.7%)	1 (0.6%)
Bronchopulmonary Aspergillosis	0	1 (0.6%)
Cellulitis	13 (4.5%)	6 (3.9%)
Clostridium Difficile Colitis	1 (0.3%)	2 (1.3%)
Clostridium Difficile Infection	2 (0.7%)	0
Cystitis	0	2 (1.3%)
Diabetic Foot Infection	0	1 (0.6%)
Diverticulitis	1 (0.3%)	1 (0.6%)
Emphysematous Cystitis	1 (0.3%)	0
Endocarditis	2 (0.7%)	0
Erysipelas	2 (0.7%)	0
Gangrene	22 (7.7%)	11 (7.1%)
Gastritis Viral	1 (0.3%)	0
Gastroenteritis	1 (0.3%)	2 (1.3%)
Groin Abscess	1 (0.3%)	0
Herpes Zoster	1 (0.3%)	1 (0.6%)
Infected Skin Ulcer	3 (1.0%)	0
Influenza	2 (0.7%)	0
Intervertebral Discitis	1 (0.3%)	2 (1.3%)
Localised Infection	10 (3.5%)	5 (3.2%)
Lung Abscess	1 (0.3%)	0
Osteomyelitis	21 (7.3%)	16 (10.3%)
Paronychia	1 (0.3%)	0
Pneumonia	15 (5.2%)	7 (4.5%)
Pneumonia Bacterial	0	2 (1.3%)
Postoperative Wound Infection	2 (0.7%)	0
Pyelonephritis	1 (0.3%)	1 (0.6%)
Sepsis	8 (2.8%)	5 (3.2%)
Septic Shock	2 (0.7%)	3 (1.9%)
Serratia Bacteraemia	1 (0.3%)	0
Sputum Purulent	0	1 (0.6%)
Subcutaneous Abscess	0	1 (0.6%)
Urinary Tract Infection	9 (3.1%)	6 (3.9%)
Urosepsis	1 (0.3%)	2 (1.3%)
Vaginal Infection	0	1 (0.6%)
Wound Infection	8 (2.8%)	2 (1.3%)
Injury, Poisoning And Procedural Complications	113 (39.4%)	63 (40.6%)
Anaemia Postoperative	1 (0.3%)	1 (0.6%)
Coronary Artery Restenosis	2 (0.7%)	0
Fall	2 (0.7%)	2 (1.3%)
Femoral Neck Fracture	0	1 (0.6%)
Femur Fracture	1 (0.3%)	1 (0.6%)
Forearm Fracture	0	1 (0.6%)
Fracture	1 (0.3%)	0
Hand Fracture	2 (0.7%)	0

Body System Preferred Term	DCB Subjects (N=287) n (%)	PTA Subjects (N=155) n (%)
Hip Fracture	2 (0.7%)	1 (0.6%)
Humerus Fracture	3 (1.0%)	0
Iatrogenic Injury	1 (0.3%)	0
Joint Dislocation	0	1 (0.6%)
Laceration	1 (0.3%)	1 (0.6%)
Lower Limb Fracture	0	1 (0.6%)
Lumbar Vertebral Fracture	1 (0.3%)	1 (0.6%)
Meniscus Injury	1 (0.3%)	0
Muscle Strain	0	1 (0.6%)
Overdose	1 (0.3%)	1 (0.6%)
Patella Fracture	1 (0.3%)	0
Peripheral Arterial Reocclusion	35 (12.2%)	11 (7.1%)
Peripheral Artery Restenosis	62 (21.6%)	36 (23.2%)
Post Procedural Haematoma	1 (0.3%)	0
Postoperative Wound Complication	1 (0.3%)	0
Radius Fracture	1 (0.3%)	0
Rib Fracture	1 (0.3%)	0
Skin Injury	0	1 (0.6%)
Spinal Compression Fracture	0	2 (1.3%)
Subcutaneous Haematoma	1 (0.3%)	0
Subdural Haematoma	3 (1.0%)	0
Tendon Rupture	1 (0.3%)	0
Thermal Burn	0	1 (0.6%)
Thoracic Vertebral Fracture	1 (0.3%)	0
Tibia Fracture	1 (0.3%)	0
Traumatic Haematoma	2 (0.7%)	0
Upper Limb Fracture	0	1 (0.6%)
Vascular Graft Complication	1 (0.3%)	0
Vascular Graft Occlusion	1 (0.3%)	0
Vascular Graft Thrombosis	1 (0.3%)	0
Vascular Pseudoaneurysm	3 (1.0%)	2 (1.3%)
Wound	15 (5.2%)	6 (3.9%)
Wound Dehiscence	2 (0.7%)	1 (0.6%)
Wound Haemorrhage	1 (0.3%)	0
Wound Necrosis	0	1 (0.6%)
Investigations	5 (1.7%)	4 (2.6%)
Blood Creatinine Increased	0	1 (0.6%)
Blood Culture Positive	1 (0.3%)	0
Blood Glucose Fluctuation	1 (0.3%)	0
Blood Pressure Decreased	1 (0.3%)	0
Haemoglobin Decreased	1 (0.3%)	1 (0.6%)
Investigation	0	1 (0.6%)
Radioisotope Scan Abnormal	1 (0.3%)	0
Troponin Increased	1 (0.3%)	1 (0.6%)
Metabolism And Nutrition Disorders	14 (4.9%)	10 (6.5%)
Decreased Appetite	1 (0.3%)	0
Dehydration	3 (1.0%)	1 (0.6%)
Diabetes Mellitus	3 (1.0%)	2 (1.3%)
Diabetic Ketoacidosis	1 (0.3%)	0
Fluid Overload	0	1 (0.6%)
Hyperglycaemia	4 (1.4%)	1 (0.6%)
Hyperkalaemia	0	2 (1.3%)
Hypoglycaemia	2 (0.7%)	1 (0.6%)
Hypokalaemia	1 (0.3%)	1 (0.6%)
Malnutrition	0	1 (0.6%)
Musculoskeletal And Connective Tissue Disorders	21 (7.3%)	8 (5.2%)
Arthralgia	0	1 (0.6%)
Arthritis	2 (0.7%)	0
Back Pain	0	1 (0.6%)
Bursitis	1 (0.3%)	0
Cervical Spinal Stenosis	1 (0.3%)	0
Foot Deformity	2 (0.7%)	0
Intervertebral Disc Protrusion	4 (1.4%)	0
Joint Contracture	0	1 (0.6%)
Joint Effusion	1 (0.3%)	0
Lumbar Spinal Stenosis	1 (0.3%)	0
Muscular Weakness	1 (0.3%)	0
Musculoskeletal Chest Pain	1 (0.3%)	1 (0.6%)
Myositis	1 (0.3%)	0
Osteoarthritis	7 (2.4%)	1 (0.6%)
Pain In Extremity	0	2 (1.3%)
Rhabdomyolysis	1 (0.3%)	0
Rotator Cuff Syndrome	0	1 (0.6%)

Body System Preferred Term	DCB Subjects (N=287) n (%)	PTA Subjects (N=155) n (%)
Soft Tissue Mass	1 (0.3%)	0
Spinal Osteoarthritis	0	2 (1.3%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	16 (5.6%)	9 (5.8%)
Adenocarcinoma Pancreas	1 (0.3%)	0
Adenosquamous Cell Lung Cancer	1 (0.3%)	0
Basal Cell Carcinoma	1 (0.3%)	0
Breast Cancer	1 (0.3%)	0
Colon Cancer	1 (0.3%)	1 (0.6%)
Colorectal Cancer	1 (0.3%)	0
Gastric Cancer	1 (0.3%)	1 (0.6%)
Lip And/Or Oral Cavity Cancer	1 (0.3%)	0
Lung Neoplasm Malignant	2 (0.7%)	0
Lymphoma	1 (0.3%)	0
Malignant Melanoma	1 (0.3%)	0
Meningioma	0	1 (0.6%)
Neuroma	1 (0.3%)	0
Non-Hodgkin's Lymphoma	1 (0.3%)	0
Non-Small Cell Lung Cancer	0	1 (0.6%)
Pancreatic Carcinoma Metastatic	2 (0.7%)	0
Pharyngeal Cancer	0	1 (0.6%)
Prostate Cancer	0	1 (0.6%)
Rectal Cancer	0	2 (1.3%)
Renal Cancer	0	1 (0.6%)
Squamous Cell Carcinoma Of Lung	1 (0.3%)	0
Nervous System Disorders	43 (15.0%)	11 (7.1%)
Amnesia	1 (0.3%)	0
Brain Stem Stroke	1 (0.3%)	0
Carotid Artery Stenosis	4 (1.4%)	3 (1.9%)
Carpal Tunnel Syndrome	3 (1.0%)	0
Cerebral Haemorrhage	2 (0.7%)	1 (0.6%)
Cerebral Infarction	5 (1.7%)	1 (0.6%)
Cerebrovascular Accident	6 (2.1%)	3 (1.9%)
Cerebrovascular Disorder	0	1 (0.6%)
Convulsion	1 (0.3%)	0
Dementia	1 (0.3%)	0
Dizziness	1 (0.3%)	0
Embolic Stroke	1 (0.3%)	0
Encephalopathy	3 (1.0%)	2 (1.3%)
Hemiparesis	1 (0.3%)	0
Hypoaesthesia	0	1 (0.6%)
Lacunar Infarction	1 (0.3%)	0
Metabolic Encephalopathy	1 (0.3%)	0
Parkinson's Disease	2 (0.7%)	0
Precerebral Artery Occlusion	1 (0.3%)	0
Somnolence	1 (0.3%)	0
Spinal Cord Compression	1 (0.3%)	0
Subarachnoid Haemorrhage	1 (0.3%)	0
Syncope	6 (2.1%)	1 (0.6%)
Toxic Encephalopathy	1 (0.3%)	0
Transient Ischaemic Attack	4 (1.4%)	0
Vascular Dementia	1 (0.3%)	0
Psychiatric Disorders	7 (2.4%)	3 (1.9%)
Anxiety	1 (0.3%)	0
Depression	0	1 (0.6%)
Mental Status Changes	5 (1.7%)	2 (1.3%)
Neglect Of Personal Appearance	1 (0.3%)	0
Renal And Urinary Disorders	30 (10.5%)	11 (7.1%)
Bladder Mass	1 (0.3%)	0
Calculus Urinary	1 (0.3%)	0
Haematuria	3 (1.0%)	2 (1.3%)
Nephropathy	1 (0.3%)	0
Nephropathy Toxic	1 (0.3%)	0
Obstructive Uropathy	0	1 (0.6%)
Pyuria	0	1 (0.6%)
Renal Artery Stenosis	2 (0.7%)	0
Renal Failure	10 (3.5%)	7 (4.5%)
Renal Failure Acute	12 (4.2%)	3 (1.9%)
Renal Impairment	1 (0.3%)	0
Ureteric Stenosis	1 (0.3%)	0
Urinary Retention	1 (0.3%)	1 (0.6%)

Body System Preferred Term	DCB Subjects (N=287) n (%)	PTA Subjects (N=155) n (%)
Reproductive System And Breast Disorders	1 (0.3%)	1 (0.6%)
Benign Prostatic Hyperplasia	0	1 (0.6%)
Vaginal Haemorrhage	1 (0.3%)	0
Respiratory, Thoracic And Mediastinal Disorders	29 (10.1%)	13 (8.4%)
Acute Pulmonary Oedema	1 (0.3%)	1 (0.6%)
Acute Respiratory Failure	3 (1.0%)	2 (1.3%)
Aspiration	0	1 (0.6%)
Chronic Obstructive Pulmonary Disease	5 (1.7%)	5 (3.2%)
Dyspnoea	6 (2.1%)	0
Hypoxia	1 (0.3%)	0
Lung Disorder	1 (0.3%)	0
Pleural Effusion	6 (2.1%)	1 (0.6%)
Pneumonia Aspiration	2 (0.7%)	1 (0.6%)
Pulmonary Embolism	3 (1.0%)	0
Pulmonary Mass	1 (0.3%)	1 (0.6%)
Pulmonary Oedema	2 (0.7%)	2 (1.3%)
Respiratory Arrest	1 (0.3%)	1 (0.6%)
Respiratory Failure	2 (0.7%)	5 (3.2%)
Sleep Apnoea Syndrome	1 (0.3%)	1 (0.6%)
Skin And Subcutaneous Tissue Disorders	23 (8.0%)	16 (10.3%)
Decubitus Ulcer	1 (0.3%)	1 (0.6%)
Diabetic Foot	1 (0.3%)	1 (0.6%)
Diabetic Ulcer	1 (0.3%)	1 (0.6%)
Dry Gangrene	0	2 (1.3%)
Leukocytoclastic Vasculitis	1 (0.3%)	1 (0.6%)
Pruritus	1 (0.3%)	0
Skin Necrosis	3 (1.0%)	0
Skin Ulcer	17 (5.9%)	12 (7.7%)
Vascular Disorders	128 (44.6%)	60 (38.7%)
Accelerated Hypertension	1 (0.3%)	0
Aortic Aneurysm	0	1 (0.6%)
Aortic Stenosis	2 (0.7%)	0
Arterial Rupture	1 (0.3%)	0
Arteritis	1 (0.3%)	0
Deep Vein Thrombosis	6 (2.1%)	2 (1.3%)
Diabetic Macroangiopathy	1 (0.3%)	0
Embolism Arterial	4 (1.4%)	2 (1.3%)
Extremity Necrosis	3 (1.0%)	0
Femoral Artery Occlusion	1 (0.3%)	1 (0.6%)
Haemorrhage	0	2 (1.3%)
Hypertension	4 (1.4%)	1 (0.6%)
Hypertensive Crisis	3 (1.0%)	2 (1.3%)
Hypertensive Emergency	3 (1.0%)	0
Hypotension	2 (0.7%)	2 (1.3%)
Intermittent Claudication	0	3 (1.9%)
Orthostatic Hypotension	3 (1.0%)	2 (1.3%)
Peripheral Arterial Occlusive Disease	58 (20.2%)	16 (10.3%)
Peripheral Artery Dissection	9 (3.1%)	2 (1.3%)
Peripheral Artery Stenosis	58 (20.2%)	35 (22.6%)
Peripheral Artery Thrombosis	3 (1.0%)	3 (1.9%)
Peripheral Ischaemia	5 (1.7%)	2 (1.3%)
Varicose Vein	0	1 (0.6%)
Vascular Insufficiency	1 (0.3%)	0
Vasospasm	3 (1.0%)	2 (1.3%)
Venous Insufficiency	0	2 (1.3%)
Venous Thrombosis	1 (0.3%)	0
Vessel Perforation	1 (0.3%)	0
AE Uncoded	5 (1.7%)	4 (2.6%)
Uncoded: Acute Ischemia Left Lower Leg	0	1 (0.6%)
Uncoded: Admission To Psychatry	1 (0.3%)	0
Uncoded: Chest Pain Syndrome With Acute Moderate Pericardia	1 (0.3%)	0
Uncoded: Claudication Left Leg	0	1 (0.6%)
Uncoded: Gangrene On Left Great Toe	0	1 (0.6%)
Uncoded: I & D With Partial Left Hallux Amputation	0	1 (0.6%)
Uncoded: Occluded Left Sfa Stent	1 (0.3%)	0
Uncoded: Occlusion Of Right At & Dp	1 (0.3%)	0
Uncoded: Oclussion Of Left At And Stenosis Of Left Tpt	0	1 (0.6%)
Uncoded: Profundus Stenosis	1 (0.3%)	0
Uncoded: Ulcerated Basalioma Left Eyelid	1 (0.3%)	0

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

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

10.3 Lutonix Global BTK Real-World Registry

10.3.1 Objective

The primary objective of the Lutonix Global BTK real-world Registry (Global BTK Registry) was to demonstrate safety and assess the clinical use and outcomes of the Lutonix™ DCB for treatment of stenosis or occlusion of native below-the-knee arteries in a heterogeneous patient population in real world clinical practice.

10.3.2 Study Design

The Global BTK Registry is a prospective, global, multicenter, single arm registry with primary effectiveness endpoint of freedom from TLR at 6 month and primary safety endpoint of composite safety at 30 days (major adverse limb events and all-cause death).

Following informed consent, 371 subjects were enrolled at 26 clinical sites across 11 countries. Patient follow-up compliance through 6 months is 83.3% and follow-up through 12 months is 76.3%.

Table 11. Subject Disposition

Summary	Global BTK Registry
ITT Subjects (Enrolled Subjects), n	371
Follow-up by Visit, % (n/N)	
30 Days	94.9% (352/371)
Month 6	83.3% (309/371)
Month 12	76.3% (283/371)
Month 24	63.3% (235/371)
Duration of Follow-up (Days), Mean ± SD (n)	357.6 ± 204.0 (371)

10.3.3 Baseline and Demographics

Table 12 and **Table 13** 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 92.2% of subjects and final procedure bailout spot stenting occurred in 37.1% of the subjects.

Table 12. Selected Demographics

Summary	Global BTK Registry (N=371)
Age (Years), Mean ± SD (n)	73.5 ± 9.59 (371)
Gender, % (n/N)	
Male	72.2% (268/371)
BMI (kg/m^2), Mean ± SD (n)	27.3 ± 5.29 (366)
Median (Min, Max)	26.8 (13.8, 69.5)
Hypertension, % (n/N)	87.1% (323/371)
Dyslipidemia, % (n/N)	62.8% (233/371)
Type of Diabetes, % (n/N)	
Type I	6.8% (16/237)
Type II	93.2% (221/237)
Smoking Status, % (n/N)	
Current Smoker	12.9% (48/371)
Previous Smoker	38.8% (144/371)
Non-Smoker	48.2% (179/371)
History of Vascular Disease, % (n/N)	75.5% (280/371)
Baseline Target Limb Rutherford Grade, % (n/N)	
3	24.1% (89/370)
4	10.5% (39/370)
5	65.4% (242/370)
Subjects with One or More Interventions, % (n/N)	14.0% (52/371)
Number of Interventions, % (n/N)	
1	82.7% (43/52)
2	13.5% (7/52)
3	3.8% (2/52)
Arteries Treated, % (n/N)[1]	
Popliteal	5.8% (3/52)
Tibioperoneal Trunk	11.5% (6/52)
Anterior Tibial	65.4% (34/52)
Posterior Tibial	19.2% (10/52)
Peroneal	11.5% (6/52)

Summary	Global BTK Registry (N=371)
Types of Intervention, % (n/N)[1]	
PTA alone	59.6% (31/52)
Drug-coated or drug-eluting balloon	21.2% (11/52)
Cutting balloon	1.9% (1/52)
Crossing balloon	1.9% (1/52)
Stent	11.5% (6/52)
Thrombectomy/thrombolysis	5.8% (3/52)
Other	3.8% (2/52)

Table 13. Baseline Angiographic Data, Subject Level Information

Summary	Global BTK Registry (N=371)
Total Number of Treated Lesions	441
Artery Location by Subject (n/N)	
Popliteal	6.2% (23/370)
Tibioperoneal Trunk	20.3% (75/370)
Anterior Tibial	50.8% (188/370)
Posterior Tibial	22.2% (82/370)
Peroneal	22.4% (83/370)
Total Target Length (mm), Mean ± SD (n)	121 ± 98.7 (370)
Average Diameter Stenosis (%), Mean ± SD (n)	91 ± 9.16 (370)
Maximum Diameter Stenosis (%), Mean ± SD (n)	92 ± 9.02 (370)
Average RVD (mm), Mean ± SD (n)	2.7 ± 0.52 (367)
Maximum RVD (mm), Mean ± SD (n)	2.7 ± 0.55 (367)
Subjects with Calcification, % (n/N)	68.4% (242/354)
Subjects with Severe Calcification, % (n/N)	20.5% (73/356)
Highest Subject TASC, % (n/N)	
Type A	25.1% (93/370)
Type B	25.7% (95/370)
Type C	17.3% (64/370)
Type D	14.1% (52/370)
Unknown	17.8% (66/370)

Table 14. Procedural Data

Summary	Global BTK Registry (N=371)
Access Method and Inflow Artery Information by Subject	
Access Method, % (n/N)	
Contralateral	25.9% (96/371)
Ipsilateral	73.9% (274/371)
Other	0.3% (1/371)
Patent Inflow Artery, % (n/N)	94.3% (350/371)
Pre-dilatation by Subject	
Any Pre-dilatation Performed, % (n/N)	92.2% (342/371)
Average Post Pre-dilatation % Stenosis, Mean ± SD (n)	35 ± 23.5 (335)
DCB Dilatation Information Overall Information by Subject	
Multiple DCB Devices Used, % (n/N)	29.8% (110/369)
Total DCB Devices Used by Lesion for Multiple Devices	
2	54.5% (60/110)
3	40.9% (45/110)
4	4.5% (5/110)
Any Overlap for Multiple Balloons, % (n/N)	83.6% (92/110)
DCB Dilatation Information by Subject	
Average Balloon Ratio (Diameter/Average RVD), Mean ± SD (n)	1.01 ± 0.13 (367)
Average Transit Time (sec), Mean ± SD (n)	21.9 ± 19.84 (364)
Average Inflation Time (sec), Mean ± SD (n)	132.0 ± 41.02 (370)
Max Post-DCB % DS, Mean ± SD (n)	11.5 ± 18.13 (369)
Post-DCB Dilatation and Final Stenosis by Subject	
Any Post-DCB Dilatation Performed, % (n/N)	9.2% (34/368)
Max Post-DCB % DS, Mean ± SD (n)	21 ± 27.2 (34)
Any Post-treatment Dissection, % (n/N)	4.9% (18/366)
Max Dissection Grade	
Type A	66.7% (12/18)
Type B	27.8% (5/18)
Type C	5.6% (1/18)
Final Max Post-Treatment % DS by Subject, Mean ± SD (n)	10 ± 16.5 (369)

Additional treatments were also utilized outside of dilatation procedures. These are shown in **Table** below.

Table 25: Additional Treatments Performed During Initial Procedure

Summary	BTK Registry (N=371)
Any Additional Treatments Performed, % (n/N)	9.2% (34/371)
Additional Treatment Modality by Treatment, % (n/N)	
Atherectomy	12.8% (5/39)
New Bypass graft	2.6% (1/39)
Other	17.9% (7/39)
PTA alone	12.8% (5/39)
Retrograde access	2.6% (1/39)
Scoring/Cutting Balloon	2.6% (1/39)
Stent/bailout stent	33.3% (13/39)
Thrombectomy/Thrombolysis	15.4% (6/39)
Reason for Additional Treatment, % (n/N)	
Calcification	18.4% (7/38)
Dissection	18.4% (7/38)
Other	63.2% (24/38)
Timing of Additional Treatment, % (n/N)	
After use Lutonix Balloon	69.2% (27/39)
Prior to Lutonix Balloon	30.8% (12/39)
Was Additional Treatment Successful by Treatment, % (n/N)	97.4% (38/39)

[1] Subjects may have more than one additional treatment

10.3.4 Methods

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

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

This registry study enrolled subjects presenting with claudication, or critical limb ischemia (Rutherford Category 3- 5) and an angiographically significant (≥ 70%) native artery lesion appropriate for angioplasty that is below the knee. Subjects were considered enrolled in the study after being consented and the Lutonix™ DCB has entered the subject's body. For each subject, clinical data and follow-up information at 1, 6, 12 and 24 months were reported. Subject contact was made either by a clinical visit or telephone.

All required clinical data were collected in web-based standardized electronic case report forms. Monitoring was performed to ensure compliance. All death, major adverse limb events, and device related serious adverse events were adjudicated by an independent Clinical Events Committee.

10.3.5 Results

Results are presented below. No hypothesis testing was pre-specified in this study.

10.3.5.1 Primary Effectiveness Endpoint

Primary effectiveness endpoint is defined as freedom from clinically driven target lesion revascularization (TLR) at 6 months. Total of 321 subjects were evaluable for the primary effectiveness endpoint analysis. The TLR Free rate by subject counts was 90.0% at 6 months, 79.9% at 12 months, and 74.2% at 24 months. The Kaplan-Meier estimates TLR-Free survival was 92.8% at 6 months,82.3% at 12 months, and 78.9% at 24 months.

Table 15. Primary Effectiveness Endpoint

Primary Effectiveness Endpoint	Success % (n/N)	95% CI[1]
Freedom from TLR at 6 months	90.0% (289/321)	86.2%, 93.1%

[1] Exact binomial confidence interval

10.3.5.2 Primary Safety Endpoint

The primary safety endpoint is defined as freedom at 30 days from major adverse limb event and all-cause death. A total of 360 subjects were evaluable for the primary safety endpoint analysis. The success by subject counts was 98.3% for the primary safety endpoint. Freedom from primary safety events by Kaplan Meier estimates for 6 months was 94.2% and at 12 months was 92.7%. Note: Primary safety events beyond 30 days were included in the Kaplan-Meier analyses.

Table 16. Primary Safety Endpoint

Primary Safety Endpoint	Success % (n/N)	95% CI[1]
Freedom from primary safety events at 30 days (MALE and POD)	98.3% (354/360)	96.4%, 99.4%

[1] Exact binomial confidence interval

10.3.5.3 Secondary Effectiveness Endpoint

Primary Patency of the target lesion is by investigator assessment based on presenting symptoms and clinical exam and by absence of a CEC adjudicated TLR event. Total of 273 subjects were evaluable for primary patency at 6 months and 230 subjects at 12 months. The primary patency success rate at 6 months as determined by subject counts was 81.0% and was 70.0% at 12 months. The primary patency rate for all subjects as measured by Kaplan-Meier estimates resulted in 88.9% for 6 months and 70.0% at 12 months.

Table 28. Primary Patency

Secondary Effectiveness Endpoint	Success % (n/N)	95% CI[1]
Primary Patency at 6 Months	81.8% (224/274)	76.7%, 86.1%
Primary Patency at 12 Months	70.0% (177/253)	63.9%, 75.5%
Primary Patency at 24 Months	40.7% (55/135)	32.4%, 49.5%

[1] Exact binomial confidence interval

The TLR-free rate by subject counts was 79.9% at 12 months and 74.2% at 24 months (Table 27). The respective Kaplan-Meier estimates for TLR-free survival were 82.3% and 78.9%. The calculations are performed per patient, not per lesion for patients with multiple target lesions.

Table 29. Clinically-Driven TLR-Free

	CL0024-01 BTK Registry (N=371)	
Measure	Success % (n/N)	95% CI[1]
Clinically-Driven TLR-Free at 6 Months	90.0% (289/321)	86.2%, 93.1%
Clinically-Driven TLR-Free at 12 Months	79.9% (239/299)	74.9%, 84.3%
Clinically-Driven TLR-Free at 24 Months	74.2% (187/252)	68.3%, 79.5%

[1] Exact binomial confidence interval

10.3.5.4 Secondary Safety Endpoint

Freedom from secondary safety endpoints was evaluated at 6,12, and 24 months follow-up time periods. TVR free at 6,12, and 24 months was 89.7%, 79.2%, and 73.8%, respectively. The freedom from all cause death rate was 99.4% at 30 days. Target limb survival from major amputation rates were 95.7%, 93.2%, and 93.2% at 6,12, and 24 months, respectively. No unexpected device or drug related events occurred through 24 months.

Table 30. Freedom from Secondary Safety Endpoint - ITT

	BTK Registry (N=371)	
Freedom from Event	% (n/N)	95% CI[1]
All Cause Death at 30 Days	99.4% (357/359)	98.0%, 99.9%
All Cause Death at 6 Months	92.1% (314/341)	88.7%, 94.7%
All Cause Death at 12 Months	87.6% (282/322)	83.5%, 91.0%
All Cause Death at 24 Months	67.5% (131/194)	60.4%, 74.1%
TVR at 6 Months	89.7% (287/320)	85.8%, 92.8%
TVR at 12 Months	79.2% (236/298)	74.1%, 83.7%
TVR at 24 Months	73.8% (186/252)	67.9%, 79.1%
Major Amputation at 6 Months	95.7% (308/322)	92.8%, 97.6%
Major Amputation at 12 Months	93.2% (275/295)	89.7%, 95.8%
Major Amputation at 24 Months	91.4% (224/245)	87.2%, 94.6%
Reintervention for Thrombosis at 6 Months	95.9% (306/319)	93.1%, 97.8%
Reintervention for Thrombosis at 12 Months	90.1% (265/294)	86.1%, 93.3%
Reintervention for Thrombosis at 24 Months	86.5% (211/244)	81.5%, 90.5%
Reintervention for Distal Embolization at 6 Months	100.0% (316/316)	98.8%, 100.0%
Reintervention for Distal Embolization at 12 Months	100.0% (288/288)	98.7%, 100.0%
Reintervention for Distal Embolization at 24 Months	100.0% (235/235)	98.4%, 100.0%
Unexpected Device or Drug Related Event at 6 Months	100.0% (316/316)	98.8%, 100.0%
Unexpected Device or Drug Related Event at 12 Months	100.0% (288/288)	98.7%, 100.0%
Unexpected Device or Drug Related Event at 24 Months	100.0% (235/235)	98.4%, 100.0%

[1] Exact binomial confidence interval

Rutherford Category Analysis
The majority of subjects were classified as Rutherford Category 5 (65.4%) at baseline. Improvement by at least 1 class was observed in 72.5% of subjects at 6 months and 80.4% at 12 months.

Table 31. Rutherford Category by Visit, ITT Subjects

Summary	BTK Registry (N=371)
Total Treated Limbs, % (n/N)	
Left	50.0% (185/370)
Right	50.0% (185/370)
Baseline Target Limb Rutherford Grade, % (n/N)	
0	0.0% (0/370)
1	0.0% (0/370)
2	0.0% (0/370)
3	24.1% (89/370)
4	10.5% (39/370)
5	65.4% (242/370)
6	0.0% (0/370)
Month 6 Target Limb Rutherford Grade, % (n/N)	
0	36.3% (103/284)
1	18.0% (51/284)
2	12.7% (36/284)
3	8.8% (25/284)
4	1.1% (3/284)
5	22.5% (64/284)
6	0.7% (2/284)
Month 6 Shift in Rutherford Class, Mean ± SD (n)	-2.4 ± 1.86 (284)
Median (Min, Max)	-3.0 (-5.0, 1.0)
Month 6 Shift in Rutherford Grade, % (n/N)	
Improved by 5 Levels	19.0% (54/284)
Improved by 4 Levels	12.0% (34/284)
Improved by 3 Levels	24.3% (69/284)
Improved by 2 Levels	12.3% (35/284)
Improved by 1 Level	4.9% (14/284)
No Change	26.1% (74/284)
Worsened by 1 Level	1.4% (4/284)
Month 12 Target Limb Rutherford Grade, % (n/N)	
0	41.9% (111/265)
1	18.5% (49/265)
2	14.7% (39/265)
3	8.3% (22/265)
5	16.2% (43/265)
6	0.4% (1/265)
Month 12 Shift in Rutherford Class, Mean ± SD (n)	-2.8 ± 1.78 (265)
Median (Min, Max)	-3.0 (-5.0, 1.0)
Month 12 Shift in Rutherford Grade, % (n/N)	
Improved by 5 Levels	23.8% (63/265)
Improved by 4 Levels	11.7% (31/265)
Improved by 3 Levels	27.2% (72/265)
Improved by 2 Levels	13.2% (35/265)
Improved by 1 Level	4.5% (12/265)
No Change	18.5% (49/265)
Worsened by 1 Level	1.1% (3/265)

10.3.6 Discussion

While the defined primary endpoints of the Global BTK Registry and the Lutonix BTK IDE Trial study are different (i.e. Primary effectiveness of Freedom from TLR for Global BTK Registry vs. Limb Salvage and Primary Patency for the Lutonix BTK IDE Trial), similar safety and effectiveness endpoints were evaluated in both studies – reference the **Table 30** below for comparison of the clinical outcomes. As shown, the DCB results from the Global BTK Registry are well aligned with the clinical results from the Lutonix BTK IDE Trial study.

Table 17. Comparison of Outcomes – Global BTK Registry and Lutonix BTK IDE Trial study

Description	Global BTK Registry – Lutonix DCB	Lutonix BTK IDE Trial [2]	
		Lutonix DCB	Standard PTA
	Success Rate - % (n/N)		
Freedom from TLR at 6 Months	90.0% (289/321)	90.8% (275/303)	82.6% (142/172)
Primary Patency at 6 Months	81.8% (224/274)	126 / 163 (77.3%)	56 / 86 (65.1%)
Primary Safety at 30-days (MALE + POD)[1]	98.3% (354/360)	99.3% (284/286)	99.4% (154/155)

[1] Composite safety events are all-cause death, above-ankle amputation or major reintervention of the index limb involving a BTK artery. [2] Results for all vessels.

Additional Data
A summary of additional Lutonix BTK data can be found below, summarizing the baseline characteristics across the datasets and the **Table 32** providing a summary of the endpoints.

Additional real-world VQI data showed a 6-month freedom from TLR of 96.1% for the Lutonix DCB group and 95.2% for the PTA Control group (p=0.332) with the separation continuing through 12 months (91.8% vs 88.6%, respectively). In addition, the Japanese Hemodialysis RCT (n=36), the key efficacy endpoint of composite of limb salvage and primary patency through 6 months success rate by flow pathway was 70.0% for the DCB arm and 38.9% for the PTA arm in the HD study, for a 31.1% (95% CI -3.1%, 59.4%) net benefit for DCB.

Table 33. Baseline Characteristics Across Datasets

Baseline Characteristics	**IDE (DCB / PTA)**	**BTK Registry**	**BTK IDE/Registry Propensity-Adjusted**	**VQI Registry (DCB/PTA)**	**Japan HD RCT**
Study Design	Prospective, Randomized	Prospective, Single Arm	Statistical analysis comparing DCB and PTA treatment outcomes based on the combination of the IDE and Registry	(Real-world) Registry-based collaborative of physicians and hospitals	Prospective, Randomized
Geography	Global: U.S., Canada, Japan, Europe	Global: Europe, Saudi Arabia	Global Data	510 hospitals in U.S. and Canada; Procedures performed from 2017 onward, at 200 sites and conducted by 750 physicians	Japan
Follow-up Period	3 years (recently extended to 5 years)	2 years	12 months	12 months	24 months
Treatment Arms	DCB: PTA (2:1)	DCB only	DCB (IDE+Registry) & PTA (IDE)	DCB & PTA	DCB: PTA (1:1)
# Subjects	287 DCB and 155 PTA	371 DCB	658 DCB (IDE+Registry) and 155 PTA (IDE)	167 DCB and 397 PTA	19 DCB and 17 PTA
Rutherford Class	DCB (n=287) R3: n=26 (9.1%) R4: n=100 (34.8%) R5: n=161 (56.1%) PTA (n=155) R3: n=16 (10.3%) R4: n=52 (33.5%) R5: n=87 (56.1%)	DCB (n=370) R3: n=89 (24.1%) R4: n=39 (10.5%) R5: n=242 (65.4%)	N/A	DCB (n=167) R1: n=4 (2.4%) R2: n=9 5.4%) R3: n=22 (13.2%) R4: n=24 (14.4%) R5: n=68 (40.7%) R6: n=40 (24.0%) PTA (n=397) R1: n=40 (10.1%) R2: n=29 (7.3%) R3: n=32 (8.1%) R4: n=49 (12.3%) R5: n=194 (48.9%) R6: n=53 (13.4%)	For DCB (n=19) R4: n=7 (36.8%) R5: n=12 (63.2%) For PTA (n=17) R4: n=8 (47.1%) R5: n=9 (52.9%)
# Flow Pathways	DCB: 323 vessels PTA: 184 vessels [1]	441 lesions	727 DCB (IDE 323+Registry 404) and 184 PTA (IDE)	Total # vessels treated not specified	DCB: 23 vessels PTA: 21 vessels

[1] The entire vessel in which the target lesion is located. One or two below-the-knee arterial flow pathways to the foot are allowed as Target Vessel(s); i.e., peroneal or posterior tibial arteries may involve tibioperoneal trunk lesions and tibial arteries may involve popliteal lesions. Each target vessel(s) (flow path) must reconstitute(s) at or above the ankle with inline flow to at least one patent (<50%) inframalleolar outflow vessel (planned treatment below-the-ankle is not allowed). Note: Up to 2 flow pathways were allowed to be treated with the same randomized device

Baseline Characteristics	IDE (DCB / PTA)	BTK Registry	BTK IDE/Registry Propensity-Adjusted	VQI Registry (DCB/PTA)	Japan HD RCT
Mean Lesion Length	DCB:111.8mm PTA: 94.7mm	DCB: 102 ± 84.3 mm	111.0mm (DCB Registry) / 122.0mm (DCB IDE) / 111.5mm (PTA)	DCB: 167 mm ± 176 mm PTA: 130 mm ± 133 mm	DCB: 148.6 ±87.77 PTA: 154.9 ±100.4
Any Calcification, n/N (%)	DCB: 211/352 (59.9%), PTA: 115/212 (54.2)	DCB:285/441 (64.6%)	453/709 (63.9%) DCB (IDE+Registry) and 102/181 (56.4%) PTA	DCB: 120/167 (71.9%) PTA: 188/397 (47.4%)	DCB: 21/23 (91.3%) PTA: 20/21 (95.2%)

Table 34. Summary of the Endpoints Across Datasets

Endpoint	IDE Result (DCB / PTA)	BTK Registry Result	BTK IDE/Registry Propensity-Adjusted Result	VQI Registry Result (DCB/PTA)	Japan HD RCT
Composite of Limb Salvage and Primary Patency (6mo)	Binary: 74.7% / 64.2% KM: 85.8% / 71.4%	N/A - Not reported	IPW: 85.5% / 66.9% Binary IPW: 76.6% / 58.9%	*N/A – Not reported*	14/20 (70.0%) / 7/18 (38.9%)
Composite of Limb Salvage and Primary Patency (12mo)	Binary: 51.0% / 56.8% KM: 60.3% / 60.9%	N/A - Not reported	IPW: 63.5% / 55.8% Binary IPW: 58.1% / 52.3%	*N/A – Not reported*	53% / 38.9%
Composite of Limb Salvage and Primary Patency (24mo)	Binary: 36.8% / 43.9% KM: 45.7% / 49.4%	*N/A - Not reported*	IPW: 51.7% / 44.0% Binary IPW: 36.8% / 39.8%	*N/A – Not reported*	*N/A – not yet available*
Composite of Limb Salvage and Primary Patency (36mo)	Binary: 27.6% / 29.0% KM: 38.7% / 47.0%	*N/A - Not reported*	*N/A - Not reported*	*N/A - Not reported*	*N/A*
Freedom from CD-TLR (6mo)	Binary: 90.8% / 82.6% KM: 93.8% / 85.6%	Subject counts: 90.0% KM: 92.8%	Binary IPW: 90.6% / 77.9%	96.1% / 95.2%	91.3% / 71.4%
Freedom from CD-TLR (12mo)	Binary: 76.9% / 76.3% KM: 80.3% / 79.4%	Subject counts: 79.9% KM: 82.3%	Binary IPW: 78.3% / 71.4%	91.8% / 88.6%	67.6% / 71.4%
Freedom from CD-TLR (24mo)	Binary: 67.9% / 65.4% KM: 72.6% / 72.3%	Subject counts: 74.2% KM: 78.9%	Binary IPW: 70.5% / 60.2%	*N/A - Not reported*	*N/A – not yet available*
Freedom from CD-TLR (36mo)	Binary: 56.7% /52.5% KM: 67.3% / 70.3%	*N/A - Not reported*	*N/A - Not reported*	*N/A - Not reported*	*N/A*
Primary Patency (6mo)	Binary: 75.6% / 65.7% KM: 86.8% / 73.0%	Subject Counts: 81.8% KM: 89.1%	Binary IPW: 78.7% / 60.3%	93.4% / 92.0%	78.0% / 44.4%
Primary Patency (12mo)	Binary: 51.6% / 58.1% KM: 61.0% / 62.2%	Subject Counts: 70.0% KM: 72.3%	Binary IPW: 59.8% / 53.6%	87.2% / 84.7%	53.0% / 38.9%
Primary Patency (24mo)	Binary: 37.3% / 45.4% KM: 46.2% / 51.3%	Subject Counts: 40.7% KM: 66.5%	Binary IPW: 38.2% / 41.2%	*N/A - Not reported*	*N/A – not yet available*
Primary Patency (36mo)	Binary: 28.0% / 30.5% KM: 39.1% / 50.4%	*N/A - Not reported*	*N/A - Not reported*	*N/A - Not reported*	*N/A*

11 HOW SUPPLIED

- Sterile: This device is sterilized with ethylene oxide gas. Do not use if package is opened or damaged. For one use only. Do not resterilize.
- The Lutonix™ Catheter has a protective sheath placed over the balloon, is stored within a standard dispensing hoop, and is sterilized within a dual chamber pouch. The dual chamber pouch contains both a catheter compartment and desiccant compartment. The compartments are separated by a sterile barrier. The desiccant compartment contains packets used to help control package environment and should not be opened.
- Contents: One (1) Lutonix™ 014 Drug Coated Balloon PTA Catheter.
- Storage: Store in a dry, dark place. Store at 15-30°C (59-86°F). Do not store near radiation or ultra-violet light sources.

12 DIRECTIONS FOR USE

12.1 Equipment

In addition to the Lutonix™ Catheter, the following standard materials may also be required:

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

12.2 Inspection Prior to Use

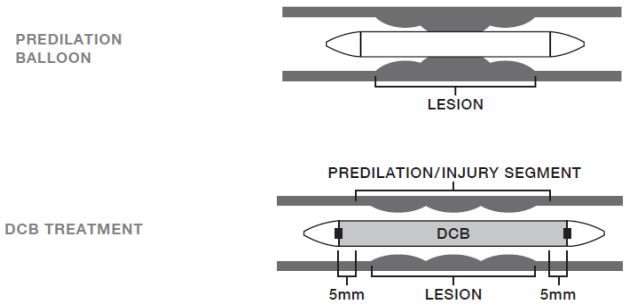
Prior to angioplasty, carefully examine all equipment to be used during the procedure, including the dilatation catheter, to verify proper function. Verify that the catheter and sterile packaging have not been damaged in shipment.

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

12.3 Use of Multiple Lutonix™ Catheters

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

Precaution: The safety and effectiveness of using multiple Lutonix™ drug coated balloons that deliver greater than 7.6 mg paclitaxel in a patient has not been clinically evaluated.



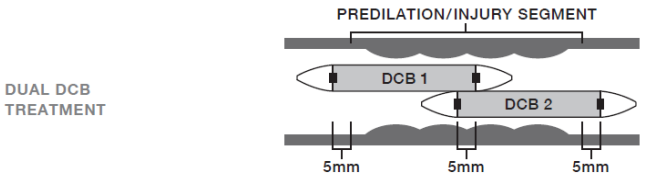


Figure 10. Balloon placement

12.4 Target Lesion Vessel Preparation

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

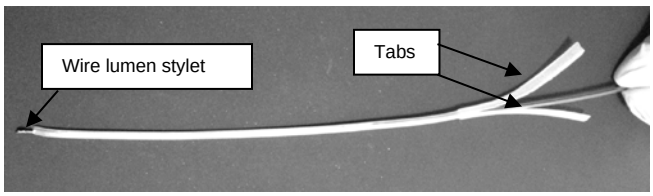
12.5 Lutonix™ Catheter Preparation

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

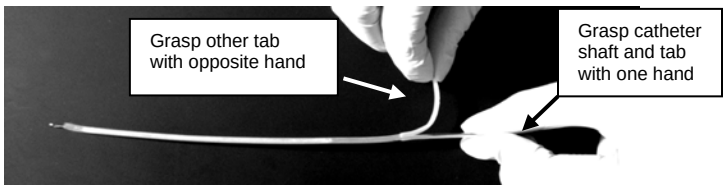
   Warning: Use the recommended balloon inflation medium of contrast and sterile saline (≤50% contrast). Never use air or any gaseous medium to inflate the balloon.
4. Prior to use, the air in the balloon catheter should be removed. To facilitate purging, select a syringe or inflation device with a 10 ml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

12.6 Use of the Lutonix™ Catheter

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

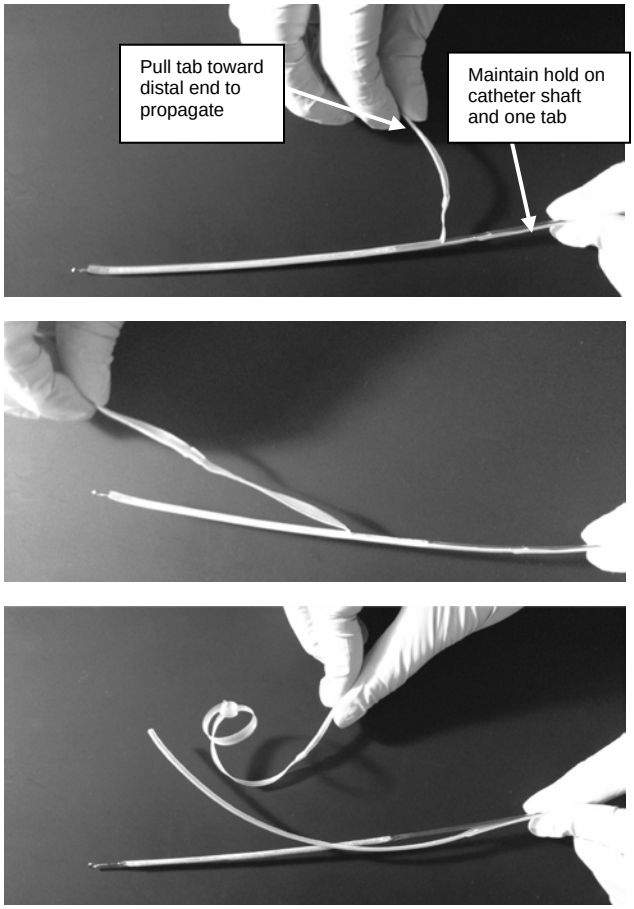


Step 1- Leaving the wire lumen stylet in place; use one hand to grasp both a single tab of the balloon protector and the catheter shaft as shown below. Caution should be taken to not kink or crush the catheter shaft. Using the opposite hand, grasp the other tab of the balloon protector

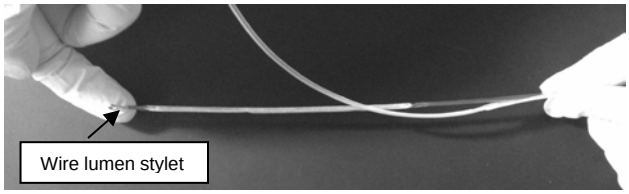


Step 2- With the hand holding the balloon protector tab only; gently pull the balloon protector tab toward the distal end of the balloon. Continue to pull the tab and hold the other balloon protector tab with the catheter

shaft until the balloon protector fully propagates and separates into two pieces.

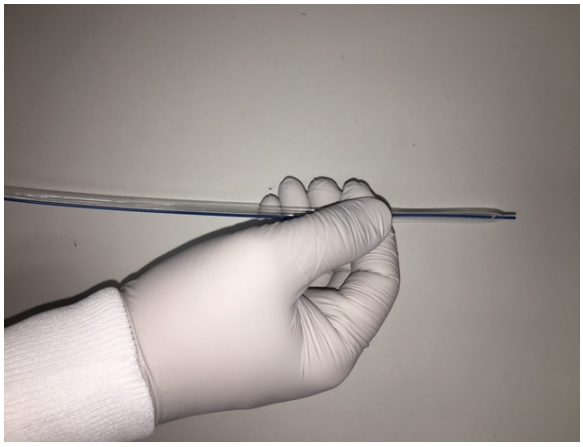


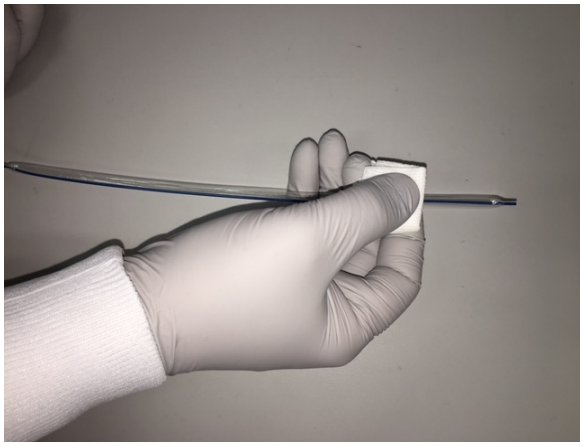
Step 3- Maintaining the grasp on the catheter shaft with one hand; use the opposite hand to remove the wire lumen stylet. Do this by gently pulling the hoop of the wire lumen stylet protruding from the distal end of the balloon.



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

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





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

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

   Warning: Do not exceed the Rated Burst Pressure (RBP) recommended for this device. Balloon rupture may occur if the RBP rating is exceeded. To prevent over-pressurization, use of a pressure monitoring device is recommended.
8. Maintain balloon inflation for a minimum of 2 minutes (120 seconds). The balloon may remain inflated as long as is required by the standard of care to achieve a good angioplasty outcome.
9. Apply negative pressure to fully deflate the Lutonix™ Catheter. Prior to removal, confirm that the balloon is fully deflated under fluoroscopy.
10. Perform angiography to confirm dilatation of the lesion.

11. Best outcomes are obtained when the final % diameter stenosis is 0 – 20%. To achieve the suggested % diameter stenosis, if needed, post-dilatation is allowed with another PTA catheter or used Lutonix™ catheter.
12. Withdraw the Lutonix™ Catheter from the body under negative pressure. Maintain the guidewire across the stenosis.
13. After confirming that a satisfactory dilatation was achieved, remove all equipment from the body and close access site per standard clinical practice.
14. Refer to **Section 5.5** for Pre- and Post-Procedure Antiplatelet Regimen for the dual antiplatelet pharmacological therapy recommended with use of the Lutonix™ Catheter.
15. After use, this product may be a potential biohazard. Handle and dispose of in accordance with acceptable medical practices and applicable laws and regulations.

13 DISCLAIMER OF WARRANTY

Lutonix, Inc. warrants to the first purchaser of this product, that this product will be free from defects in materials and workmanship for a period of one year from the date of first purchase and liability under this limited product warranty will be limited, to repair or replacement of the defective product, in Lutonix's sole discretion, or refunding your net price paid. Wear and tear from normal use or defects resulting from misuse of this product is not covered by this limited warranty.

TO THE EXTENT ALLOWABLE BY APPLICABLE LAW, THIS LIMITED PRODUCT WARRANTY IS IN LIEU OF ALL OTHER WARRANTIES, WHETHER EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IN NO EVENT WILL Lutonix BE LIABLE TO YOU FOR ANY INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES RESULTING FROM YOUR HANDLING OR USE OF THIS PRODUCT.

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