LUTONIX® 014 DRUG COATED PTA DILATATION CATHETER

SPONSOR EXECUTIVE SUMMARY

CIRCULATORY SYSTEM DEVICES PANEL

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LIST OF ABBREVIATIONS

Abbreviation	Term
ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
AFS	Amputation-Free Survival
API	Active Pharmaceutical Ingredient
AT	As Treated
ATK	Above the Knee
BTK	Below the Knee
CD-TLR	Clinically Driven Target Lesion Revascularization
CEC	Clinical Events Committee
CFA	Common Femoral Artery
CIP	Clinical Investigation Plan
CLI	Critical Limb Ischemia
DCB	Drug Coated Balloon
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GEE	Generalized Estimating Equations
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
JITT	Japanese Intent to Treat
LTX	LUTONIX
MACE	Major Adverse Cardiovascular Event
MALE	Major Adverse Limb Event
MLD	Minimum Lumen Diameter

LIST OF ABBREVIATIONS

Abbreviation	Term
OTW	Over the Wire
PAD	Peripheral Arterial Disease
POD	Perioperative Death
PP	Per Protocol
PTA	Percutaneous Transluminal (Balloon) Angioplasty
QVA	Quantitative Vascular Angiography
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SFA	Superficial Femoropopliteal Artery
TIA	Transient Ischemic Attack
TLR	Target Lesion Revascularization
UADE	Unanticipated Adverse Device Effect

1 SYNOPSIS

1.1 Introduction

Patients with critical limb ischemia (CLI) associated with below-the-knee (BTK) lesions suffer with severe pain. They may face repeated interventions to maintain blood flow to their lower limbs throughout their lives; lives which are shortened due to their CLI and multiple comorbidities. Help for these patients requires restoration of blood flow, lifestyle changes, and medical management of their chronic diseases.

Unlike the treatment of isolated lesions, for example in the aorta, patients with CLI often present with multilevel peripheral artery disease. Their physicians must determine which lesions to treat to make the greatest impact on blood flow with the least amount of intervention. The cadence of interventions, and number of reinterventions, is extremely important to these patients. The BTK arteries are often the most severely diseased in patients with CLI, yet current treatment options for BTK lesions are limited and the tools that are available in other parts of the body do not exist for these vessels. While drug-coated balloons (DCB) have shown promise in the femoropopliteal disease, no DCB is yet approved for use in the BTK vessels.

The LUTONIX 014 Drug Coated Balloon Percutaneous Transluminal Angioplasty (PTA) Dilatation Catheter (LUTONIX DCB) is a combination device/drug product incorporating an over-the-wire type PTA catheter with a LUTONIX drug coating on the surface of the balloon. The LUTONIX 014 DCB consists of a combination of a cleared 0.014" guidewire-compatible PTA catheter and the LUTONIX paclitaxel balloon coating, which is the same coating on the approved Lutonix 035 and 018 DCB catheters. Based on the ULTRAVERSE™ 014 (the uncoated PTA version of the LUTONIX DCB), the LUTONIX 014 DCB is designed specifically for smaller arteries. These small vessels require the use of low-profile guidewires and smaller diameter balloons, in contrast to above the knee (ATK) vessels where larger guidewires and balloons are appropriate.

The initial mode of operation for the LUTONIX DCB is mechanical dilation of the artery, as with PTA balloons without a drug coating, including the ULTRAVERSE™ 014 PTA catheter. In addition, however, the paclitaxel-based drug coating is intended to slow the development of intimal hyperplasia, thereby delaying the incidence of restenosis and the need for reinterventions during the time the drug is active in the vascular wall.

The proposed indication for use is as follows:

> 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.

In support of this indication, data from the pivotal IDE trial suggests that the LUTONIX DCB is as safe as PTA without a drug coating (i.e., uncoated PTA, hereafter referred to as "PTA"). Furthermore, data support that this device provides an effective treatment option based on the 6-month primary composite endpoint of patency and amputation-free survival. Data from real-world experience and published literature corroborate the findings of the LUTONIX DCB Trial.

1.2 PTA Background and Unmet Clinical Need

1.2.1 Clinical Context

1.2.1.1 Patients in Need

By 2030 the US prevalence of CLI is forecast to exceed 4 million.[1] CLI is associated with peripheral complications such as ulceration, gangrene, infection, and a 10% to 40% risk of major lower limb amputation at 6 months. The risks are greatest in patients without options for revascularization.[2] The majority (an estimated 60%) of CLI patients suffer from diabetes.[3] Studies by Baser et al. and one by Spreen et al. suggest that the probability of amputation is at least 50% higher in CLI patients with diabetes compared with non-diabetics.[4,5] The life expectance of patients with CLI is poor and significantly worse once a major amputation is necessary.[6-9]

CLI is a manifestation of severe atherosclerosis and represents the end-stage symptom of this relentless, progressive peripheral arterial disease. Although a crucial factor in restoring blood flow, interventions alone may not be adequate to restore flow over time and restoring blood flow may not be sufficient to provide clinical improvements such as wound healing. Lifestyle changes (e.g., smoking cessation, dietary changes, exercise) are critical in reducing the risk of failed revascularization and generalized cardiovascular complications. While restoring blood flow is one factor in addressing risks associated with CLI, many complications, including amputation, are multi-factorial. The multitude of other factors include, but are not limited to, appropriate footwear and wound care.

Caring for CLI patients entails a holistic approach. Treating CLI patients requires a team of experts, including the primary care clinician, the dietician, the interventionalist, the wound care specialist, and the physical therapist. Multiple interventions will likely be needed, with a goal of maintaining blood flow through patent BTK vessels. Newer, percutaneous interventions such as DCB hold the potential to extend the time between reinterventions and reduce the number of reinterventions as compared to PTA. In addition, percutaneous interventions reduce the

procedural risk compared with open surgical revascularization. A broad range of less invasive interventions should be in physicians' tool kit for the comprehensive care of the CLI patient.

1.2.1.2 Current Treatment Options and Limitations

While many devices are available for interventional treatment of ATK arterial occlusive disease, the only on-label endovascular treatment options for patients with BTK lesions are PTA, with or without atherectomy or plaque modification (e.g., scoring balloons), and the TACK Endovascular System (Intact Vascular, Inc.) for the repair of dissections after intervention. As compared to the treatment of superficial femoral or popliteal lesions, BTK lesions are more challenging as they are typically longer, and the vessel diameters are smaller.[10]

Patency rates for uncoated PTA of BTK vessels are marginally acceptable and would benefit from improvements to limit restenosis and occlusion. Due to a lack of other on-label options for treating BTK lesions, physicians use devices designed for larger vessels. This involves off-label use of larger ATK DCB catheters which, even at their smallest diameters, are twice the diameter needed for proper treatment of most BTK arteries. Physicians have also used off-label implantation of coronary drug-eluting stents to treat BTK disease. The availability of an on-label option using a device sized for the smaller BTK arteries can be expected to provide improvement over this off-label use.

In addition to PTA, the other treatment option for BTK lesions is open surgical repair. However, most CLI patients are at high risk of morbidity and mortality with open repair due to their multiple comorbidities.[11] As a result, open surgical repair is not offered to many patients with CLI.[6]

1.3 Product Overview

The LUTONIX 014 Drug Coated Balloon PTA catheter (LUTONIX DCB) is an over-the-wire PTA catheter with low-dose paclitaxel (2 μg/mm^2) on the surface of the balloon. The LUTONIX DCB 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.

1.3.1 Relevant Devices

The BD ULTRAVERSE™ is the uncoated version of the LUTONIX DCB, cleared for peripheral PTA. The indications for use for this device are:

> ULTRAVERSE™ 014 and ULTRAVERSE™ 018 PTA Dilatation Catheters are recommended for use in percutaneous transluminal angioplasty (PTA) of the renal,

popliteal, tibial, femoral, and peroneal arteries. These catheters are not for use in coronary arteries.

The LUTONIX 014 DCB catheter is modified as compared to the approved and commercially available LUTONIX 035 and 018 DCB catheters in that it utilizes a smaller profile guidewire and smaller balloon diameters to treat smaller arteries effectively and safely. As noted above, the purpose of adding the drug coating is to provide an ancillary effect of decreasing the incidence of restenosis.

The relevant indication for use for the LUTONIX 035 and 018 Drug Coated Balloon PTA catheter is for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo, restenotic, or in-stent restenotic lesions up to 300 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm. For hemodialysis access, the indication for the LUTONIX 035 Drug Coated Balloon PTA catheter has an indication for PTA after pre-dilatation, for the treatment of stenotic lesions in dysfunctional native arteriovenous dialysis fistulae that are 4 mm to 12 mm in diameter and up to 80 mm in length. The LUTONIX 035 was approved for marketing in the US in 2014 for femoropopliteal indications, and for dysfunctional arteriovenous dialysis fistulae access in 2017. The LUTONIX 018 Drug Coated Balloon PTA catheter was approved in 2019.

1.4 IDE Study Design and Results

BD conducted a prospective, global, multicenter, single-blind, randomized controlled clinical trial comparing the LUTONIX DCB to PTA in the treatment of obstructive lesions in the distal popliteal, tibial, and peroneal arteries. The trial was conducted under an approved investigational device exemption (IDE) (b) (4) . Patients were randomized 2:1 to treatment with the LUTONIX DCB or a standard PTA catheter. A total of 442 randomized patients (287 DCB and 155 PTA) were enrolled into the LUTONIX BTK IDE Trial from the US (n=275), Europe (n=122), Japan (n=40), and Canada (n=5).

Summary information is provided in this section for safety results at 30 days, 6 months, 12 months, and 36 months. Effectiveness results are provided for 6 months, 12 months and 36 months. These intervals were selected to include the timing of the primary endpoint for safety, as well as the safety and effectiveness at the timing for the primary effectiveness endpoint (i.e., 6 months), at 12 months to be consistent with common reporting practices, and at 36 months to show the longest-term data for the study. Complete data can be found in **Sections 8 and 9** for safety and effectiveness, respectively.

1.4.1 Clinical Study Iterations

Section 5 of this briefing document provides information on the challenges encountered with the conduct of the LUTONIX BTK IDE Trial. The study was designed and initiated at a time when few BTK CLI studies had been attempted. As a result, several major protocol changes were incorporated as lessons were learned:

1) As additional insights were obtained regarding the treatment of patients with CLI and BTK lesions, the primary effectiveness endpoint was changed to 6 months rather than 12 months to be more reflective of the aggressive nature of the disease. The 6-month endpoint is now standard in CLI studies.[12]
2) While agreeing to the 6-month timepoint for the primary endpoint, FDA also emphasized the importance of long-term data.
3) Due to uncertainty with design assumptions, an adaptive sample size design was introduced, allowing for interim analyses.
4) Current knowledge of the disease state suggested that there may be two distinctly different, heterogeneous, restenosis pathologies that exist in below the knee arteries, based on differences in location, concentration, and morphology of calcium observed in these vessels. Therefore, an additional subgroup analysis for the primary effectiveness endpoint was planned for lesions in the proximal segment of the BTK anatomy (refer to **Section 6.5.5**).

With the introduction of the adaptive design, to control the type I error rate for the study the threshold for the one-sided p-value was reduced from 0.025 to 0.017. With the addition of the subgroup analysis, the threshold was further reduced to 0.0085.

The complexities of patients with CLI and BTK disease explained a slow enrollment rate in the study. As a result, enrollment was terminated earlier than originally planned. As such, some statistical power was lost for detection of the primary effectiveness endpoint.

1.4.2 Safety

The primary safety endpoint was freedom from a major adverse limb event (MALE) or perioperative all-cause mortality through 30 days post index procedure. MALE was defined as the composite of above-ankle amputation or major reintervention, where major reintervention included placement of a new bypass graft, a jump/interposition graft revision, or thrombectomy/ thrombolysis of the index limb involving a BTK artery. This endpoint was met. The proportion of patients that did not have a safety event, as defined above, through Day 30 was 99.3% in the DCB arm, and 99.4% in the PTA arm (non-inferiority $p<0.0001$ single-sided).

Major Adverse Cardiovascular Event (MACE) was defined as any myocardial infarction, stroke, or all-cause death. All MACE events through 12 months have been adjudicated by a Clinical Events Committee (CEC). MACE rates were low in both treatment arms and similar through 36 months: 7.9% DCB vs. 6.0% PTA at 6 months, 11.1% DCB vs. 10.0% PTA at 12 months, and 27.5% DCB vs. 26.3% PTA at 36 months.

The freedom from major amputation rate was notably high (i.e., beneficial) for both treatment arms for the duration of the study, by binary analysis, 98.5% DCB vs. 97.9% PTA at 6 months, 97.2% DCB vs. 97.7% PTA at 12 months, 93.1% DCB vs. 90.5% PTA at 36 months. At 36 months there was a treatment difference of 2.5% (95% CI: -5.2%, 10.3%) in favor of DCB. The low rate of major amputation reflects the eligibility criteria; criteria chosen to exclude patients with significant comorbidities that might preclude survival through the protocol-specified follow-up.

The unplanned minor amputation rate was similar for the treatment arms (12.0% DCB vs. 12.9% PTA at 6 months, 14.8% DCB vs. 18.5% PTA at 12 months, and 24.2% DCB vs. 36.1% PTA at 36 months).

Importantly, all-cause death rates were similar between treatment arms at all study time points (96.8% DCB vs. 96.0% PTA at 6 months, 92.4% DCB vs. 92.4% PTA at 12 months, 81.0% DCB vs. 81.0% PTA at 36 months) The 36-month freedom from all-cause death 81.0% in both DCB and PTA arms (p=0.946) as analyzed by the Kaplan-Meier with a 3-year Hazard Ratio of 1.04 (95% CI: 0.631-1.711). No difference in safety, including mortality, was demonstrated through three years. The relatively low mortality rates reflect the inclusion/exclusion criteria designed to assure that a high proportion of patients would reach the follow-up time points. The sponsor has modified the protocol to collect vital status through 5 years.

1.4.3 Effectiveness

1.4.3.1 Trial Background

The primary effectiveness endpoint was defined as freedom from a composite of above-ankle amputation, target lesion occlusion, and CD-TLR through 6 months. This was the first IDE trial of CLI patients. Designed to evaluate the effects of paclitaxel-enhanced angioplasty, the study excluded confounders, such as patients with advanced infection, ulceration, and gangrene. Such patients carry an increased risk of major amputation irrespective of successful revascularization.

Narrowing the indications to exclude those patients with severe gangrene, proximal wounds, and infection, where even successful revascularization might not prevent limb loss, decreased the observed rate of major amputation. In effect, this rendered the composite effectiveness

endpoint (major amputation, CD-TLR, or vessel occlusion) into essentially a primary patency endpoint, driven by ultrasound or angiography-assessed occlusion and clinically driven reintervention. An equally important point to remember is that patients who experienced a patency failure in this trial received prompt and successful reintervention, in part due to the intensive follow-up typical of IDE trials and the skills of the dedicated clinicians who participate in those trials. Timely and successful reintervention no doubt blunted any major amputation signal that might otherwise have resulted from the increased early loss of patency in the PTA arm.

1.4.3.2 Effectiveness Results

The primary effectiveness endpoint is defined as freedom from a composite of above-ankle amputation, target lesion occlusion, and CD-TLR through 6 months. This endpoint can also be described as a combination of limb salvage and primary patency.

The effectiveness analyses were based on pathways, not patients. A patient could have interventions in more than one vessel. If the vessels were in series, they counted as one pathway. If not, they were counted as separate pathways. A random effect model was used to account for correlation within patients.

There was a 10.5% difference in the composite primary effectiveness endpoint in favor of DCB at 6 months (74.7% DCB vs. 64.2% PTA, with a p-value of 0.0222). The primary effectiveness endpoint analysis by Kaplan-Meier (KM) showed benefit for the DCB with 14.4% net difference (85.8% DCB vs. 71.4% PTA). Due to study design changes (see **Section 1.4.1**), a p-value of 0.0085 had to be reached to claim statistical superiority for the primary effectiveness endpoint. Noting the p value of 0.0222, the primary endpoint was not met.

The above-the-ankle amputations were numerically similar between the groups (see **Section 1.4.2**). Thus, the measured difference in the primary endpoint was driven by patency measures, including reduced CD-TLR. The number of reinterventions through 6 months was lower in the DCB arm; 36 DCB and 36 PTA, with 2:1 randomization for DCB:PTA. A post hoc analysis comparing the mean time to the first reintervention showed a difference of 73.7 days between the DCB group and the PTA group.

By 12 months the difference in the composite primary effectiveness endpoint analyzed by a binary endpoint by pathway was not maintained (51.0% DCB vs. 56.8% PTA at 12 months and 27.6% DCB vs. 29.0% PTA at 36 months). Correspondingly, the difference in freedom from CD-TLR as a binary endpoint was not maintained (76.9% DCB vs. 76.3% PTA at 12 months and 56.7% DCB vs. 52.5% PTA at 36 Months). In contrast to vital status which can be more easily ascertained, there are challenges with the interpretation of longer-term effectiveness

results. Challenges relate to the amount of missing data due to withdrawal and loss-to-follow-up, with potential differential follow-up by randomized group, and differences in baseline characteristics for those missing/not missing endpoint data.

Although patients in both study groups showed improvement, differences were not demonstrated in infection rate, major amputations, wound healing, or quality of life based on measurement tools through the duration of the study.

The longer duration between reinterventions during the early follow-up period is something that is noticeable and meaningful to patients, compared with patency – a measure that is, in part, an imaging finding. Thus, there is benefit in reducing the inconvenience and risk associated with interventions for this patient cohort with a high number of comorbidities.

1.5 FDA Guidance on Determination of Benefit Risk

The sponsor has fully explored the benefit-risk assessment as per the FDA's Guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications" (August 30, 2019). Details of this can be found in **Section 13.5**. Per the Benefit-Risk Guidance, "benefit should be considered based on the assessment of the data, whether or not the results are statistically significant." Additionally, "benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate." For the LUTONIX DCB Trial, the surrogate is the reduced rate of reinterventions through 6 months and the longer time to first reintervention.

1.6 Benefit-Risk Summary Analysis

There is a need for more effective devices to restore blood flow to aid in the treatment of patients with CLI. This need is evidenced by the off-label clinical use of drug coated balloons to treat below-the-knee lesions. The LUTONIX 014 DCB was developed to fill this need by augmenting the marketed BD ULTRAVERSE™ PTA catheter with a drug coating.

Patients benefit from PTA which provides mechanical dilation of blood vessels. The LUTONIX DCB is a PTA balloon. The benefits associated with PTA are augmented when the antiproliferative drug therapy is added.

Early DCB benefits in the primary effectiveness measure at 6 months (binary point estimate 10.5%, Kaplan Meier estimate 14.4%) were associated with a lower reintervention rate (36 TLRs in the DCB arm and 36 TLRs in the PTA arm through 6 months, with 2:1 randomization for DCB:PTA). There was a longer time to the first reintervention for the DCB group (73.7 additional days). The patency benefits realized at 6 months diminished over time, with no difference observed by the 1-year follow-up interval. Though not sustained in the long-term,

the short-term benefits attributable to the presence of the drug on the balloon are important to patients with CLI considering their limited life expectancy.

Improvements as compared to baseline were observed in infection rates, major amputations, wound healing, and quality of life using available measurement methodology, in both treatment arms. Differences between the treatment groups were not demonstrated as the study sample size was based only on power for the primary endpoints.

The risks associated with the LUTONIX DCB are consistent with those for PTA, that is, the presence of the drug on the balloon was not associated with an increased risk of any kind during the evaluation period.

The level of uncertainty associated with the trial data is expected for a study of patients with a degenerative disease such as CLI.

In summary, the purpose of balloon angioplasty is to restore blood flow. The data suggest that the LUTONIX DCB provides improved blood flow at 6 months compared with PTA; an effect which gradually diminishes such that there is no difference at the 1-year follow-up interval. Although the performance of the device was evaluated through 36 months, a longer-term patency benefit was not expected due to the complexity of the patient population and the transition to standard of care for reinterventions (i.e., the DCB could only be used for the index intervention and reinterventions were performed with PTA or other non-DCB modalities). As the device was shown to be as safe as PTA during the evaluation period, the benefits outweigh the risks.

1.7 Request for Panel Consideration

The Company requested FDA bring this PMA to panel in order for FDA to seeks insights from the Panel on BD's belief that the data from the IDE trial and the supportive data from other studies of the LUTONIX DCB in BTK arteries (see **Section 11**) provide a reasonable assurance of the effectiveness of the device. In sum, BD believes:

- The 10.5% advantage of DCB over PTA at 6 months for the primary effectiveness endpoint ($p = 0.0222$) was clinically meaningful though not statistically significant.
- Sufficient data are not available to allow for a meaningful long-term comparison of patency. Nevertheless, a long-term improvement in patency would not be expected given the progressive, degenerative nature of the atherosclerotic disease.
- The patency benefit in the first 6 months, associated with clinical improvements in time to the first intervention and reintervention rates at 6 months as compared to PTA are

sufficient to demonstrate a reasonable assurance of effectiveness and quality of life benefits for CLI patients.

- The supportive clinical information described in **Section 11** corroborates the findings from the IDE trial and supports the benefit of the Lutonix DCB.
- Given the observed safety of the device, equivalent to PTA in all aspects during the evaluation period, the benefits outweigh the risks.

2 BACKGROUND ON CRITICAL LIMB ISCHEMIA

Summary

- Patients with below-the-knee lesions suffer with severe pain at rest and fear of amputation.
- Today, there are no treatment options that provide consistent improvement of blood flow within the critical early time frame to disrupt a relentless cascade of tissue loss, progressing to amputation.
- CLI currently afflicts 2 to 3.4 million of those with PAD. By 2030 the US prevalence of CLI is forecast to exceed 4 million.
- CLI is associated with peripheral complications such as ulceration, gangrene, infection and a high risk of lower limb amputation estimated in 10%–40% of patients at 6 months, especially in non-treatable patients.
- The LUTONIX DCB offers physicians an on-label safe option that may provide a longer time to reintervention which is crucial for patients with CLI.

2.1 Overview of Critical Limb Ischemia

Critical limb ischemia (CLI) represents the most advanced form of lower extremity peripheral artery disease (PAD).[a] CLI is characterized by rest pain, non-healing wounds, and gangrene, each most commonly located in the foot.[13] CLI currently afflicts 2 to 3.4 million patients and the US prevalence is expected to exceed 4 million by 2030. In an analysis of 72,199 Medicare beneficiaries, the mean age of patients with CLI was 74±12 years and 52% were men.[2] The life expectancy of patients with CLI is short, with 20% of patients dying within 6 months after diagnosis and 50% within 5 years.[14] This high rate of mortality may be related to the generalized atherosclerosis and systemic cardiovascular diseases often found in CLI patients, including coronary artery disease, cerebrovascular arterial disease, and renal insufficiency.[7,15]

The peripheral complications of infection, ulceration, and gangrene underlie the high risk of lower limb amputation, estimated to be necessary in 10% to 40% of patients at 6 months.[3] CLI is typically associated with reduced quality-of-life (QOL), principally related to diminished ambulatory status, pain, and nonhealing wounds. The wounds require treatment such as antibiotics, local wound care, and a non-weight bearing status.[16] Irrespective of local wound

[a] The term "Critical limb threat ischemia" or "CLTI" is also used in the field. For the purposes of this document, the acronym CLI is used but is synonymous with CLTI.

care, the development of infection, extensive tissue loss, and gangrene prompt the need for major amputation unless adequate arterial perfusion can be restored.

CLI patients with diabetes are at a significantly higher risk of major amputation than CLI patients without diabetes. Studies by Baser et al. and Spreen et al. suggest that the probability of amputation is at least 50% higher in CLI patients with diabetes versus those without this comorbidity.[4,5] This increased risk is associated with a higher prevalence of rigid, calcific, incompressible (ABI >1.4) calf vessels, and more severe ischemia at presentation. It is estimated that up to 85% of diabetic foot-related amputations could be prevented with prompt intervention and education of individuals about proper foot care. Wulkich et al. conducted a study aimed to identify the most-feared complications of diabetic patients, finding that patients with diabetic foot pathology feared major lower-extremity amputation more than death.[17]

2.2 Current Treatment Options and Limitations

Prompt revascularization with endovascular or open surgical procedures is indicated in CLI patients to prevent limb loss, maintain limb function, and relieve rest pain. A meta-analysis by Abu Dabrh et al. found that 22% of untreated CLI patients will require major amputation within the first year after diagnosis.[2] A review of claims data by Armstrong and colleagues documented a two-fold higher risk of major amputation or inpatient death in CLI patients treated with conservative therapy compared to open surgical or endovascular intervention.[18] For these reasons, revascularization by either surgical or endovascular means is attempted in at least 50% of the CLI patients, increasing to greater than 90% at specialized interventional centers.

Despite reinterventions, approximately 30% of patients with CLI will undergo major amputation during their lifetime. Rehospitalization of CLI patients is also common and up to 60% are readmitted within 6 months.[8] Major amputation may be the only option when less invasive treatment cannot be used or has failed.

Minor amputations such as single toe amputations or transmetatarsal amputations of the forefoot are often required for tissue loss as part of a planned, staged approach. Revascularization is performed first, followed by minor amputation once adequate distal perfusion has been restored.

The choice of endovascular or open surgical revascularization depends on the severity of ischemia. The Trans-Atlantic Societal Consensus (TASC II) assessment of anatomic complexity of disease provided recommendations for the type of intervention, endovascular or open surgical, based on the anatomy of the arterial occlusive disease.[19] Balloon angioplasty continues to be the most common endovascular intervention for BTK CLI. However, the long-

term patency after balloon angioplasty remains suboptimal. In a recent meta-analysis of 6,769 patients treated with standalone PTA for BTK disease, primary patency was 63.1% at 1 year. In this same study, 14.9% of patients necessitated a repeat vascularization procedure, 14.9% underwent amputation, and 15.1% of these patients died (all-cause mortality).[20]

Specific patterns of the disease may require open surgical revascularization. However, there are added risks of open surgery, including perioperative myocardial infarction, stroke, and death. Open surgical options are often contraindicated in these high-risk patients with multiple comorbidities.

In this regard, less invasive interventions such as the LUTONIX DCB hold the potential for an increased time to reintervention over other endovascular interventions. With limited life expectancy, even short-term improvements can be meaningful to the patient and their families.

2.3 Regulation of BTK Devices and Combination Products

Notably, almost all devices used to treat peripheral vascular lesions are regulated as Class II devices, based on their risk profile and amount of regulatory oversight needed to ensure safety and effectiveness throughout the device lifecycle. Examples include cutting balloons, lithotripsy, PTA catheters, and orbital atherectomy catheters. This contrasts with coronary interventions which generally have all been regulated as Class III devices based on their risk profiles, with certain PTCA catheters having been reclassified to Class II around 2010. Combination products, including the LUTONIX DCB, are regulated as Class III devices based on their risk profiles, with evidence needed to demonstrate that the drug does not adversely impact safety, and to ensure their safety and effectiveness throughout the product life cycle. An example of the additional regulatory oversight needed are the PMA approval and reporting requirements associated with manufacturing changes.

The differences in regulatory classification are associated with some differences in clinical study evidence. For example, the initial clearance of the first lithotripsy catheter for treatment of peripheral lesions was based on a non-randomized study of 95 patients. This distinction is important as there are limited randomized clinical studies on current treatment options for peripheral revascularization.

2.4 Unmet Medical Need

Current treatment options provide a temporary disruption of the relentless cascade of ischemia, tissue loss, and progression to major amputation. Repeat interventions are needed for most patients, and reinterventions with PTA are associated with a high rate of mortality and major amputation. A review of 16,800 surgical and endovascular procedures at California nonfederal

hospitals between 2005 and 2013 evaluated amputation-free survival and time to reintervention for open versus endovascular treatments.[21] The median time to reintervention for patients in the "endovascular-first" group was 4 months (IQR=1.7–12.6). The endovascular first approach was associated with higher rates of reintervention (hazard ratio, 1.19; 95% CI 1.14–1.23).

Rates of recurrence of CLI after endovascular intervention in patients with diabetic foot ulcers has been reported to be high.[22] Seventy-four of 304 patients (24.3%) needed repeat PTA. The mean time to repeat PTA was 3.5 ± 0.6 months. When compared with patients who did not require repeat PTA, those with reinterventions had a lower rate of healing (28.5% vs. 71.9% $p = 0.0001$), higher rate of ulcer recurrence (20% vs. 10.3% $p = 0.03$), major amputation (24.3% vs. 4.3% $p = 0.0005$), and death (33.3% vs. 7.9% $p = 0.002$). In a review of CLI patients initially treated with four different modalities, the 4-year rate of amputation or death was 54.7% when the initial treatment was PTA, compared with 49.3% after atherectomy, 51.4% after surgical bypass, and 53.7% after stent placement ($p<0.05$ for pairwise comparisons). Among Medicare beneficiaries who received PTA, failure was first manifest between 90 and 180 days. At 12 months, the highest rates of mortality were among patients treated with PTA followed by patients who received surgical bypass. Also, at 1 year the highest rate of major amputation was among patients who received PTA, increasing from 3.8% at 6 months to 5.3% at 1 year, whereas surgical bypass patients had a 5.2% rate of major amputation at 6 months and 7.1% at 1 year (pairwise comparison $p<0.054$). These observations from the literature suggest that PTA, while better than observation alone, is associated with suboptimal results. The availability of a new therapy with fewer early reinterventions would benefit patients with CLI and potentially result in improved patient outcomes.[2]

Drug coated technologies may enhance current uncoated angioplasty balloons by inhibiting smooth muscle cell proliferation and maintaining patency for longer time periods. In the US, the smallest peripheral DCB has a 4 mm diameter, almost twice as large as BTK arteries, commonly 2 to 3 mm in diameter. As well, drug eluting stents (DES) approved for percutaneous coronary interventions have been used off-label in the BTK setting. Coronary DESs, however, are balloon-expandable and prone to crushing when used in the periphery.[23] Further, coronary DES lengths are suboptimal for longer BTK lesions. A summary of DES use in the BTK arteries is included in the Appendix (**Section 14.9**).

In summary, in conjunction with proper wound care, appropriate pharmacotherapy, lifestyle modification (smoking cessation, diet modification, and exercise), and appropriate footwear, the LUTONIX DCB has the potential to solve an unmet need – offering physicians a safe, on-label alternative to PTA to restore arterial perfusion and delay BTK artery reocclusions and reinterventions. The initial 6 months of treatment is critical for tissue healing, gait restoration,

and increased mobility - all of which can be very important in CLI patients with a markedly reduced life-expectancy due to their concurrent medical comorbidities.[24]

3 PRODUCT DESCRIPTION

Summary

- The LUTONIX 014 Drug Coated Balloon PTA catheter is an over-the-wire percutaneous transluminal angioplasty (PTA) catheter with low-dose paclitaxel (2 µg/mm^2) on the surface of the balloon.
- The base balloon for the LUTONIX 014 DCB catheter is the BD ULTRAVERSE™ 014 PTA Dilatation Catheter which is indicated for use in percutaneous transluminal angioplasty (PTA) of the renal, popliteal, tibial, femoral, and peroneal arteries.
- The proposed indication for the LUTONIX 014 DCB is 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.
- The total paclitaxel dose is below or within the dose for the LUTONIX 035 and 018 Drug Coated Balloon PTA catheters, approved by FDA in 2014 and 2018, respectively.
- The LUTONIX 014 DCB catheter is different from the LUTONIX 035 and 018 DCB catheters in that it has a smaller profile guidewire and smaller balloon diameters to treat smaller arteries effectively and safely (2.0-4.0 for 014 vs. 4.0-7.0 for 035 and 018).

3.1 Proposed Indication

BD is seeking the following indication:

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.

3.2 Device Description

The LUTONIX 014 Drug Coated Balloon PTA catheter (LUTONIX DCB) is an over-the-wire percutaneous transluminal angioplasty (PTA) catheter with low-dose paclitaxel (2 µg/mm^2) on the surface of the balloon (**Figure 3-1**). The LUTONIX DCB 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. The base balloon is the BD ULTRAVERSE™ 014 PTA Dilatation Catheter which is indicated for use in percutaneous transluminal angioplasty (PTA) of the renal, popliteal, tibial, femoral, and peroneal arteries.

There are radiopaque marker bands delineating the working length of the balloon. These are located under the proximal and distal ends of the balloon to facilitate fluoroscopic visualization of the balloon during delivery and placement. The proximal portion of the catheter includes an inflation female luer lock hub and a guidewire female luer lock hub. Each product is packaged with a balloon protector that has been positioned over the balloon and a disposable wire lumen stylet, both of which are to be removed prior to use.

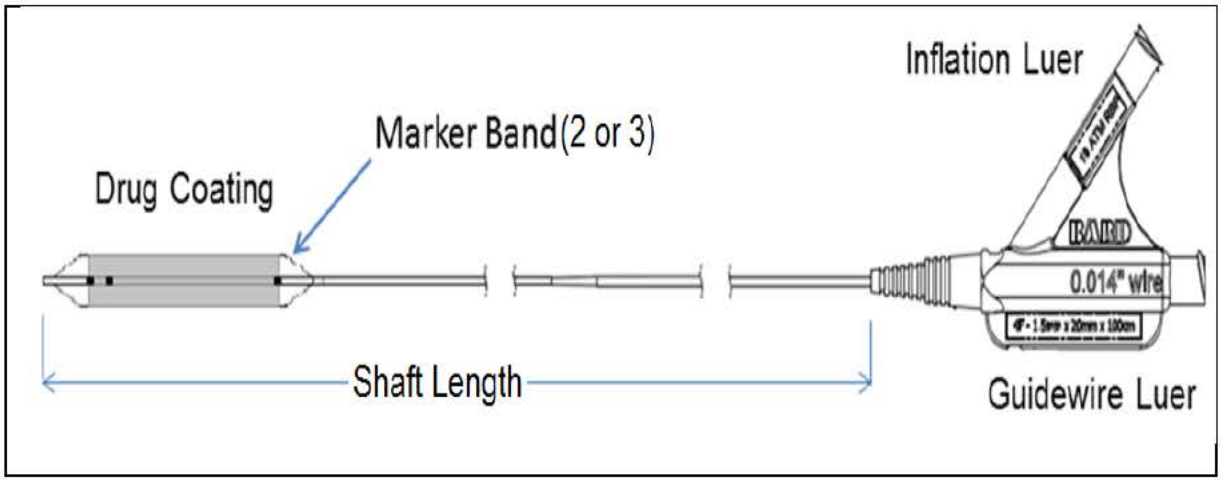

Figure 3-1. LUTONIX 014 DCB (Model 9005)

The balloon size range covered in the PMA Application is shown below in **Table 3-1**. The LUTONIX DCB is available in shaft lengths of 100 cm, 130 cm and 150 cm and is compatible with 0.014" guidewire.

Table 3-1. Balloon Size Matrix

Balloon Diameter	Balloon Length					
	40 mm	60 mm	80 mm	100 mm	120 mm	150 mm
2.0 mm	X	X	X	X	X	X
2.5 mm	X	X	X	X	X	X
3.0 mm	X	X	X	X	X	X

Table 3-1. Balloon Size Matrix

Balloon Diameter	Balloon Length					
	40 mm	60 mm	80 mm	100 mm	120 mm	150 mm
3.5 mm	X	X	X	X	X	X
4.0 mm	X	X	X	X	X	X

3.3 Paclitaxel

The LUTONIX drug coating contains paclitaxel, an anti-proliferative drug, as the active pharmaceutical ingredient (API), and excipients with known history of safety with human intravenous use - polysorbate, sorbitol and methanol residual solvent. The balloon is coated with a constant 2 µg/mm^2 of paclitaxel and the total dosage of paclitaxel per balloon size is correlated to the balloon surface area and is shown in **Table 3-2** below. The paclitaxel released during the short inflation time inhibits restenosis.

Table 3-2. Total Drug Dosage (Paclitaxel) by Balloon Size

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

Notably, the LUTONIX DCB has the same dose of low-dose paclitaxel (2 µg/mm^2) as the commercially available LUTONIX 035 and 018 DCBs. As such, the total dosage (mg) for the LUTONIX 014 DCB is lower than, or within the same dosage range as, the LUTONIX 035 and 018 DCB catheters.

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

Table 3-3. Paclitaxel Drug Substance Nomenclature and Structure

Nomenclature	
United States Adopted Name (USAN)	Paclitaxel
Chemical Name:	(2aR,4S,4aS,6R,7E,9S,11S,12S,12aR,12bS)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-7,11-methano-1H-cyclodeca[[d]benzoxetine-6,9,12,12b-tetrayl 6, 12b-diacetate 12-benzoate 9 -[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate] or 5β,20-epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate]
CAS Registry Number	33069-62-4
Compendial Name (USP):	Paclitaxel
Structure	
Molecular Formula	$C_{47}H_{51}NO_{14}$
Relative Molecular Mass	M_r: 854

3.4 Circulatory System Devices Panel Review of Paclitaxel Device for SFA

The use of paclitaxel was the subject of the June 19-20, 2019, FDA meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee to discuss and make recommendations on the topic of a potential late mortality signal after treatment with paclitaxel-coated balloons and paclitaxel-eluting stents to treat PAD in the SFA. The panel concluded there was a late mortality signal associated with the use of paclitaxel-coated devices to treat femoropopliteal PAD. The Panel and the FDA agreed that the magnitude of the signal 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.

The Panel determined, and the FDA concurred, that additional clinical study data are needed to fully evaluate the late mortality signal. The Panel also concluded that the benefits of paclitaxel-

coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks.

Thereafter, a recent interim report of the SWEDEPAD randomized trial of endovascular therapy in 2289 patients with lower extremity peripheral arterial disease found no increase in mortality with DCB compared to PTA.[25] Through a mean follow-up of 2.5 years, 293 of 1149 patients (25.5%) who were assigned to the DCB group died, compared with 281 of 1140 patients (24.6%) who were assigned to the PTA group (hazard ratio, 1.06, 95% CI 0.92, 1.22). In the CLI subset, death occurred in 33.4% and 33.1% of the DCB and PTA treated patients with CLI. arms, respectively.

Regarding the LUTONIX 014 DCB, there is not a mortality signal, with no safety concerns raised by FDA as part of the PMA review.

3.5 Mechanism of Action

As an angioplasty catheter, the primary mode of action for the LUTONIX DCB is achieved through the mechanical dilatation of the vessel during the balloon inflation. The drug delivery during the dilatation is designed to provide an ancillary benefit of reducing restenosis.

The mechanism by which neointimal growth is inhibited by the addition of the drug coating has not been established. In general, paclitaxel is a lipophilic, anti-mitotic agent that prevents microtubule destruction, which has been reported in prior studies to prevent migration/proliferation of smooth muscle cells, inflammatory cells and fibroblasts as well as inhibit the secretion of extracellular proteins. Several studies in animal models have also shown that paclitaxel applied locally reduces restenosis by inhibiting smooth muscle cell proliferation and neointimal hyperplasia.

The LUTONIX DCB catheter is a BD ULTRAVERSE™ 014 PTA Dilatation Catheter, modified to add the drug coating. The device is similar to the LUTONIX 035 Drug Coated Balloon PTA Catheter, approved by the FDA in 2014, and the LUTONIX 018 Drug Coated Balloon PTA Catheter, approved by the FDA in 2019, utilizing a smaller profile guidewire and smaller balloon diameters for the indicated BTK arteries.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The LUTONIX 014 Drug Coated Balloon was CE Marked in 2013 and is commercially available in over 40 countries for treatment of stenotic or obstructive vascular lesions in the below the knee arteries.
- While there were no questions raised by FDA regarding the safety of the LUTONIX DCB for the evaluation period, FDA has had questions regarding the interpretation of the effectiveness data regarding the device, ultimately issuing two Not Approvable Letters.
- Upon the request of the company, FDA agreed to convene this advisory committee meeting to gain expert input on the nature and magnitude of the benefit of the device as part of the PMA review process.

4.1 Pre-Clinical Studies and Pharmacokinetics

Safety, and Safety Margin and Pharmacokinetic (PK) animal studies were conducted with the LUTONIX DCB in accordance with FDA's Good Laboratory Practices (GLP) regulations (21 CFR Part 58). Safety and safety margin studies out to 180 days indicated no long-term local or systemic toxicity. Even at a total dose of 37 mg paclitaxel which is approximately 10x the dose of the DCB with the longest length and diameter (3.8 mg), there were no clinically significant findings in the treated arteries nor downstream tissue effects at 90 days.

In pharmacokinetic studies in porcine femoral arteries for 60 days, the treated artery paclitaxel mean concentration varied from 10.4 µg/g tissue at 1 hour to 47.3 ng/g at 60 days, while plasma drug mean concentration decreased from 5.94 ng/g three (3) minutes after the procedure to 0.0173 ng/g at 7 days and non-measurable at all subsequent time points, resulting in mean C_{max} 5.94 ng/mL, Area Under the Curve (AUC_{last}) 1.70 ng*d/mL and $t_{1/2slow}$ 0.914 days.

The effect of paclitaxel in arterial tissue, as well as downstream tissue and systemic toxicity were evaluated using histopathology of porcine arteries treated with PTA control, and the LUTONIX DCB formulation (2 µg/mm^2). The treated arteries, downstream vascular beds, and organs were assessed histologically at 28, 90, and 180 days. In the treated artery, at 90 days, the drug effect peaked, as reflected by medial smooth muscle cell (SMC) loss, but was still observed at 180 days, as compared to PTA control. In parallel to medial SMC loss, proteoglycan, and collagen accumulation, an integral aspect of arterial repair after injury from paclitaxel, increased with time and peaked at 90–180 days, suggesting sustained drug effects

and healing within the artery through these periods. Furthermore, no evidence of ischemia from downstream emboli or systemic toxicity were observed.[26]

4.2 Investigational Device Exemption (IDE)

To begin the process of bringing the LUTONIX 014 DCB to the US market, BD submitted an Investigational Device Exemption (IDE) to FDA in January 2013. In April 2013, FDA granted conditional approval to begin the BTK IDE clinical trial. Patient enrollment in the LUTONIX BTK IDE TRIAL began on June 3, 2013 and was closed on January 18, 2018. The last patient was randomized and enrolled on December 12, 2017.

During the conduct of the IDE there were lessons learned that resulted in changes in the clinical study protocol, which were approved by FDA in IDE Supplements (see **Section 6** for additional information). The Sponsor was blinded to the study results at the time of these changes. Some of these changes affected the primary effectiveness evaluation:

1) The primary effectiveness endpoint was modified to 6 months (previously 12 months),
2) An adaptive sample size design was incorporated, and
3) An analysis by proximal segment length was added.

Changing the primary endpoint from 12 to 6 months reflected an evolution in the understanding of the aggressive nature of CLI after the study was initiated. This change is consistent with the importance of early benefits in the management of this challenging disease, with the 6-month endpoint being the best practice for CLI trials.[24] This modification did not affect the collection of longer-term data which was still found important to characterize the benefits and risks of the device; however, the duration of follow-up was changed from 3 to 5 years.

The adaptive design was pursued due to the slow enrollment of the study. In addition, literature reports suggested that two restenosis mechanisms may occur in BTK arteries, each related to increasing arterial calcium content with progression distally in the arterial tree.[27] The first restenotic mechanism is early recoil,[28] an effect hypothesized to be more evident in the less calcified, proximal BTK arteries. The second mechanism is classical intimal hyperplasia after angioplasty, possibly more prominent in the more calcified distal vessels. An attempt to address this issue was introduced with a subgroup analysis of the proximal segment of the treated vessels. In retrospect, this was not an issue but as a result of the adaptive design and proximal segment analysis, a p-value of 0.0085 had to be reached to claim statistical superiority for the primary effectiveness endpoint to preserve the study type I error rate.

4.3 Premarket Approval (PMA)

The study was terminated early due to slow enrollment. In March 2018, the first Premarket Approval (PMA) module was submitted to FDA. The final PMA module (clinical module) was submitted to FDA in October 2018.

In total, three Clinical Study Reports were generated and submitted to FDA. As part of the routine process of monitoring, collecting, and cleaning of accruing longer-term data, updated data sets were included. The updated data sets all utilized the same endpoints and primary analysis methods. Differences in results were strictly due to the updated underlying data. There were no changes in the study conclusions based on these changes.

In March 2019, the Office of Product Evaluation and Quality (OPEQ) determined that outside feedback was necessary prior to the determination made resulting in the first Not Approvable Letter (June 2019). Rather than a public Circulatory Systems Devices Panel meeting, the OPEQ preferred an Agency Directed Assignment ("Homework Assignment") using two panel members. It is important to note that BD was not provided with details of the assignment.

The feedback FDA received from the homework assignment was reflected in the Not Approvable Letter issued by FDA in June 2019. The primary basis for the Not Approvable Letter was the failure to meet the pre-specified primary effectiveness endpoint of superiority of the DCB vs. PTA at 6 months for the "all flow pathway" analysis (10.2% difference, p=0.0273; p<0.0085 needed for significance).[b] Specifically, the FDA stated, "Though sufficient safety has been demonstrated at early time points, FDA does not agree that the totality of the data adequately demonstrate effectiveness of the LUTONIX DCB in the BTK vasculature, and thus a favorable benefit-risk profile, for this use for the following reasons." In summary, the reasons cited by the agency were:

1) The primary effectiveness endpoint did not meet the statistical success criteria.
2) The "proximal lesion segment" analysis does not provide sufficient evidence.
3) The numeric benefit at 6 months is not sustained at 12 months and beyond and there is a "patency disadvantage compared to the control device at these later time points."
4) The patency improvement at 6 months does not clearly correlate with improved clinical outcomes, "such that a clear benefit is established by adding a non-proliferative drug therapy to improve the angioplasty outcome."

[b] Results reflect an analysis based on an earlier close of the database.

5) Improvement in wound healing cannot be demonstrated. “There was no meaningful improvement observed for the treatment group for any of the remaining secondary endpoint results.”

The FDA recommended BD conduct an additional prospective clinical trial and suggested considering “whether any additional analyses of available data demonstrate a sufficiently favorable benefit in clinically meaningful patient subpopulations or outcomes.”

Upon receipt of the Not Approvable Letter, BD met with FDA to discuss their proposed response to the cited deficiencies which included supportive clinical data from the LUTONIX Global BTK Registry and the Society of Vascular Surgery (SVS) Vascular Quality Initiative (VQI) registry, as well as additional information and analyses on secondary endpoints in the IDE trial.

In a second Not Approvable Letter dated August 19, 2020, the FDA communicated that the agency had reviewed all the available data and analyses provided to support the effectiveness of the device and continued to believe that a reasonable assurance device effectiveness had not been demonstrated. In summary:

1) The primary endpoint did not reach statistical significance and the robustness of the treatment effect is not demonstrated (consistent with items #1 and 3 above).

2) There are limitations in the supportive clinical information that preclude using these sources to demonstrate effectiveness.

3) Improvements in cumulative TLR and unplanned minor amputations are “clinically important” but not sufficient alone to demonstrate a reasonable assurance of device effectiveness.

The FDA again suggested that a new, prospectively designed clinical trial be conducted. Of note, FDA's current recommendations in study design focus on the same safety and effectiveness measures used in the LUTONIX BTK IDE; however, a new study may have similar enrollment challenges as seen in the LUTONIX BTK IDE Trial.

While there are no existing concerns on safety based on the available data, FDA continues to have questions regarding the interpretation of the effectiveness data regarding the device.

Noting that conducting an additional, pre-approval, prospective clinical trial is not feasible, following the second Not Approvable Letter, the company requested, and FDA agreed, to convene this advisory panel meeting to gain expert input on the benefit-risk profile of the device.

4.4 Marketing History

The LUTONIX 014 Drug Coated Balloon, the subject of this PMA, was CE Marked in 2013 and is commercially available in over 40 countries, including but not limited to Canada, Europe, Mexico, Argentina, Singapore, Taiwan, Korea, and Australia, for treatment of stenotic or obstructive vascular lesions in the below the knee arteries for the purpose of improving limb perfusion and decreasing the incidence of restenosis. No LUTONIX DCB product lines have been withdrawn from the market in any country for any reason.

5 EVOLUTION OF THE CLINICAL TRIAL DESIGN

Summary

- The most significant changes in the clinical trial design were:
  - Updating the primary endpoint assessment to be performed at 6 months (rather than 12 months),
  - Implementation of an adaptive design for sample size re-estimation, and
  - The inclusion of a subgroup analysis for proximal segments.
- The Sponsor remained blind to the study results when the changes were made.
- These changes led to changes in the threshold for success.

The LUTONIX BTK IDE pivotal trial was designed and initiated at a time when few BTK CLI studies had been attempted. There were several design features that were required to satisfy the requirement of stakeholders including investigators, regulators, and the study participants themselves. The major study design needs can be summarized as follows:

- A need for reasonably long-term follow-up.
- Enrollment of a population with a reasonable likelihood of surviving through follow-up, despite the high rate of comorbidities common in patients with CLI and BTK arterial disease. Patients with severe renal insufficiency, acute limb ischemia, or recent myocardial infarction or stroke.
- A need to subdivide the CLI study population for assessment of variables that might confound safety and effectiveness evaluations, excluding wounds in certain locations or above a certain size, infected wounds, or target lesions with insufficient in-line outflow to the foot.

With consideration of these constraints and their limitations on enrollment, multiple changes were implemented throughout the course of the trial. Each of the changes were made in a blinded manner, without any knowledge of interim study outcomes and based only upon knowledge gained from new literature. A summary of the most important protocol versions is provided in Appendix **Section 14.2**. The most significant changes were that the primary endpoint assessment was updated to be performed at 6 months (rather than 12 months), an adaptive design for sample size was implemented, and a subgroup primary effectiveness analysis was introduced, the latter

two changes resulting in a strict threshold for success of the primary effectiveness endpoint (i.e., p-value of 0.0085) to control the type I error rate.

The primary endpoint assessment was changed from 12 months to 6 months to reflect the aggressive nature of CLI disease and to align with evolving changes in the then current standard for BTK studies. FDA concurred with this change, adding that long term data would still be important. The adaptive design was implemented because of unanticipated slow enrollment; this trial design allowed for interim analyses.

Many of the other changes formalized procedural recommendations (e.g., clarified medication regimen, removed the requirement for blood analyses apart from a pregnancy test). Changes to the IFU were based on knowledge gained from SFA trials and aimed to improve angioplasty and drug delivery (e.g., balloon sizing, balloon inflation time).

There were a total of 34 IDE supplements; 13 protocol revisions, six shelf life extension requests, five administrative changes (change in contact, extension request), four supplements to provide FDA with certificate of analysis (COA) prior to clinical product release, two responses to FDA questions for full IDE approval, two compassionate use requests, one supplement to add an additional balloon length, one minor change in sterilization testing, and one notification of end of enrollment.

The IDE supplements for major protocol changes are summarized in **Table 5-1**, along with the major statistical implications of the trial design changes. Most importantly, the p-value threshold to meet the primary effectiveness endpoint was initially 0.025. Due to changes, the threshold decreased to 0.0085, along with an adjustment in the sample size from up to 480 pathways to up to 840 pathways. Details regarding the effect of the changes in sample size can be found in **Section 6.12**.

Table 5-1. Major Protocol Changes – Statistical Implications

Revision	Changes	Sample Size	P-Value Threshold for Effectiveness	Reason for Change
Original (b) (4)	**Initial Protocol**	**320 patients to obtain up to 480 pathways**	**0.025 1-sided**	
(b) (4) Submitted 13Feb 2015 Approved 13Mar 2015	Protocol Revision 7: Change to ABI/TBI	N/A	N/A	Change to reduce screen failures. As well, BTK disease can result in falsely elevated ABI for

Table 5-1. Major Protocol Changes – Statistical Implications

Revision	Changes	Sample Size	P-Value Threshold for Effectiveness	Reason for Change
	Hemodynamic Criteria			two reasons, calcific, incompressible vessels and disease located distal to the ankle cuff. While TBI measurements do not suffer from the same limitations, many centers are not skilled in the performance of TBI testing.
(b) (4) Submitted 25Nov 2015 Approved 21Dec2015	Protocol Revision 8: Allowed R3 Changed screen failures	N/A	N/A	The proposal change was based on a clinical site survey that indicated high exclusion rates of patients with BTK disease in Rutherford 3, who had failed medical management.
(b) (4) Submitted 05 Feb 2016 Approved 09 Mar 2016	Protocol Revision 9: Adjusted for 12.6% anticipated treatment effect Introduced adaptive sample size/interim analysis plan	Up to 840 pathways	0.0163	As a result of learnings from other DCB trials (Lutonix SFA), a change was made to use a more conservative patency outcome.
(b) (4) Submitted 17 Jun 2016 Approved 19 Jul 2016	Protocol Revision 10: 1st interim analysis at 400, not 300 Changed endpoint from 12m to 6m	Up to 840 pathways	0.017	Change to reflect the aggressive nature of CLI disease and to align with evolving changes in the then current standard for BTK studies. Also addressed FDA recommendations as a part of (b) to move

Table 5-1. Major Protocol Changes – Statistical Implications

Revision	Changes	Sample Size	P-Value Threshold for Effectiveness	Reason for Change
	Changed analysis from patient-based to pathway-based			from an interim analysis at 300 patients to 400 patients to make sure that there are enough data collected for the patients after the changes are in place.
(b) (4) Submitted 22 Aug 2016 Approved 21Sep 2016	Protocol Revision 11: Primary analysis changed from proportion-based testing to a repeated measures logistic model of pathway success that included treatment and a patient random effect.	Up to 840 pathways	0.017	This supplement is in response to FDA considerations in (b) to account for multiple vessels from the same patient.
(b) (4) Submitted 14Oct 2016	Control Type 1 error	N/A	0.015	This supplement is in response to the FDA requested study design consideration in response to (b) .
(b) (4) Submitted 07 Sep 2017 Approved 04 Oct 2017	Protocol Revision 12: Allowed for a proximal-segment analysis as a back up to the primary analysis.	Up to 840 pathways	0.0085	The sponsor communicated in a pre-submission (b) (4) to FDA prior to proposing this protocol change in a supplement. FDA agreed that an evaluation of a more restricted proximal BTK vascular bed is acceptable but notes that specific indications and labeling will be

Table 5-1. Major Protocol Changes – Statistical Implications

Revision	Changes	Sample Size	P-Value Threshold for Effectiveness	Reason for Change
				determined from the clinical data. Change in reporting of mechanical recoil events within 30 days as these are mechanical vascular response and are unlikely to be related to the "drug effect."

Although the FDA approved the supplements requesting protocol changes, they communicated some future considerations and clinical study design considerations. This feedback is described **Table 5-2**, with the BD approach to addressing the concerns.

Table 5-2. Supplements with FDA Considerations and BD Responses

Supplement	FDA Consideration	Response
(b) (4)	FDA notes that robust objective CLI definitions uniformly involve hemodynamic assessment. For this reason, FDA strongly recommends the use of hemodynamic information to clearly define the patient population in a pre-market pivotal trial, as the use of these objective criteria will facilitate interpretation of the resulting data.	These data were captured for all patients enrolled in the study. ABI and TBI did not provide useful insights into the safety and effectiveness of the Lutonix DCB as compared to PTA.
(b) (4)	Therefore, in order to ensure that the appropriate analyses are planned, we recommend that you modify your investigational plan to include planned analyses which will ensure that the impact of these variables [i.e., embolic protection and some Rutherford Class 3 patients] is adequately assessed and controlled.	The requested analysis for Rutherford Category was completed, however, the number of enrolled Rutherford 3 patients was small.
	FDA believes there is value to having uniform collection of this information as it may inform adverse events adjudication (e.g., creatinine for renal insufficiency, hematocrit for significant bleeding).	Not performed since laboratory testing was not consistent with clinical practice during follow-up visits.

Table 5-2. Supplements with FDA Considerations and BD Responses

Supplement	FDA Consideration	Response
	Therefore, please consider the continued inclusion of these assessments [i.e., blood analyses].	
(b) (4)	Therefore, we recommend that you modify your hypothesis testing approach to account for the correlation between two vessels from the same patient.	This was incorporated in the analyses as requested.
(b) (4)	FDA recommends using an alpha of 0.025. FDA also questioned if sequential testing of the endpoints would be done.	After the primary endpoint was missed, the sequential secondary analyses were not performed.
	FDA does not believe that it is appropriate to use this information [i.e., an analysis that excludes early events] to support any claims.	No claims are proposed regarding an analysis that excludes early events.

6 STUDY DESIGN: LUTONIX BTK IDE TRIAL

Summary

- The LUTONIX BTK was the first PMA IDE trial of CLI patients.
- The LUTONIX BTK IDE Trial was a prospective, global, multicenter, single-blind, randomized study designed to evaluate the safety and effectiveness of the LUTONIX DCB compared with standard PTA for the treatment of stenosis or occlusion of BTK arteries.
- As in many studies of diseases with high overall mortality, eligibility criteria purposefully selected patients who would be able to participate.
- Frequentist analyses were used to assess endpoints.
- The primary effectiveness endpoint is defined as freedom from a composite of above-ankle amputation, target lesion occlusion, and CD-TLR through 6 months.
- The primary safety endpoint was freedom from a major adverse limb event (MALE) or perioperative all-cause mortality through 30 days post index procedure.
- The study sample size was based only on power for the primary endpoints.

6.1 Introduction

The LUTONIX BTK IDE Trial is a prospective, global, multicenter, single-blind, randomized study designed to evaluate the safety and effectiveness of the LUTONIX 014 DCB compared with standard PTA for the treatment of stenosis or occlusion of BTK arteries. The study utilized a 2:1 DCB: PTA randomization of patients in the US, Europe, Japan, and Canada.

Safety endpoints were assessed on a per-patient basis while effectiveness was evaluated by pathway. Up to two pathways per patient could be treated with the study device.

6.2 Eligibility Criteria

The eligibility criteria considered the high mortality in the patient population. These criteria were designed to balance the need for a study population that approximated the real-world setting but still have adequate number of patients who survive and continue with the study assessments through the follow-up period (see the constraints summarized in **Section 5**). A complete list of selection criteria for the trial can be found in Appendix **Section 14.3**. Eligible

patients had to meet each of the inclusion and exclusion criteria to be enrolled in the study. The most pertinent criteria are as follows:

6.2.1 Inclusion Criteria

6.2.1.1 Clinical Inclusion Criteria

- Rutherford Clinical Category 3, 4 or 5. Patients categorized as a Rutherford Clinical Category 3 must have failed medical management per physician discretion.

6.2.1.2 Angiographic Inclusion Criteria

- Significant stenosis (≥ 70%) or occlusion of one or two native artery(s) below the tibial plateau and above the tibiotalar joint appropriate for angioplasty per operator visual assessment.
- Cumulative length of target lesion(s) ≤ 320 mm;
- NOTE: Maximum allowed cumulative length of all DCBs ≤ 360 mm;
- A patent inflow artery from the aorta to the target lesion free from significant (≥ 50%) stenosis as confirmed by angiography;
- Target vessel(s) diameter between 2 and 4 mm and able to be treated with available device size matrix;
- Target vessel(s) 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).

6.2.2 Exclusion Criteria

- Any severe medical comorbidities (untreated CAD/CHF, severe COPD, metastatic malignancy, etc.) that would preclude compliance with the study protocol or currently receiving immune-suppressive, chemotherapeutic, or radiation therapy;
- Gangrene extending proximal to the digit-metatarsal skin crease (target limb);
- Ischemic ulceration that extends more than 4 cm proximal to digit-metatarsal skin crease (target limb);
- Neurotropic ulcer or heel pressure ulcer or ulcer potentially involving calcaneus (target limb);
- Planned major amputation (of either leg);
- Prior major amputation if amputation occurred less than one year prior to enrollment and if patient is not independently ambulating;

- Acute limb ischemia (symptom onset within 2 weeks);
- In-stent restenosis of target lesion;
- Presence of thrombus in the target vessel.

6.3 Study Procedures

Informed consent was obtained for all patients. A flowchart of the study procedures is presented below in **Figure. 6-1.**

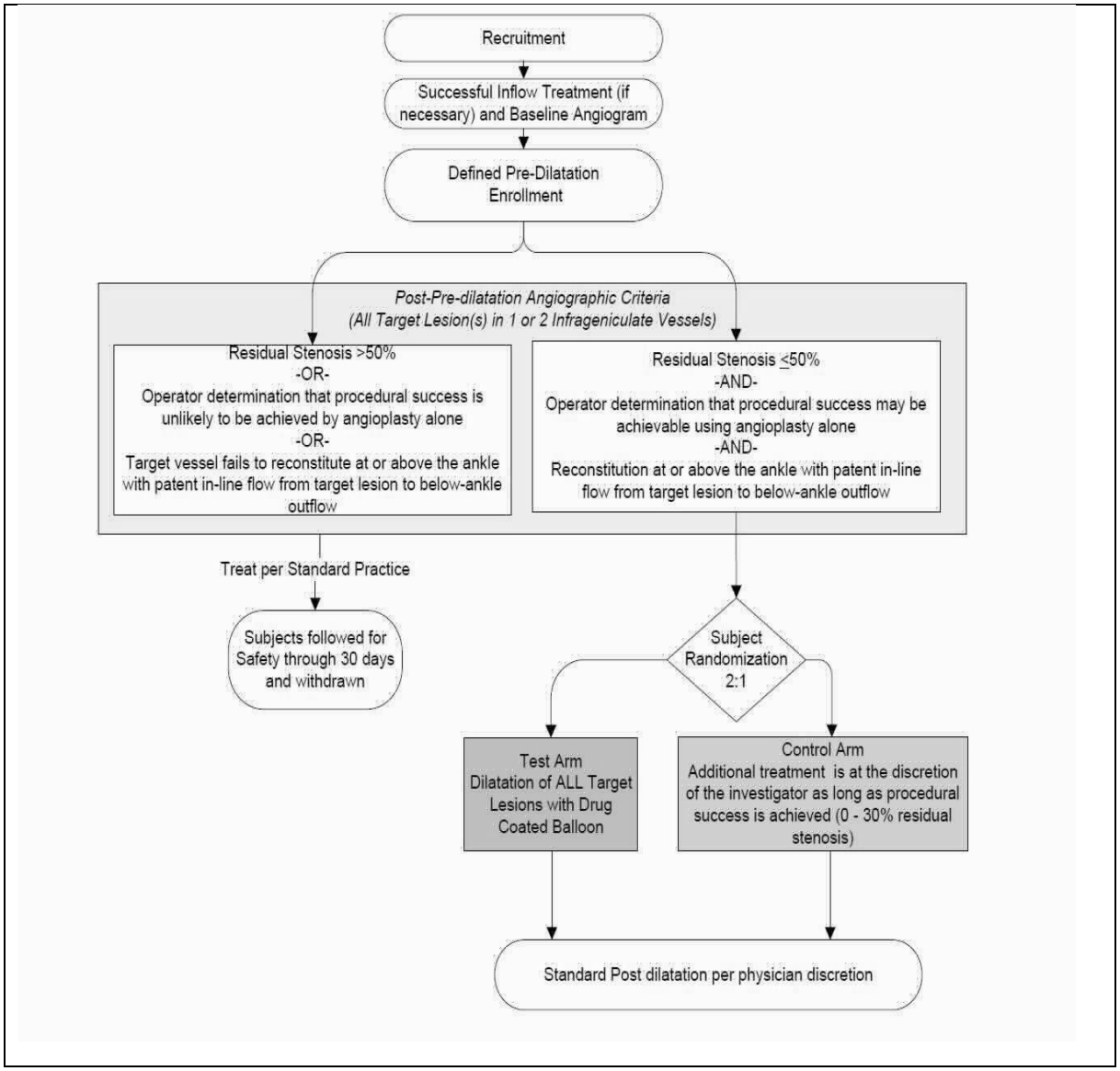

Figure. 6-1 Study Flowchart

6.3.1 Baseline Angiography

Baseline angiography was obtained to confirm that the patient met the angiographic inclusion criteria. Concurrent or staged treatment of iliac, SFA, and above-knee popliteal artery lesion was allowed if successfully performed (residual diameter stenosis ≤ 30%) without major vascular complications. Treatment of SFA/popliteal inflow lesions must have terminated 30 mm above the tibial plateau, i.e., a segment of healthy artery between any treated inflow lesions

and potential target vessel lesions below the knee was required. Treatment of aortic and common femoral lesions was not allowed.

Antegrade pre-dilatation of target lesion(s) was performed with a standard PTA catheter appropriately sized for the reference vessel diameter. Successful pre-dilatation was defined as residual stenosis ≤ 50% and operator determination that procedural success may be achievable by angioplasty alone. Multiple lesions up to 320 mm in cumulative length may be pre-dilated, but all target lesions must be successfully pre-dilated and assessed prior to randomization. Outflow was assessed after pre-dilatation. Each target vessel(s) (flow path) must have reconstituted at or above the ankle with inline flow to at least one patent (< 50%) inframalleolar outflow vessel.

A patient was considered enrolled when both of the following occurred:

- Baseline angiographic confirmation that the target lesion(s) met all inclusion and exclusion criteria.
- Pre-dilatation balloon inflation was begun.

Patients with target lesion(s) that, after baseline angiography, did not meet all inclusion/exclusion criteria and were not pre-dilated per protocol were considered screen failures and were not to be enrolled or randomized in the study.

6.3.2 Randomization

If after pre-dilatation(s), patients were determined to meet the criteria for randomization, they were stratified by Rutherford Category and randomized using a pre-specified site randomization system. Patients were randomized in a 2:1 fashion in each stratum to DCB or standard PTA, and all target lesions in up to two target pathways meeting the entry criteria were treated with the as-randomized device.

6.3.3 Treatment

For patients randomized to the Control arm, treatment with an additional standard uncoated PTA catheter (control device) was at the discretion of the investigator. Control PTA treatment should have maintained balloon inflation for minimum of 2 minutes.

For patients randomized to the DCB arm, the study protocol instructed the operators to follow the current IFU for procedural details, preparation, and use of the study device (see **Section 6.3.3**). Multiple DCBs could be used; each balloon was used only once for adequate drug delivery to the vessel wall. DCBs could be overlapped as necessary to ensure coverage of a pre-

dilated injury segment or lesion without geographic miss. The total length of all DCBs used during the procedure was limited to 360 mm.

Post-treatment and provisional (bailout) stenting were performed only if the investigator deemed that a stent was required to avoid an open surgical revascularization or amputation. If bailout stenting was required, a bare metal stent was used; drug-eluting stents were not allowed.

6.3.4 Blinding

The patient remained blinded to the treatment until after completion of the 6-month follow-up visit. Members of the CEC were blinded to the treatment assignment. The investigator was not blinded; however, the clinical status of the patient (for assessment of clinical and primary safety endpoints) was to be established prior to performing the DUS and angiography to minimize potential bias. The quality-of-life questionnaires were completed by the patient prior to evaluation by the investigator to also minimize bias.

6.3.5 Antiplatelet Therapy

Pre-procedure, aspirin (75-325 mg/day) and a P_2Y_{12} inhibiter, either clopidogrel (75 or 300 mg loading dose), ticagrelor (180 mg loading dose), or prasugrel (10 mg/day or loading dose of 60 mg) were suggested.

Post-procedure, dual antiplatelet therapy was recommended for at least one month. For patients on chronic warfarin, both aspirin and a P_2Y_{12} inhibiter were not required; only a single agent in addition to warfarin was sufficient once the INR was therapeutic. Prolonged dual antiplatelet therapy was indicated for non-study reasons and was allowed at the investigators' discretion.

A suggested medication schedule pre- and post-procedure was provided in the protocol and is shown in **Table 6-1**. It was preferred that all patients be treated with clopidogrel and aspirin for one month, followed by aspirin thereafter throughout the duration of the study. Sites were however, instructed to follow the anti-platelet therapy per their institution's standard of care.

Table 6-1. Suggested Medication Schedule

Drug	Pre-Procedure	Procedure	Post-Procedure*
Aspirin	75-325 mg/day	NA	75–100 mg/day indefinitely
Clopidogrel OR Ticagrelor	75 mg or 300 mg loading dose	NA	75 mg daily for at least 1 month
	180 mg loading dose	NA	90 mg BID

Table 6-1. Suggested Medication Schedule

Drug	Pre-Procedure	Procedure	Post-Procedure*
OR Prasugrel	10 mg/day or loading 60 mg loading dose	NA	For at least 1 month (discontinue with active bleeding) >60 kg - 10 mg/day <60 kg - 5 mg/day**
Anticoagulation	Per Hospital Standard Practice		

**For cases of provisional (bailout) stenting, refer to the Stent IFU for dosing instructions.*
***The effectiveness and safety of this dose has not been prospectively studied*

6.3.6 Follow-up Procedures

Table 6-2 specifies the required schedule of assessments and procedures from screening through the 36-month follow-up period.

Table 6-2. Schedule of Assessments

Event	Screening	Pre-Procedure	Procedure	Post-Procedure	30 days ±2 wk	6 Months ±1 mo	12 Months ±1 mo	24 Months ±2 mo	36 Months ±2 mo
Inclusion/Exclusion Criteria	X	X	X						
Informed Consent		X							
Medical History		X							
Physical Examination		X		X	X	X	X	X	X
ABI/TBI		X			X	X	X	X	X
Rutherford Classification		X			X	X	X	X	X
Pregnancy Test*		X							
WIQ		X			X	X	X	X	X
EQ-5D		X				X	X	X	X
Angiography			X						
Adverse Event Monitoring			X	X	X	X	X	X	X
Duplex Ultrasound									
Wound Healing Assessment†		X							

Table 6-2. Schedule of Assessments

Event	Screening	Pre-Procedure	Procedure	Post-Procedure	30 days	6 Months	12 Months	24 Months	36 Months
					±2 wk	±1 mo	±1 mo	±2 mo	±2 mo

**For females of childbearing potential, blood or urine*

†Wound imaging for those with tissue loss

6.4 Analysis Populations

All safety and effectiveness analyses were performed on an Intent-to-Treat (ITT) basis. In addition, the primary safety and effectiveness analyses were performed on the As Treated, Per Protocol, and Japanese ITT populations as sensitivity analyses.

The definitions of the analysis populations are included in Appendix **Section 14.3.4.**

6.5 Study Endpoints

The study had powered primary safety and effectiveness endpoints (**Section 6.5.1** and **Section 6.5.2**), four hypothesis-tested secondary endpoints (**Section 6.5.6**), and a series of additional secondary endpoints (**Section 6.5.7**).

6.5.1 Primary Safety Endpoint

The primary safety endpoint was freedom from a major adverse limb event (MALE) or perioperative all-cause mortality through 30 days post index procedure. MALE was defined as the composite of above-ankle amputation or major reintervention, where major reintervention included placement of a new bypass graft, a jump/interposition graft revision, or thrombectomy/thrombolysis of the index limb involving a BTK artery.

Safety measures were assessed on a per-patient basis, where the unit of assessment (the denominator) for all assessments was the number of patients with observations.

6.5.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the composite of limb salvage and primary patency at 6 months.

- Limb salvage was defined as freedom from above-ankle amputation in the index limb. Primary patency was defined as freedom from target lesion occlusion or clinically driven target lesion revascularization.
- Clinically driven target lesion revascularization was CEC adjudicated as a reintervention at the target lesion due to worsening of the Rutherford Category, stagnant or worsening wound healing in those with ulcers or gangrene, or a new or recurrent wound in the index limb.

6.5.3 Flow Pathways as the Unit of Effectiveness Assessments

Effectiveness endpoints were assessed by "*flow pathways*" (**Figure 6-2**). A "flow pathway" (or "pathway") was defined as the entire vessel in which the target lesions were located, and each pathway could contain multiple lesions. The peroneal and posterior tibial arteries could involve the tibioperoneal trunk, and the anterior tibial and tibioperoneal vessels could involve the below knee popliteal artery. For example, where a peroneal artery and a tibioperoneal trunk lesions were present, the pathway was the contiguous arterial segment from the tibioperoneal trunk through the peroneal artery.

Each patient could have up to two pathways treated, but randomization was performed by patient. If a patient had two pathways, both received the same treatment, DCB or PTA. Use of a random effect statistical model addresses the potential for within patient correlation.

6.5.4 Primary Effectiveness Post Hoc Analyses

While the primary effectiveness analyses were performed with pathway as the unit of assessment, post-hoc analyses for the primary effectiveness endpoint, primary patency, and clinically driven TLR were also performed on a per patient basis. See **Section 6.5.5** for the hierarchical assessment of the primary effectiveness endpoint.

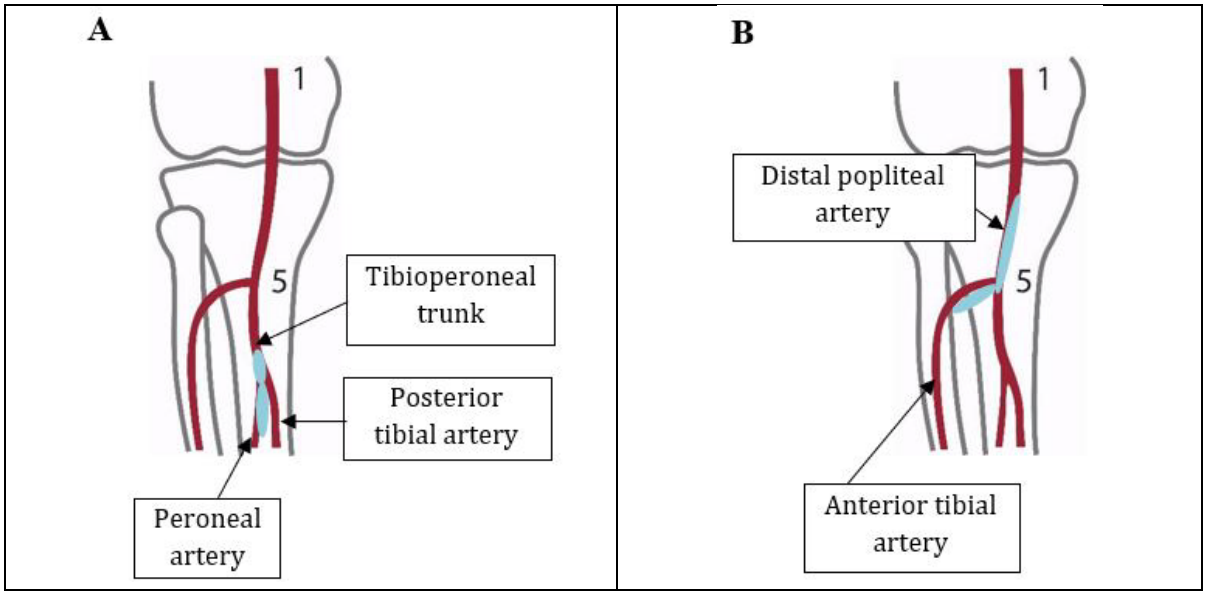

Figure 6-2. Schematic of Flow Pathways. Peroneal or posterior tibial artery lesions (diffuse or focal) that extend into the tibioperoneal trunk can be counted as one target artery (Panel A). Similarly, lesions (diffuse or focal) in the anterior tibial artery that extend into the popliteal artery can be counted as one target artery (Panel B).

6.5.5 Proximal Segment Subgroup Analysis

During the conduct of the LUTONIX BTK IDE Trial, knowledge was gained from published literature (i.e., from studies independent of the trial) with respect to the response of BTK arteries to interventions.[29,30] Based on this knowledge, a subgroup analysis was added to the statistical analysis plan in effort to determine whether more proximal lesions would respond better to treatment. Additional information regarding this analysis is included in Appendix **Section 14.3**.

Upon study completion it was found that there was insufficient representation of distal segment lesions to allow for a meaningful analysis. As such, the proximal segment analysis was very similar to the overall analysis and, for the purposes of this panel meeting, BD will not be addressing the proximal segment analysis further.

6.5.6 Hypothesis-Tested Secondary Endpoints

The following secondary endpoints were to be hypothesis tested if the primary effectiveness endpoint was met. It is important to note that the study sample size was based only on power for the primary endpoints.

- DCB arm is superior to the PTA arm in 6-month primary patency with exclusion of early mechanical recoil.
- DCB arm is superior to the PTA arm in 6-month primary patency.
- DCB arm is superior to the PTA arm in 6-month freedom from clinically driven TLR.
- DCB arm is superior to PTA arm in the 6-month composite of freedom from above-ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically-driven Target Vessel Revascularization (TVR).

Since the primary effectiveness endpoint was not met, these endpoints were reported with descriptive statistics alone.

6.5.7 Other Secondary Endpoints

The following secondary endpoints were not planned to be hypothesis-tested, and included:

- Device, Technical, and Procedural Success
- Change in Quality of Life from baseline as measured by the EQ-5D survey (6, 12, 24, and 36 months)
- The following endpoints assessed at 30 days, 6 months, 12 months, 24 months, and 36 months:
    - Composite of limb salvage and primary patency (primary effectiveness endpoint at other time points)
    - Wound healing including overall burden of incurred, new and recurrent wounds
    - Change in Rutherford Category in target limb
    - Composite of freedom from the following in the index limb: 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 from baseline
    - Amputation (Major): Above ankle amputation of the index limb
    - Unplanned minor (below the ankle) amputations
    - Total (Cumulative) TLR, Total TVR, Overall burden of BTK reinterventions
    - Composite of POD, index limb-related death, BTK reinterventions, or major amputation of the index limb
    - Death (any cause)
    - SVS CLI endpoints including:

- MALE, the composite of above ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)
- MALE+POD: Perioperative death (30days), or any MALE
- MACE (Major Adverse Cardiovascular Event): MI, stroke or death (any cause)
- AFS (Amputation free survival): Freedom from above ankle amputation of the index limb or death (any cause)
- RAO: Any reintervention or above ankle amputation of the index limb
- RAS: Any reintervention, above ankle amputation of the index limb, or stenosis.

6.6 Site Monitoring

Monitoring of investigational sites was performed by the Sponsor's Clinical Research Associates (CRAs) or the CRAs from the Sponsor's Contract Research Organization.

A site initiation visit was performed for each site by a CRA or Clinical Field Specialist. Interim monitoring visits were performed at a frequency specified in the Monitoring Plan. All data presented in this report was 100% monitored and query-free.

6.7 Adverse Event Reporting and Evaluation

Adverse events requiring adjudication and occurring through Day 395 were adjudicated by an independent CEC. This included all site-reported stroke events, Major Adverse Cardiovascular Events (MACE), myocardial infarctions, and all-cause death, all target limb related events, and all device- and/or procedure-related AEs. These AEs were source verified and were adjudicated by the CEC as to whether they were related to the device or procedure. All adverse events occurring in this study are classified in accordance with the adverse event signs or symptoms.

6.8 Missing Data

Endpoints were missing because patients died, had uninterpretable imaging data, or withdrew from the study prior to the time the endpoint was measured. For both primary endpoints, the reason for the censoring of all patients with missing endpoints was recorded.

To assess the robustness of the primary effectiveness and safety analysis, each endpoint's binary outcome was analyzed in the AT and PP populations (see Appendix **Section 14.3.4** for analysis population definitions). In addition, a tipping-point analysis was performed for each primary endpoint using the ITT population, in which assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis. A multiple imputation analysis for the ITT population was also performed for the

primary effectiveness endpoint, using available results and baseline variables identified for the assessment of poolability. This set of analyses constituted the sensitivity analyses for the effect of missing data on the study results.

6.9 Handling of Core Laboratory Data

Vessel patency was assessed by independent angiographic and duplex ultrasound (DUS) core laboratories. If both angiogram and DUS assessments were performed, the angiogram data took precedence over the DUS assessment. If a later DUS exam indicated patency for a patient who was determined at an earlier visit to have loss of patency, and the patient did not undergo an amputation or reintervention, the later assessment would supersede the former assessment of patency and the vessel would be deemed patent at both the earlier and later time points. This outcome of patency would also be carried back to an earlier visit in the case of missing data where a subsequent visit indicated patency, provided that the patient did not have an amputation or reintervention between study visits.

6.10 Primary Effectiveness Endpoint Hypothesis Test

The primary effectiveness hypothesis was as follows:

H_0: $p_{DCB} \leq p_{control,}$

H_1: $p_{DCB} > p_{control}$

where p is the success rate in each arm.

The composite salvage and primary patency endpoint was evaluated as a binary endpoint at 6 months based on the following definition:

- Success: A treated flow pathway has no failure event (above ankle amputation, target lesion occlusion, or clinically driven TLR) on or before Day 210 and was confirmed to have primary patency at Day 150 or later.
- Failure: A treated flow pathway had any failure event (above ankle amputation, target lesion occlusion, or clinically driven TLR) on or before Day 210.
- Missing: A treated flow pathway would be missing for the analysis if it did not have a failure event or primary patency failure and it did not have following confirmation of success at the 6-month visit or later.

The primary analysis was based on a logistic model for pathways, with a random patient effect to account for within-patient correlation.

A Kaplan-Meier analysis was also used to estimate the survival rate for the primary efficacy endpoint in the DCB and PTA groups. The 95% CI for differences in the survival rates in by-

pathway analyses were completed using a bootstrap approach. For each bootstrap sample, sampling was done at the patient level for each group, not by pathway. Hence, the variability in the survival estimates related to multiple pathways was accommodated for in the analysis. A log-rank test comparing DCB and PTA was used to test the primary hypothesis to determine if DCB was superior to PTA.

For figures of Kaplan-Meier curves and associated log-rank test p-values, data are censored at the end of the visit window (e.g., Day 210 for 6 months). For Kaplan-Meier evaluations, the onset for a failure was the first date of any of the failure events. For a target lesion occlusion, the date of the DUS or angiogram was used as the event date with preference given to available angiography results. For flow pathways without an event, the censoring date was based on the last completed DUS or angiogram establishing the patient was still a primary patency success.

If the first (all flow pathways) primary effectiveness analysis failed to reach statistical significance at the pre-specified level, the analysis was repeated for the proximal segment with the definition for success based on freedom from the composite of above-ankle amputation, target lesion occlusion in the proximal segment of the flow pathway, and clinically driven target lesion revascularization in the proximal segment of the flow pathway.

6.11 Primary Safety Endpoint Hypothesis Test

The primary safety hypothesis was as follows:

H_0: $p_{control} - p_{DCB} \geq \delta$

H_1: $p_{control} - p_{DCB} < \delta$

where p is the success rate in each arm and δ is the non-inferiority bound. The protocol identified a non-inferiority bound of 0.12 (12%).

The composite safety endpoint was evaluated as a binary endpoint at 30 days based on the following definition:

- Success: Patient had no failure event on or before Day 30 and was confirmed to have follow-up visit assessment at or beyond the beginning of the 30-day window (relative Day 16) or later
- Failure: Patient had any failure event on or before Day 30
- Missing: A patient would be missing if they had not had a failure event but did not have a following assessment confirming their success at the 30-day visit or later

A non-inferiority Farrington and Manning test was used to test the primary safety hypothesis. The test was successful if the one-sided p-value was less than 0.025. In addition to the p-value of the test, the confidence interval of the rate in each group and the difference between the two groups was calculated.

The protocol-identified, non-inferiority bound of 0.12 (12%) was based on perioperative death and adverse limb events published in meta-analyses available at the time of the trial design,[31,32] as well as the lack of safety insights from randomized trials of drug-coated balloons in the SFA, since these trials were ongoing at the time of trial design.

6.12 Adaptive Design for Sample Size

An adaptive approach to sample size selection was used. A minimum total sample size of 400 pathways and a maximum 840 pathways were considered. Sample sizes accounted for the potential of 15% attrition. Interim looks were scheduled after the accrual of 400, 500, 600, and 700 pathways. At each interim look, the predictive probability of study success was calculated. Based on this, the following adaptive decisions were planned:

- If the probability of trial success were high with the current sample size, accrual would be stopped and the current sample size would be followed through 6 moths, at which point a final analysis would be conducted.
    - Specifically, if the predictive probability of success with the current sample size plus 6 months of follow-up was greater than 90% then accrual would stop.

If the probability of trial success by the maximum sample size of 840 was small, the trial would be stopped for futility.

- If trial success by the maximum sample size of 840 was small, the trial would be stopped for futility.
    - If the predictive probability of success by the maximum sample size of 840 fell below 1%, the trial would be stopped for futility. However, this futility rule was non-binding, and the sponsor could choose to continue the trial even when a futility threshold had been met.
- If accrual continued, another look would be made after 100 additional pathways were accrued. These 100-pathway incremental looks were to continue (500, 600, 700) until accrual was stopped or the trial enrolled the maximum of 840 pathways.
- The final analysis was based on a lower p-value threshold to control the type I error rate at the one-sided 0.025 level due to the adaptive design.

Note: The p-value was further adjusted with the introduction of the proximal subgroup analysis.

No patient management, which was exclusively performed by the clinical sites, nor study design changes were made because of knowledge obtained from the interim looks.

6.13 Final Sample Size

Interim analyses were performed after enrollment of 400 pathways in November 2016, and 500 pathways in December 2017, respectively. For both interim analyses, no stopping boundaries were met, and accrual could continue. After 4½ years of enrollment, enrollment was terminated with 442 randomized patients (507 evaluable pathways). With a decrease in enrollment rate, it was estimated that the enrollment would need to continue for over 3 years to achieve the full complement of 840 pathways. Also, given the changing clinical practice and protocol modifications, there was a risk that enrollment over an extended period could jeopardize the similarity and consistency of the enrolling population.

7 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summary

- 462 patients were enrolled in the LUTONIX BTK IDE TRIAL from June 3, 2013 to December 12, 2017 across 51 investigational centers and four geographies (U.S, Canada, Europe, and Japan).
- 442 patients were randomized 2:1 to LUTONIX DCB (n=287) and Standard PTA (n=155); notably, 10 roll-in and 10 standard practice patients were enrolled and not randomized.
- The demographics and risk factors of the patients enrolled were representative of the general CLI patient population; patients were older with multiple comorbidities.
- Patients randomized to the DCB arm had longer mean lesion lengths (DCB 112 mm, PTA 95 mm, p=0.034), and a greater numerical incidence of TASC C and D lesions (DCB 31%, PTA 22%, p=0.072).
- Overall, 83.7% of study patients completed a 6-month evaluation (370/442) and 77.1% of patients completed a 12-month evaluation (341/442). Twenty-four and 36-month follow-up visits are ongoing and vital status is being collected through 60 months in patients who consented to protocol version 13.

The LUTONIX BTK IDE Trial was conducted as a prospective, global, multicenter, single-blind, randomized study designed to evaluate the safety and effectiveness of the LUTONIX 014 Drug Coated Balloon (DCB) percutaneous transluminal angioplasty (PTA) catheter for the treatment of stenosis or occlusion of native below-the-knee (BTK) arteries. The demographics and baseline characteristics, as well as the study patient disposition are summarized below. Additional tables are in Appendix **Section 14.1**.

7.1 Demographics and Baseline Characteristics

The LUTONIX BTK IDE Trial was conducted as a prospective, global, multicenter, single-blind, randomized study. A total of 462 patients were enrolled in the LUTONIX BTK IDE TRIAL from June 3, 2013 to December 12, 2017 across four geographies (US, Canada, Europe, and Japan). A total of 442 patients were randomized 2:1 to LUTONIX DCB (n=287) and Standard PTA

(n=155) at 51 centers; 10 roll-in and 10 standard practice patients were enrolled but not randomized (**Table 7-1**).

Table 7-1. Overall Enrollment

	DCB Patients	PTA Patients	Total Patients
Randomized, n	287	155	442
Non-Randomized			
n	10	10	20
Roll-in	10	0	10
Standard Practice	0	10	10

Patient demographics are provided in **Table 7-2**. The average age of the 442 randomized patients was 72.9 ± 9.6 years, with the majority male (69.2%) and an average BMI of 28.2 ± 6.1 kg/m^2. The predominant race the patients identified with was white (80%), with 10% self-identifying as Black/African American and 9% self-identifying as Asian. None of the baseline characteristics were significantly different at the nominal 0.05 p-level between treatment arms. Rutherford Category 3, 4, and 6 patients were enrolled, with Rutherford Category 3 patients enrolled beginning with version 8 of the protocol (described in **Section 5**). Most patients were Rutherford 4 or 5, with only 9.5% of patients classified as Rutherford Category 3.

Table 7-2. Demographic and Baseline Characteristics

	DCB Patients (N=287)	PTA Patients (N=155)	Total Patients (N=442)
Age (Years):			
N	287	155	442
Mean (SD)	72.9 (9.65)	72.9 (9.62)	72.9 (9.63)
Median	74.0	75.0	74.0
Min, Max	45.0, 96.0	48.0, 91.0	45.0, 96.0
Sex, (%)			
Male	70.4%	67.1%	69.2%
Female	29.6%	32.9%	30.8%
Race, (%)			
American Indian or Alaska Native	0.3%	0.0%	0.2%
Asian	8.7%	9.7%	9.0%
Black or African American	11.5%	7.7%	10.2%
White	78.7%	81.9%	79.9%
Other	0.7%	0.6%	0.7%

7.2 Medical History

The risk factors were evenly distributed between both treatment arms (**Table 14-1,** Appendix). The comorbidity rates were as expected for this patient population,[20] with 70.1% of the patients diabetic, 77.1% with dyslipidemia, 93.2% with hypertension, 67.6% with cardiac disease, and 69.5% with peripheral vascular disease (including stroke), and 21.3% with a history of renal failure. Current or former smoking history was reported in 58.6% of patients.

Previous and planned interventions are summarized in **Table 14-2** of the Appendix. A previous peripheral vascular intervention was reported in 53.8% of patients prior to being enrolled in the study. The intervention was in the target limb in 40.0% of patients. A stent had been previously implanted in the target limb in 14.7% of patients. Subsequent interventions such as toe amputations were planned to be performed in 6.8% of patients at a procedure after the index revascularization.

7.3 Disposition of Patients

Of patients screened, 462 (4.4%) patients were enrolled: 442 randomized, 10 roll-in DCB, and 10 Standard Practice PTA. Reasons that accounted for the most common screening failures (>50%) included lack of blood flow reconstitution to the foot, failure to meet hemodynamic and Rutherford inclusion/exclusion criteria, wound location, and patient refusal to consent to the trial.

Overall, 83.7% of patients completed a 6-month evaluation (370/442) and 77.1% of patients completed a 12-month evaluation (341/442). Twenty-four and 36-month follow-up visits are ongoing. A flow diagram depicting the patient and pathway accountabilities for the LUTONIX BTK IDE Trial is shown as **Figure 7-1** and a flow diagram for pathway accountabilities is shown in **Figure 7-2**. If a visit was missed, the site was required to document a minimum of three (3) attempts to contact the patient within the follow-up window. If the patient only missed one protocol required visit, the site repeated the three (3) attempts to contact the patient followed by a certified letter. When a patient missed two (2) consecutive follow-up visits with failure of all contact attempts, the patient was then considered lost to follow up and exited from the study. Overall, the number of patients that exited the study was comparable to other CLI studies.[33-35]

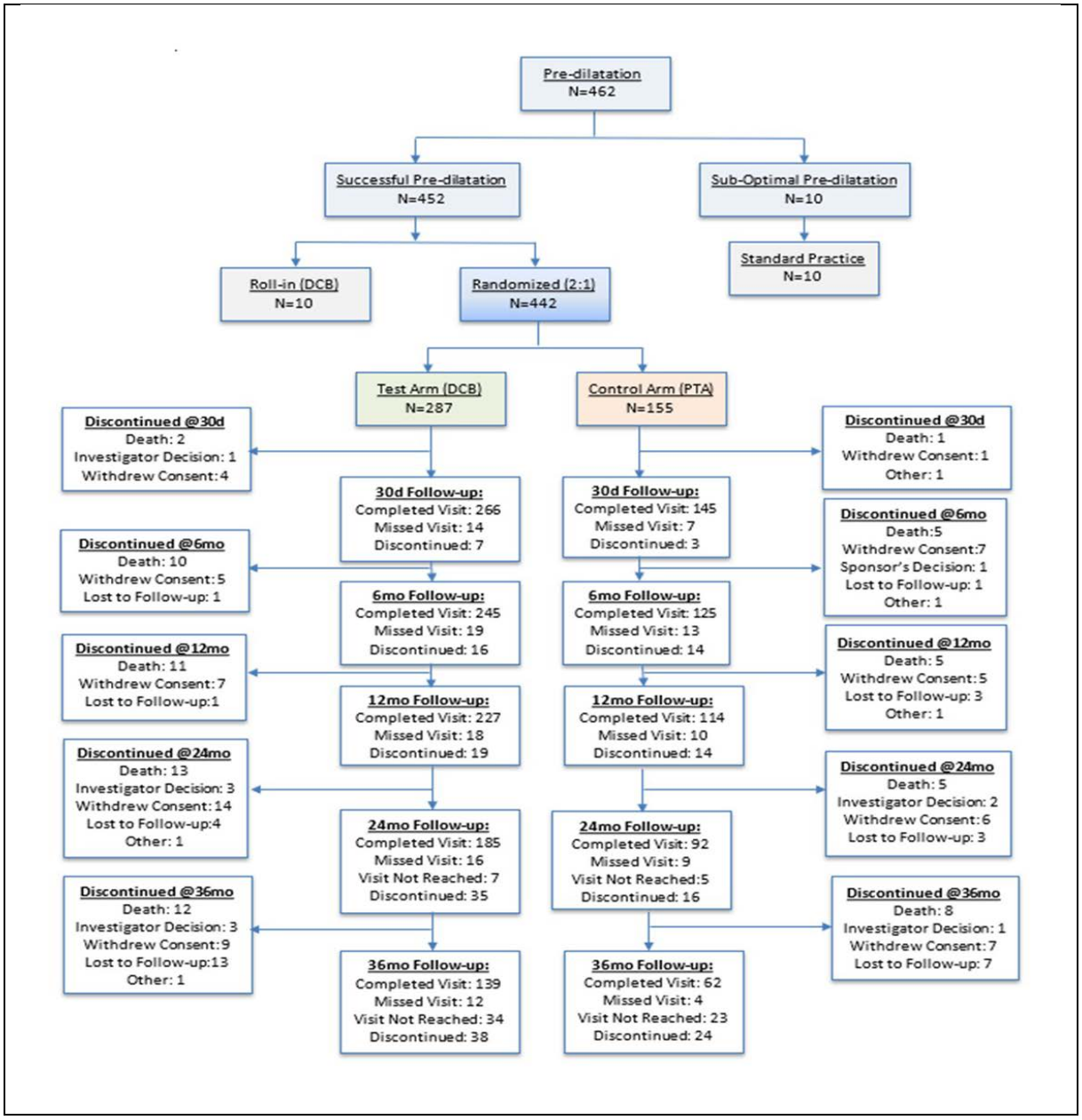

Figure 7-1. Accountability Flow Diagram, By Patient

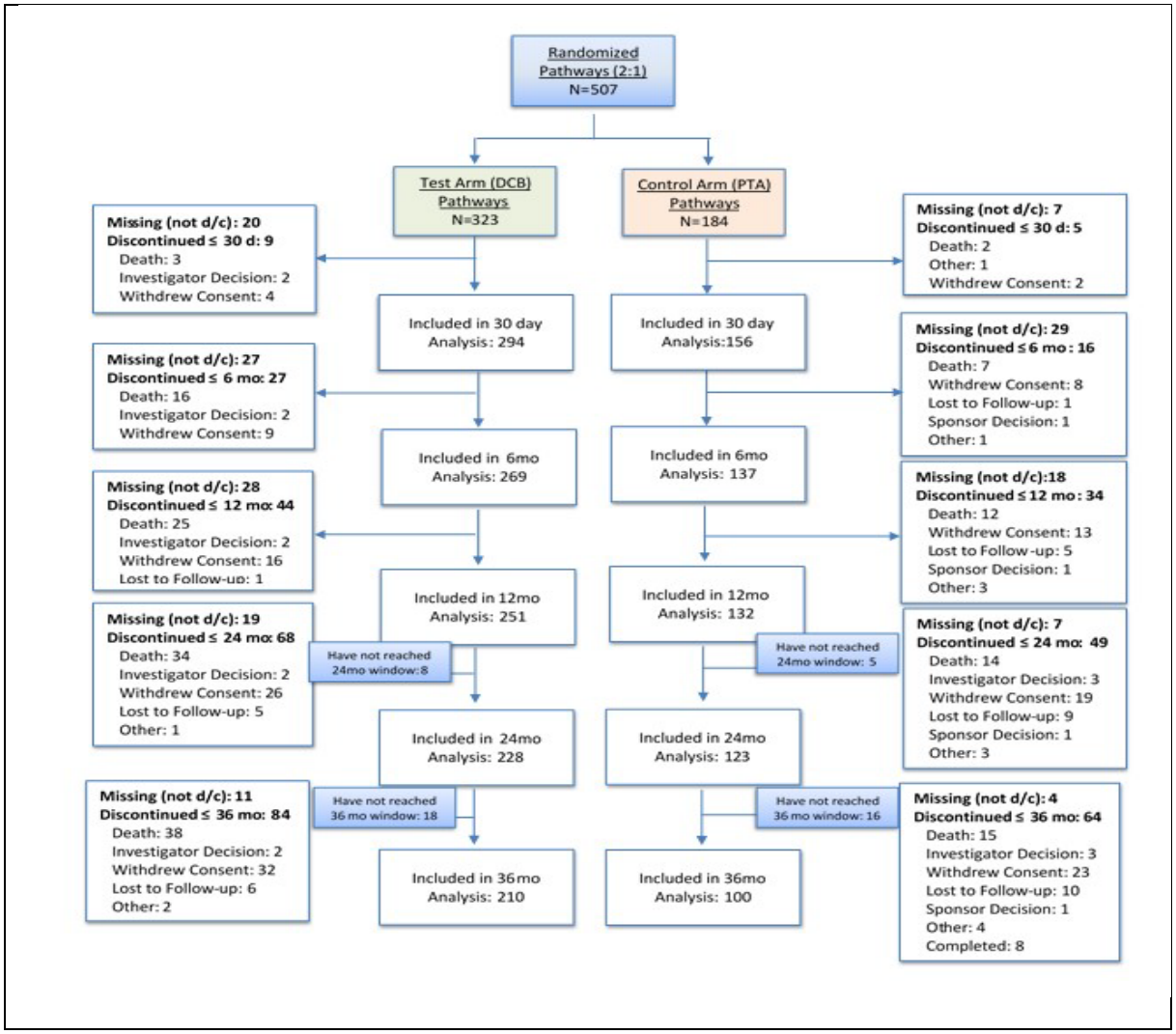

Figure 7-2. Accountability Flow Diagram, By Pathway

7.4 Target Lesion Characteristics

Notably, safety measures in this trial were assessed on a per-patient basis whereas effectiveness endpoints were assessed by flow pathways. As stated earlier, a "flow pathway" (or "pathway") was defined as the entire vessel in which the target lesions were located, and each pathway could contain multiple lesions. All lesions were reviewed by an independent angiographic core lab. Each patient could have up to two pathways treated. In total, 507 randomized pathways were analyzed (323 DCB pathways vs. 184 PTA pathways). Most pathways contained a single lesion (85.4% DCB vs. 79.2% PTA) with the most common pathway location the anterior tibial artery (41.0% DCB vs. 35.5% PTA), as shown in **Table 7-3** (as reported by sites). Information regarding the target lesions (by lesion) as reported by sites is shown in **Table 7-4.**

Table 7-3. Target Lesion Information, by Pathway

	Flow Pathways	
	DCB (N=323)	**PTA (N=184)**
Number of Pathways by Patient (ITT)		
1	251/287 (87.5%)	126/155 (81.3%)
2	36/287 (12.5%)	29/155 (18.7%)
Number of Lesions by Flow Pathway, n/N (%)		
1	275/322 (85.4%)	145/183 (79.2%)
2	39/322 (12.1%)	34/183 (18.6%)
3	7/322 (2.2%)	4/183 (2.2%)
6	1/322 (0.3%)	0/183 (0.0%)
Pathway Locations, n/N (%)		
Popliteal	33/322 (10.2%)	17/183 (9.3%)
Tibioperoneal Trunk	90/322 (28.0%)	57/183 (31.1%)
Anterior Tibial	132/322 (41.0%)	65/183 (35.5%)
Posterior Tibial	78/322 (24.2%)	50/183 (27.3%)
Peroneal	76/322 (23.6%)	45/183 (24.6%)

Table 7-4. Target Lesion Information, by Lesion

	Treated Lesions	
	DCB (N=380)	**PTA (N=225)**
Lesion Type, n (%)		
Occlusion	137/380 (36.1%)	75/225 (33.3%)
Reocclusion	6/380 (1.6%)	5/225 (2.2%)
Restenosis	8/380 (2.1%)	2/225 (0.9%)
Stenosis	229/380 (60.3%)	142/225 (63.1%)
Unknown	0/380 (0.0%)	1/225 (0.4%)
Lesion Locations, n (%)		
Popliteal	33 (8.7%)	17 (7.6%)
Tibioperoneal Trunk	91 (23.9%)	57 (25.3%)
Anterior Tibial	146 (38.4%)	81 (36.0%)
Posterior Tibial	90 (23.7%)	58 (25.8%)
Peroneal	89 (23.4%)	47 (20.9%)

Core lab assessment of the baseline angiographic measures is summarized in **Table 14-3** (Appendix **Section 14.3**). Target lesions were located entirely within the proximal segment

(defined as located entirely within the proximal two-thirds of the leg between the tibial plateau and the tibiotalar joint) or located in both the proximal and distal segments in 91.2% in the DCB arm and 90.1% in the PTA arm. By chance, patients randomized to the DCB arm had more complex lesions as follows:

- Mean total target lesion length treated in the DCB arm was longer compared to the PTA arm (DCB: 111.8 mm ± 92.64 mm vs. PTA: 94.7 mm ± 85.36 mm (p=0.034).
- Mean percent initial stenosis was numerically higher in lesions randomized to DCB vs. PTA, 86.7% vs. 84.8% respectively (p=0.090).
- There were 59.9% DCB vs. 54.2% PTA calcified lesions were treated in the DCB arm compared to the PTA arm (p=0.185).
- Calcification was considered severe in 15.1% of lesions treated with DCB compared to 13.2% of lesions treated with PTA (p=0.542).
- There was a numerically greater number of TASC C and D lesions randomized and treated with DCB compared to PTA; 30.8% vs. 22.0% respectively (p=0.072).
- The mean RVD was relatively small in both treatment arms (DCB: 2.5 ± 0.61 mm and PTA: 2.6 ± 0.62 mm), as measured by the core lab (p=0.164).

8 CLINICAL SAFETY

Summary

- The data demonstrate that the LUTONIX DCB is as safe as PTA for patients with CLI.
- The primary safety endpoint for non-inferiority of DCB to PTA was met. The proportion of patients that did not have a safety event through Day 30 was 99.3% in the DCB arm, and 99.4% in the PTA arm ($p < 0.0001$ single-sided).
- There were no differences in all-cause death at 6 months (5.0% DCB, 4.0% PTA), 12 months (8.5% DCB, 7.9% PTA), 24 months (15.4% DCB, 12.9% PTA), or 36 months (23.5% DCB, 24.5% PTA).
- Primary safety endpoint events were also analyzed through 36 months. Similar primary safety event-free rate was maintained through 36 months with a slight benefit (~2.5%) for DCB at 6 months and at 36 months.
- Amputation-free survival rates were comparable through 36 months: 11.1% DCB vs. 10.0% PTA at 12 months, 19.8% DCB vs. 17.6% PTA at 24 months, and 28.2% DCB vs. 29.5% PTA at 36 months.
- Minor unplanned amputations were similar in the two treatment arms through 6 months. Thereafter, the rates diverged such that there was a 12.0% difference (95% CI 0.1%, 24.1%), in favor of the DCB-treated patients.

The data demonstrate that LUTONIX DCB is as safe as PTA for patients with CLI. The LUTONIX BTK IDE TRIAL not only met its primary safety endpoint, but safety outcomes results were maintained through three years without an increase in the risk of mortality or morbid events in the DCB arm compared with the PTA arm.

8.1 Primary Safety Endpoint (30-Day MALE or POD)

The primary safety endpoint was the 30-day rate of Major Adverse Limb Events (MALE), defined as major amputation or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis in an ipsilateral BTK artery) or perioperative (30-day) all-cause death.

The primary safety endpoint for non-inferiority of DCB to PTA was met (**Table 8-1**). The proportion of patients free from the primary safety endpoint through Day 30 was 99.3% (95% CI 97.5%, 99.9%) in the DCB arm and 99.4% (95% CI 96.5%, 100.0%) in the PTA arm (p<0.0001 single-sided).

Table 8-1. Analysis of Primary Safety Endpoint

	DCB Patients (N=287)*	PTA Patients (N=155)	Difference in Response†	P value‡
Freedom from Primary Safety Events through 30 Days	284 / 286 (99.3%) (97.5%, 99.9%)	154 / 155 (99.4%) (96.5%, 100.0%)	-0.1% (-3.9%, 3.8%)	< 0.0001
Primary Safety Events, n§				
Death ≤ Day 30	1	1		
Above Ankle Amputation ≤ Day 30	0	0		
Major Reintervention ≤ Day 30	1	0		

n/N (%), 95% CI based exact binomial distribution.

** One DCB patient had insufficient follow-up information so freedom from a primary safety event could not be confirmed.*

† Difference and 95% CI estimated by Farrington-Manning test.

‡ P-value for non-inferiority margin of 12%, Farrington-Manning test.

§ Patients may fail primary safety due to more than one cause.

8.2 Primary Safety Events Through 36 Months

Primary safety events (MALE+POD) were analyzed through 36 months. Similar rates of freedom from primary safety events in the DCB and PTA arms were maintained through 36 months, with a slight benefit for DCB throughout. The Kaplan-Meier estimate for primary safety event-free survival through 36 months is shown below in **Figure 8-1**. The 6, 12, and 36 Kaplan-Meier estimates of freedom from primary safety events in the DCB versus PTA arms were 97.8% vs. 95.3%, 95.9% vs.94.6%, and 93.7% vs. 91.3%, respectively.

In addition, freedom from primary safety events (MALE+POD) was analyzed as a binary endpoint (**Table 8-2**). Freedom from primary safety events in the DCB and PTA arms was 97.4% (95% CI 94.8%, 99.0%) vs. 95.2% (95% CI 90.4%, 98.1%) at 6 months, 95.7% (95% CI 92.4%, 97.8%) vs. 93.9% (95% CI 88.3%, 97.3%) at 12 months, and 90.1% (95% CI 84.5%, 94.2%) vs. 85.7% (95% CI 75.9%, 92.6%) at 36 months, respectively (confidence intervals not adjusted for multiple comparisons).

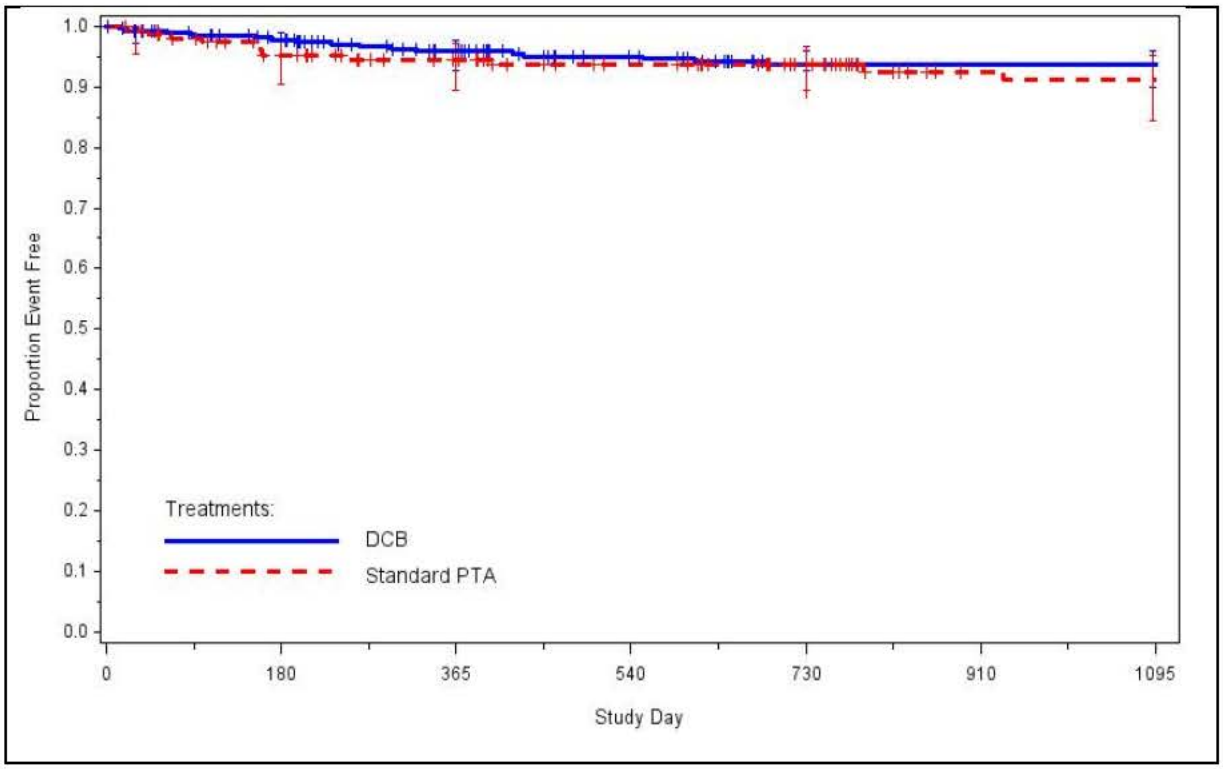

Figure 8-1. Kaplan-Meier Plot of the Primary Safety Events Through 36 Months

Group	Time Point	Freedom From MALE+POD*	Cumulative Patients with Events	Cumulative Patients Censored	Patients Left†	Difference‡
DCB	Day 1	100.0% (NA, NA)	0	1	286	
	Day 30	99.3% (97.2%, 99.8%)	2	4	281	-0.1% (-1.6, 1.5%)
	Day 44	99.3% (97.2%, 99.8%)	2	7	278	0.6% (-1.4, 2.6%)
	Day 180	97.8% (95.2%, 99.0%)	6	17	264	2.5% (-1.3, 6.4%)
	Day 210	97.5% (94.7%, 98.8%)	7	24	256	2.2% (-1.7, 6.1%)
	Day 365	95.9% (92.7%, 97.7%)	11	37	239	1.3% (-3.0, 5.7%)
	Day 395	95.9% (92.7%, 97.7%)	11	44	232	1.3% (-3.0, 5.7%)
	Day 730	93.7% (89.9%, 96.1%)	16	84	187	-0.0% (-5.0, 5.0%)
	Day 790	93.7% (89.9%, 96.1%)	16	108	163	1.1% (-4.3, 6.6%)
	Day 1095	93.7% (89.9%, 96.1%)	16	181	90	2.4% (-3.5, 8.3%)
	Day 1155	93.7% (89.9%, 96.1%)	16	248	23	2.4% (-3.5, 8.3%)

Group	Time Point	Freedom From MALE+POD*	Cumulative Patients with Events	Cumulative Patients Censored	Patients Left†	Difference‡
PTA	Day 1	100.0% (NA, NA)	0	0	155	
	Day 30	99.4% (95.5%, 99.9%)	1	1	153	
	Day 44	98.7% (94.9%, 99.7%)	2	2	151	
	Day 180	95.3% (90.4%, 97.7%)	7	13	135	
	Day 210	95.3% (90.4%, 97.7%)	7	16	132	
	Day 365	94.6% (89.4%, 97.2%)	8	26	121	
	Day 395	94.6% (89.4%, 97.2%)	8	32	115	
	Day 730	93.7% (88.3%, 96.7%)	9	53	93	
	Day 790	92.6% (86.4%, 96.0%)	10	65	80	
	Day 1095	91.3% (84.5%, 95.2%)	11	100	44	
	Day 1155	91.3% (84.5%, 95.2%)	11	127	17	

** Kaplan-Meier estimate of proportion of patients without a key safety event at the visit day (95% CI).*

† Patients ongoing without an event at the visit day

‡Difference (95% CI) from Kaplan-Meier estimates

Confidence intervals not adjusted for multiple comparisons

Table 8-2. Primary Safety Events Analyzed as a Binary Endpoint Through 36 Months

Visit	DCB Patients (N=287)		PTA Patients (N=155)		Difference (95% CI) †
	Response Rate*	95% CI†	Response Rate*	95% CI†	
30 Days	284 / 286 (99.3%)	(97.5%, 99.9%)	154 / 155 (99.4%)	(96.5%, 100.0%)	-0.1% (-1.6%, 1.5%)
6 Months	265 / 272 (97.4%)	(94.8%, 99.0%)	139 / 146 (95.2%)	(90.4%, 98.1%)	2.2% (-1.7%, 6.2%)
12 Months	242 / 253 (95.7%)	(92.4%, 97.8%)	123 / 131 (93.9%)	(88.3%, 97.3%)	1.8% (-3.1%, 6.6%)
24 Months	202 / 218 (92.7%)	(88.4%, 95.7%)	100 / 110 (90.9%)	(83.9%, 95.6%)	1.8% (-4.6%, 8.1%)
36 Months	146 / 162 (90.1%)	(84.5%, 94.2%)	66 / 77 (85.7%)	(75.9%, 92.6%)	4.4% (-4.7%, 13.5%)

** Response is freedom from MALE+POD through each visit of interest.*

† 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance.

Confidence intervals are not adjusted for multiple comparisons.

8.3 Primary Safety Endpoint: Covariate and Subgroup Analysis

A logistic regression model examined the potential impact of covariates and treatment group on the primary safety endpoint. The factors that examined are as follows:

- Protocol Version – Versions 1 through 7 and 8 through 12;

- Geographic Characteristics - geographic location (US, OUS), site location (Europe, Japan, US);
- Demographics and Baseline Characteristics - age, sex, smoking status, obesity, dyslipidemia, hypertension, diabetes, total pathways, Rutherford Category, previous intervention, baseline target limb hemodynamics;
- Target Lesion Characteristic – (by core lab) total lesion length, average baseline percent stenosis; and
- Procedural Related Characteristics, assessed by the core laboratory - average final residual stenosis (%), final residual stenosis, maximum post pre-dilatation residual stenosis, maximum post pre-dilatation residual stenosis ≤ 50%, maximum post pre-dilatation residual stenosis ≤ 75%, any dissection, any Grade D dissection, maximum dissection grade, any outflow to the foot.

Among these factors, the logistic model interaction term p-values were all close to 1, implying that the covariates had little to no effect on safety outcome. As one example, freedom from primary safety events through 30 days was similar in males (99% DCB vs. 100% PTA) and females (100% DCB vs. 98% PTA), with a p-value for treatment/factor interaction of 0.957.

8.4 Secondary Endpoints

8.4.1 Major Amputation

Major amputations were classified as those amputations at the above the ankle level in an index limb. There were no differences between the DCB and PTA arms with respect to major amputations. When analyzed as a binary endpoint, the difference in the frequency of freedom from major amputation was comparable in the DCB and PTA arms through 36 months (**Table 8-3)**: 98.5% (95% CI 96.3%, 99.6%) vs.97.9% (95% CI 94.1%, 99.6%) at 6 months, 97.2% (95% CI 94.3%, 98.9%) vs. 97.7% (95% CI 93.4%, 99.5%) at 12 months, and 93.1% (95% CI 88.0%, 96.5%) vs. 90.5% (95% CI 81.5%, 96.1%) at 36 months in the DCB and PTA arms, respectively.

Table 8-3. Freedom from Major Amputation as Binary Endpoint through 36 Months

Visit	DCB Patients (N=287)		PTA Patients (N=155)		Difference (95% CI)*
	Response Rate	95% CI*	Response Rate	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%)

** 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance.*

†Confidence intervals are not adjusted for multiple comparisons.

It is common to see no differences in limb salvage between different interventional modalities in CLI trials. A 2015 review by Sidiqi and Alexander found no difference in the 3-year rate of major amputation in patients treated with open surgical bypass or PTA, with limb salvage in 82% of patients despite patency rates of 72% versus 49% after bypass and PTA, respectively.[36] This observation may relate to the use of repeat reinterventions to rescue a limb when initial therapy fails, prior to the development of irreversible ischemia and a requirement for major amputation.

8.4.2 Unplanned Minor Amputation

Minor amputations were defined as those performed at the below the ankle level. Minor amputations were subclassified as planned or unplanned, as specified by the investigator prior to the index procedure, noting that the preoperative plan for a successful index procedure revascularization often includes the amputation of gangrenous toe or toes.

As expressed as a binary endpoint, there were no early differences between DCB and PTA with respect to unplanned minor amputations. The rate of unplanned minor amputation was relatively similar in the two treatment groups through 6 months: DCB 12.0% (95% CI 8.4%, 16.5%) vs. PTA 12.9% (95% CI 8.0%, 19.4%) (**Table 8-4**).

Thereafter, unplanned minor amputations were slightly less frequent in the DCB group: DCB 14.8% (95% CI 10.7%, 19.7%) vs. PTA 18.5% (95% CI 12.4%, 26.1%) at 12 months and DCB 24.2% (95% CI 18.1%, 31.1%) vs. PTA 36.1% (95% CI 25.9%, 47.4%) at 36 months. The difference between cumulative rate of unplanned minor amputations was -12.0% (95% CI -24.1%, 0.1%) in favor of DCB through the complete 36-month follow-up.

Table 8-4. Unplanned Minor Amputation as Binary Endpoint through 36 Months

Visit	DCB Patients (N=287)		PTA Patients (N=155)		Difference (95% CI)*
	Response Rate	95% CI*	Response Rate	95% CI*	
30 Days	14 / 286 (4.9%)	(2.7%, 8.1%)	12 / 155 (7.7%)	(4.1%, 13.1%)	-2.8% (-7.7%, 2.0%)
6 Months	33 / 274 (12.0%)	(8.4%, 16.5%)	19 / 147 (12.9%)	(8.0%, 19.4%)	-0.9% (-7.5%, 5.8%)
12 Months	38 / 257 (14.8%)	(10.7%, 19.7%)	25 / 135 (18.5%)	(12.4%, 26.1%)	-3.7% (-11.6%, 4.1%)
24 Months	43 / 226 (19.0%)	(14.1%, 24.8%)	29 / 117 (24.8%)	(17.3%, 33.6%)	-5.8% (-15.1%, 3.6%)
36 Months	43 / 178 (24.2%)	(18.1%, 31.1%)	30 / 83 (36.1%)	(25.9%, 47.4%)	-12.0% (-24.1%, 0.1%)

** 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance.*

Confidence intervals are not adjusted for multiple comparisons.

8.5 Adverse Events

Similar types and rates of AEs were observed in both treatment groups. There were no notable differences in procedure-related or device-related events between the DCB and PTA treatment arms through 36 months. There were no Unanticipated Adverse Device Effects (UADE) reported trial.

8.5.1 Common Adverse Events

The CEC determined that 11.5% of DCB patients and 9.7% of PTA patients experienced an event that met the protocol definition of a device-related event (Appendix **Section 14.5**, **Table 14-5**) through 36 months. A total of 25.4% of DCB patients and 19.4% of PTA patients experienced a procedure-related event in their 12-month window as adjudicated by the CEC (Appendix **Section 14.5**, **Table 14-6**).

8.6 Serious Adverse Events

Approximately two-thirds of patients experienced at least one SAE - 69% in the DCB arm and 65% in the PTA arm, reflecting the burden of disease in this patient population. SAEs were mostly similar between the DCB and PTA arms through 12 months (**Table 8-5**). All SAEs were reviewed and adjudicated by the blinded CEC.

Table 8-5. SAE Rates with a Preferred Term Through 12 Months in >3% of Patients

Preferred Term	DCB N=287	PTA N=155
At least one SAE	199 (69%)	101 (65%)
Peripheral arterial occlusive disease	37 (13%)	11 (7%)

Table 8-5. SAE Rates with a Preferred Term Through 12 Months in >3% of Patients

Preferred Term	DCB N=287	PTA N=155
Peripheral artery stenosis	33 (12%)	22 (14%)
Peripheral artery restenosis	39 (14%)	29 (19%)
Peripheral arterial reocclusion	23 (8%)	7 (5%)
Wound	11 (4%)	4 (3%)
Osteomyelitis	18 (6%)	12 (8%)
Gangrene	15 (5%)	9 (6%)
Cellulitis	10 (4%)	2 (1%)
Pneumonia	7 (2%)	6 (4%)
Cardiac failure congestive	11 (4%)	6 (4%)
Skin ulcers	10 (4%)	6 (4%)

Over eighty percent of DCB and PTA patients have experienced at least one SAE through 36 months (83.6% in the DCB arm, 81.3% in the PTA arm) reflecting the burden of disease, specifically cardiac and peripheral vascular disease, as well as co-morbidities that occur or worsen in this patient population over time. Similar serious adverse event types and rates were experienced in both treatment arms (Appendix **Section 14.5**, **Table 14-3**). Overall, 6.3% of DCB and 7.1% of PTA patients had experienced an event the CEC-adjudicated as a device-related SAE; 10.1% of DCB and 11.6% of PTA patients had SAEs adjudicated as procedure-related by the CEC (Appendix **Section 14.5**, **Table 14-8**).

8.7 Adverse Events of Special Interest

Distal embolization and thrombus events are of concern during percutaneous peripheral procedures due to the serious consequences that could be experienced by the patient if they occur.

8.7.1 Distal embolization

Distal embolization was reported in six DCB patients and one PTA patient during the perioperative period (through Day 30), each of which occurred on the day of the index procedure. As a binary endpoint, the rate of distal embolization reported at the 30-day visit was 2.1% (95% CI 0.8%, 4.5%) in the DCB arm and 0.6% (95% CI 0.0%, 3.5%).

Table 8-6 summarizes freedom from distal embolization as a binary endpoint though 36 months. Freedom from distal embolization in the DCB and PTA arms was 97.4% (95% CI 94.8%, 99.0%) vs. 98.6% (95% CI 95.1%, 99.8%) at 6 months, 97.2% (95% CI 94.3%, 98.9%) vs. 98.4% (95% CI 94.5%, 99.8%) at 12 months, and 95.6% (95% CI 91.2%, 98.2%) vs. 97.2% (95% CI 90.3%, 99.7%) at 36 months, respectively.

Table 8-6. Freedom from Distal Embolization through 36 Months

Visit	DCB Patients (N=287)		PTA Patients (N=155)		Difference (95% CI)*
	Response Rate	95% CI*	Response Rate	95% CI*	
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%)

** 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance. Confidence intervals are not adjusted for multiple comparisons.*

8.7.2 Thrombectomy and Thrombolytic Reinterventions

Low rates of thrombectomy/thrombolysis were observed in both groups. Through 30 days, only one DCB patient and no PTA patients required thrombectomy or thrombolysis, for a binary event rate of 0.7% (95% CI 0.0%, 1,9%) in the DCB arm and 0.0% (95% CI 0.0%, 2.4%) in the PTA arm.

Freedom from thrombectomy and thrombolysis was similar in the two groups throughout follow-up, with rates of 98.5% (95% CI 96.3%, 99.6%) DCB vs. 97.9% (95% CI 94.1%, 99.6%) PTA at 6 months, 98.0% (95% CI 95.4%, 99.4%) DCB vs. 96.1% (95% CI 91.2%, 98.7%) PTA at 12 months, and 92.0% (95% CI 86.7%, 95.7%) DCB vs. 91.8% (95% CI 83.0%, 96.9%) PTA at 36 months (**Table 8-7**).

Table 8-7. Freedom from Thrombectomy/ Thrombolysis through 36 Months

Visit	DCB Patients (N=287)		PTA Patients (N=155)		Difference (95% CI)*
	Response Rate	95% CI*	Response Rate	95% CI*	
30 Days	285 / 286 (99.7%)	(98.1%, 100.0%)	155/155 (100%)	(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%)

Table 8-7. Freedom from Thrombectomy/ Thrombolysis through 36 Months

Visit	DCB Patients (N=287)		PTA Patients (N=155)		Difference (95% CI)*
	Response Rate	95% CI*	Response Rate	95% CI*	
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%)

** 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance.*

Confidence intervals are not adjusted for multiple comparisons.

8.8 All-Cause Death

There were 74 deaths from all causes reported in the LUTONIX BTK study: one in the roll-in cohort and 73 in the randomized cohort (48/287, 16.7% DCB and 25/155, 16.1% PTA). Perioperative death (death through 30 days) occurred in one patient in each randomized group. Analyses in the Clinical Study Report included 70 CEC adjudicated deaths through 3 years (1155 days).

All-cause death rates were similar between treatment arms at all study time points, with a 36-month (1095-day) Kaplan-Meier estimate of freedom from all-cause death of 81.0% (95% CI 75.3%, 85.5%) in the DCB patients and 81.0% (95% CI 72.5%, 87.1%) in the PTA patients. The 3-year hazard ratio was near unity, at 1.04 (95% CI: 0.63, 1.71) (**Figure 8-2** and **Table 8-8**).

An additional analysis of vital statistics was performed in 2020 at FDA's request, after extension of the study protocol from 3 to 5 years. A June 17, 2020 data cut was conducted to ascertain all-cause mortality at 48 and 60 months, using additional vital statistics collected by the investigational sites. While the data available at 48 and 60 months remains limited, no differences in mortality between DCB and PTA was found. The sponsor is continuing to contact sites and collect vital statistics through 60 months. The Kaplan-Meier analyses through 60 months are presented in **Section 14.4** of the Appendix (**Figure 14-1**).

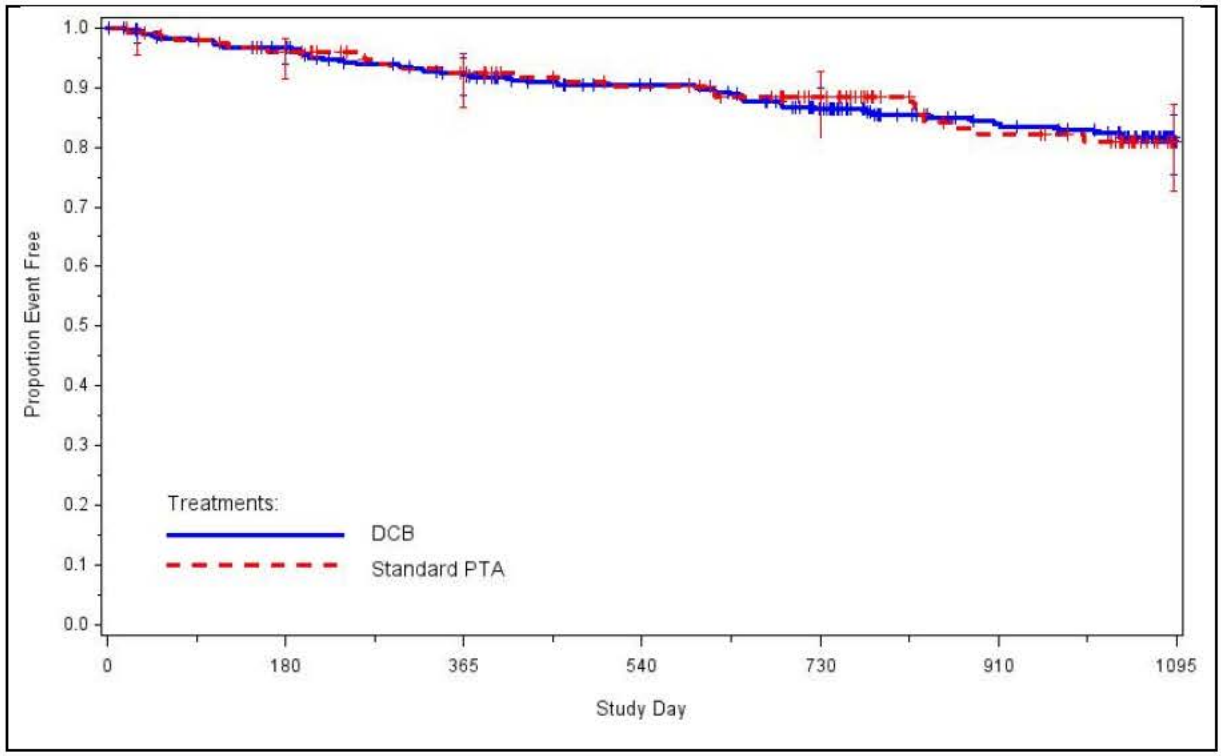

Figure 8-2. Kaplan-Meier Plot of Survival (Freedom from All-Cause Death) Through 36 Months

Group	Time Point	Freedom From MALE+POD*	Cumulative Patients with Events	Cumulative Patients Censored	Patients Left†	P-Value‡
DCB	Day 1	100.0% (NA, NA)	0	1	286	
	Day 30	99.6% (97.5%, 100.0%)	1	4	282	0.661
	Day 44	98.9% (96.8%, 99.7%)	3	5	279	0.671
	Day 180	96.8% (94.0%, 98.3%)	9	9	269	0.692
	Day 210	95.0% (91.7%, 97.0%)	14	12	261	0.636
	Day 365	92.4% (88.6%, 95.0%)	21	19	247	0.973
	Day 395	91.7% (87.7%, 94.4%)	23	24	240	0.781
	Day 730	86.4% (81.6%, 90.0%)	36	52	199	0.598
	Day 790	85.4% (80.5%, 89.2%)	38	74	175	0.476
	Day 1095	81.0% (75.3%, 85.5%)	46	145	96	0.946
	Day 1155	80.0% (73.9%, 84.8%)	47	214	26	0.880

Group	Time Point	Freedom From MALE+POD*	Cumulative Patients with Events	Cumulative Patients Censored	Patients Left†	P-Value‡
PTA	Day 1	100.0% (NA, NA)	0	0	155	
	Day 30	99.4% (95.5%, 99.9%)	1	1	153	
	Day 44	99.4% (95.5%, 99.9%)	1	2	152	
	Day 180	96.0% (91.4%, 98.2%)	6	8	141	
	Day 210	96.0% (91.4%, 98.2%)	6	12	137	
	Day 365	92.4% (86.7%, 95.7%)	11	17	127	
	Day 395	92.4% (86.7%, 95.7%)	11	23	121	
	Day 730	88.5% (81.8%, 92.8%)	16	39	100	
	Day 790	88.5% (81.8%, 92.8%)	16	52	87	
	Day 1095	81.0% (72.6%, 87.1%)	23	85	47	
	Day 1155	81.0% (72.6%, 87.1%)	23	115	17	

** Kaplan-Meier estimate of proportion of patients without a key safety event at the visit day (95% CI).*

† Patients ongoing without an event at the visit day.

‡ Log Rank Test p-value not adjusted for repeat pathways per patient.

Confidence intervals not adjusted for multiple comparisons.

When calculated as a binary endpoint, all-cause death was similar in the two groups throughout the 36-month follow-up period (**Table 8-8**). All-cause death occurred in the two treatment arms as follows: 5.0% (95% CI 2.8%, 8.2%) DCB vs. 4.0% (95% CI 1.5%, 8.5%) PTA at 6 months, 8.5% (95% CI 5.5%, 12.5%) DCB vs. 7.9% (95% CI 4.0%, 13.7%) PTA at 12 months, and 23.5% (95% CI 17.8%, 30.0%) DCB vs. 24.5% (95% CI 16.2%, 34.4%) PTA at 36 months. The difference in all-cause mortality was -1.0% (95% CI -11.5%, 9.5%) between DCB and PTA at 36 months (in favor of DCB).

Table 8-8. All-Cause Death as a Binary Endpoint Through 36 Months

Visit	DCB Patients (N=287)		PTA Patients (N=155)		Difference (95% CI)*
	Response Rate	95% CI*	Response Rate	95% CI*	
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%)

** 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance.*

†Confidence intervals are not adjusted for multiple comparisons.

The causes of death were similar in the two treatment groups (**Section 14.5, Table 14-9**). The most prevalent primary cause of death was cardiac-related, with cancer the second most prevalent.

8.9 Safety in PAD Patients Treated with Paclitaxel Devices

In December 2018, a study-level meta-analysis of randomized SFA trials showed a significantly increased mortality rate in PAD patients starting at two years after treatment with paclitaxel devices compared to patients treated with non-coated balloons or bare metal stents.[37] On June 19-20, 2019, the FDA convened a public meeting of the Circulatory System Devices Panel to discuss and make recommendations on the evidence suggesting a safety concern for PAD patients treated with paclitaxel devices.[38,39] To resolve the issue, a collaboration between industry, clinicians and regulators has taken common steps to evaluate all available data from randomized and real-world studies. Supportive information from retrospective analysis of Medicare Advantage beneficiaries who underwent peripheral vascular interventions showed no evidence of an elevated mortality risk due to paclitaxel-coated devices.[40] In addition, no association of all-cause mortality was found in patients treated with paclitaxel-coated devices in the VOYAGER PAD trial, while rivaroxaban/aspirin was superior to aspirin at preventing major adverse limb and cardiovascular events.[41] Most recently, interim data from the SWEDEPAD randomized clinical trial of 2289 patients randomly assigned to DCB or PTA found no difference in mortality rates in the two arms.[25] Among the 1480-patient subset with CLI, all-cause mortality was 33.4% in the DCB arm and 33.1% in the PTA arm, through mean follow-up of approximately 2.5 years.

8.10 Safety Conclusions

CLI is a progressive disease punctuated by clinical events that can progress to amputation. The totality of safety data from the BTK IDE Trial demonstrate that the LUTONIX DCB is safe to use. The adverse events for the DCB arm were similar to those in the standard PTA arm, both in frequency and type. Mortality and amputation rates were low and equal between treatment arms at 6 months and out to 3 years. The LUTONIX BTK IDE randomized clinical trial for BTK arterial disease confirmed the safety of DCB and demonstrated non-inferiority to PTA.

9 CLINICAL EFFECTIVENESS

Summary

- The LUTONIX DCB demonstrated an improvement in the clinically meaningful composite endpoint of limb salvage and primary patency at 6 months compared to PTA, providing an improvement in the critical early time period which is of great importance to CLI patients with limited life expectancies.
    - The 6-month success rate was 74.7% for the DCB arm and 64.2% for the PTA Control arm (10.5% difference in favor of DCB, 95% CI 0.3%, 18.8%).
    - The p-value for this difference was 0.0222, which did not meet the threshold of 0.0085.
- The Kaplan-Meier estimate for the primary effectiveness endpoint was 85.8% compared with 71.4% through 6 months, accounting for a difference of 14.4% (95% CI 5.4%, 23.5%).
- There was also a benefit in time to first reintervention and number of interventions associated with DCB, each of which are clinically important outcomes for patients.
- Improvements were observed in infection rates, major amputations, wound healing, and quality of life using available measurement methodology, in both treatment arms.
- The study sample size was based only on power for the primary endpoints.

The LUTONIX 014 DCB augments PTA catheters, with the addition of a drug coating to the surface of the balloon. Findings from the LUTONIX DCB trial showed the benefits associated with balloon dilation, with an improvement in the clinically meaningful composite endpoint of limb salvage and primary patency at 6 months compared to PTA. This benefit at the primary endpoint timepoint provided improvement during the critical early time following the procedure, a benefit which is of great importance to CLI patients with limited life expectancies.

Analyses based on the 6-month primary effectiveness endpoint are presented below, followed by information regarding missing data, then longer-term effectiveness data.

9.1 Primary Effectiveness Endpoint Analysis

The LUTONIX DCB demonstrated improvement in the composite endpoint of limb salvage and primary patency (freedom from occlusion or CEC adjudicated CD-TLR) at 6 months compared to PTA demonstrating patency of the treated pathway (**Table 9-1**). There were 406 treated flow pathways with data available for analysis at 6 months, 269 in the DCB arm and 137 in the PTA arm. The 6-month success rate was 74.7% for the DCB arm and 64.2% for the PTA arm, accounting for a 10.5% difference in favor of DCB (95% CI 0.3%, 18.8%). The p-value for this difference was 0.0222, which did not meet the threshold of 0.0085 for the primary effectiveness endpoint.

Table 9-1. Primary Effectiveness Endpoint at 6 Months (By Pathway)

	DCB n/N (%) (95% CI)*	PTA n/N (%) (95% CI)*	Difference in Response (95% CI)†	P-value‡
Free from Primary Effectiveness Failure at 6 Months	201/269 (74.7%) (69.1%, 79.8%)	88/137 (64.2%) (55.6%, 72.2%)	10.5% (0.3%, 18.8%)	0.0222
Composite Endpoint Failure Events, n¶				
Patients with major amputation ≤ Day 210	4	3		
Pathways with clinically driven TLR ≤ Day 210	28	30		
Pathways with primary patency failure ≤ Day 210	65	46		

** 95% CI based exact binomial distribution.*

†Based on the model estimated response rates in both groups.

‡ One-sided Wald Test based on model estimate of DCB treatment effect and pathway as a random effect.

¶ Pathways may fail primary effectiveness due to more than one cause and TLR failure is a component of primary patency failure.

It is important to note that in the DCB and PTA arms, 27/269 and 12/137 pathways (with 6-month effectiveness outcomes) were in Rutherford Category 3 (severe claudication) patients, respectively. The response rate for these pathways was excellent in both groups (93.1% DCB and 100% PTA). Although this was post-hoc analysis, these pathways diluted the benefit observed in the differential response rate of DCB and PTA in Rutherford Categories 4 and 5 pathways. The difference in the primary effectiveness endpoint was favorable for DCB; 12.5% (95% CI -2.5%, 27.6%) and 9.0% (95% CI -4.6%, 22.5%) for Rutherford Category 4 and 5 pathways, respectively. By contrast, the difference for Rutherford Category 3 pathways was -6.9% (95% CI -16.1%, 2.3%), in favor of PTA (confidence intervals are based on nominal levels and not adjusted for multiple comparisons).

9.2 Individual Components of the Primary Effectiveness Endpoint

The individual components of the primary endpoint are summarized below, evaluating each as a binary endpoint with exact binominal confidence intervals unadjusted for multiple comparisons.

9.2.1 Freedom from Major Amputation through 6 months (By Patient)

Freedom from major amputation was favorable and similar in the two treatment arms through 6 months. Assessed by patient, freedom from major amputation was 267/271 or 98.5% (95% CI 96.3%, 99.6%) in the DCB patients and 142/145 or 97.9% (95% CI 94.1%, 99.6%) in the PTA patients.

9.2.3 Freedom from Clinically Driven TLR through 6 Months (By Pathway)

Clinically driven TLR was numerically higher in the DCB pathways compared with the PTA pathways, 275/303 or 90.9% (95% CI 86.9%, 93.8%) and 142/172 or 82.6%, (95% CI 76.0%, 87.9%), respectively, through 6 months. This accounted for a difference of 8.2% (95% CI 1.5%, 13.3%) in favor of DCB.

9.2.4 Primary Patency Through 6 Months (By Pathway)

Primary patency (freedom from occlusion or CD-TLR) was higher in the DCB pathways compared with the PTA pathways through 6 months, 201/266 or 75.6% (95% CI 69.9%, 80.6%) and 88/134 or 65.7% (95% CI 57.0%, 73.7%), respectively. The difference between the two arms was 9.9% (95% CI -0.4%, 18.1%) through 6 months, in favor of DCB.

9.3 Post-Hoc Analysis of Missing Data

The primary effectiveness endpoint was a composite of major amputation, clinically driven TLR, and patency. Assessment of major amputation required that the patient be in the study at least until the start of the visit window. Assessment of patency required an evaluable duplex ultrasound study (DUS) or angiogram reviewed by the core laboratory. CD-TLR required CEC adjudication of a reported TLR. In sum, the effectiveness endpoint was missing when a) a patient was not followed to the analysis window (and did not meet the endpoint prior), or b) a DUS or angiogram was not performed or was of insufficient quality for core laboratory assessment.

An analysis of missing effectiveness data was performed with the following findings: First, the amount of missing data varied between randomized groups, as well as over time (**Table 9-2**). In general, there were more missing effectiveness endpoint values in the PTA arm.

Table 9-2. Rates of Missing Effectiveness Endpoint Data Over Time (By Pathway)

Missing Endpoint	30 Days		6 Months		12 Months		24 Months		36 Months	
	DCB	PTA	DCB	PTA	DCB	PTA	DCB	PTA	DCB	PTA
n/N	29/323	28/184	54/323	47/184	72/323	52/184	95/323	61/184	113/323	84/184
%	9.0%	15.2%	16.7%	25.5%	22.2%	28.2%	29.4%	33.2%	35.0%	45.7%

Second, there were differences in baseline variables between missing versus not missing data at the different time points. A complete list of all covariates assessed for missing/non-missing values is summarized in **Table 14-11** (Section 14.7 of the Appendix) for the 6, 12, 24, and 36-month timeframes. As an example of potential imbalances, **Table 9-3** compares three risk factors, age, sex, and dyslipidemia, with missing and non-missing data at the 12-month timepoint.

Table 9-3. Some Baseline Variables that Differed for Missing and Non-Missing Status

Risk Factors	DCB Pathways		PTA Pathways	
	Missing 12-Month Status	Not Missing 12-Month Status	Missing 12-Month Status	Not Missing 12-Month Status
Age (Mean Years)	76	72	76	72
Female Sex (%)	32%	28%	46%	30%
Dyslipidemia (%)	76%	80%	63%	80%

Observations on missing data confirm that missingness created imbalances in risk factors over time. These treatment arm imbalances rendered longer-term comparisons of effectiveness between the two groups challenging.

9.4 Sensitivity Analyses of the Primary Effectiveness Endpoint

There were three sensitivity analyses performed. These analyses included a tipping point analysis, a multiple imputation for missing values, and a sensitivity analysis by site and treatment group for the primary effectiveness endpoint of freedom from amputation or lost primary patency (occlusion or clinically driven TLR).

9.4.1 Tipping Point Analysis (By Pathway)

Tipping point analyses were pre-specified to ascertain the stability of the analysis; vis a vis the number of DCB successes or PTA failures in the missing data that would result in achieving the 0.0085 p-value threshold for success.

The rate of pathways with missing data for the primary effectiveness endpoint of freedom from amputation and loss of primary patency at 6 months was 17.3% (54/323) in the DCB arm and 25.5% (47/184) in the PTA arm. A tipping point analysis for the ITT population assessed all combinations of study outcomes based on imputing none to all missing data for successes in both treatment arms. The analysis demonstrated the DCB and PTA response rates that would have resulted in meeting the threshold of $p<0.0085$. These results appear in **Figure 9-1**, described as follows:

- Varying rates of the 6-month primary effectiveness outcome appear along the Y-axis for DCB and along the X-axis for PTA.
- Green dots indicate the DCB/PTA response rates where the primary effectiveness endpoint was met. Red dots indicate those rates where the endpoint was not met.
- The blue crosshairs and the dot depict the actual results of the study using multiple imputation for missing values.

The proximity of the current response rates (e.g., DCB 74.7%, PTA 64.2%) to the green area of the chart is an indication of the sensitivity for meeting the primary endpoint to small changes in the response rates in the two treatment arms.

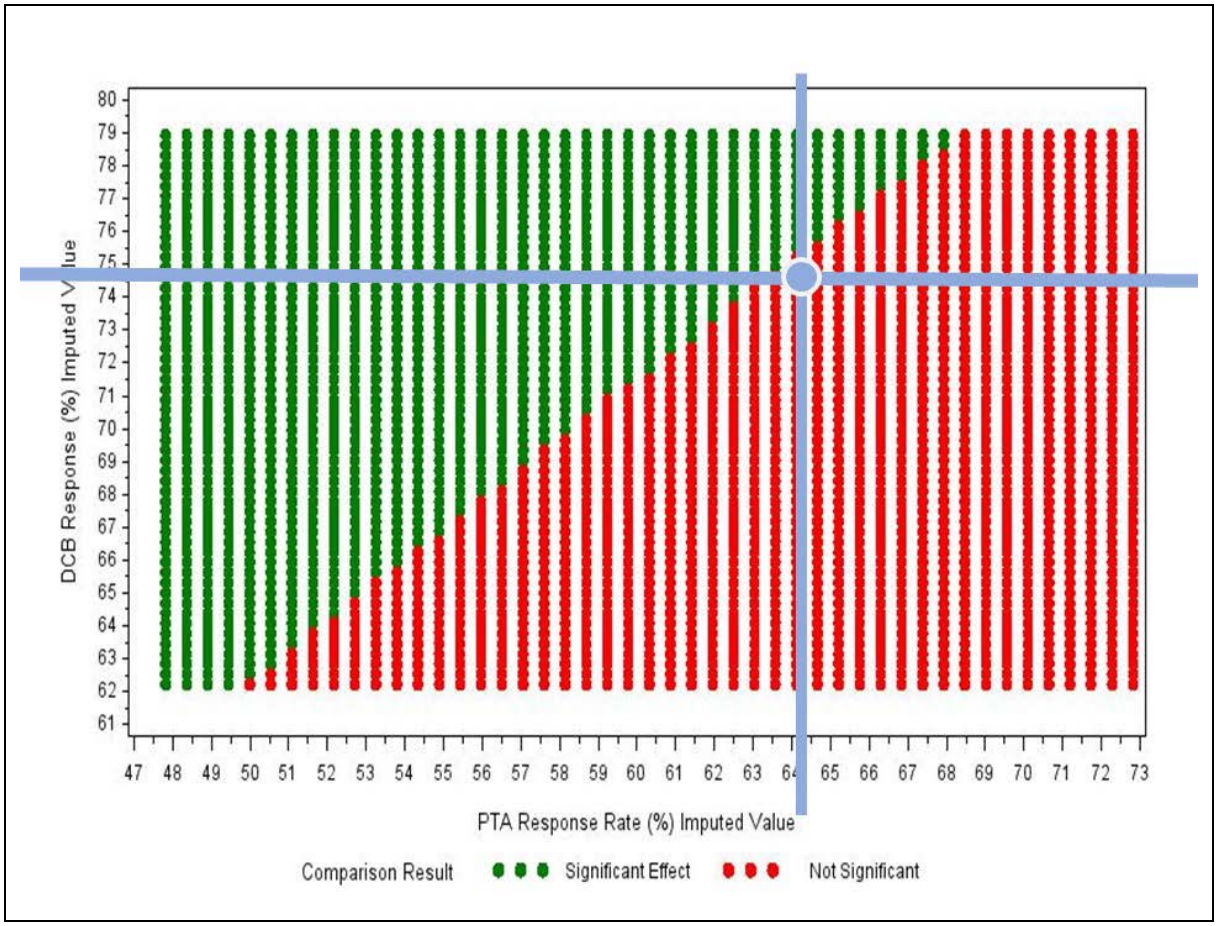

Figure 9-1. Tipping Point Analysis for 6-Month Primary Effectiveness

9.4.2 Multiple Imputation Analysis (By Pathway)

Two multiple imputation post-hoc analyses were performed. The first imputation was reviewed by FDA but the second was not. Each analysis used 100 imputations of the study data using key demographic, target lesion, and procedural characteristics to model patient outcome information. The p-value for the treatment comparison was from the logistic model treatment effect with a random patient intercept based on the imputed data sets.

The first multiple imputation analysis imputed treated all missing pathways, regardless of treatment group, as having the same response pattern as the combined non-missing data. The first multiple imputation model was used to obtain an estimated difference in the primary effectiveness endpoint of 7.9% (95% CI -1.6%, 16.0%); with individual rates of 74.2% in DCB vs. 66.3% in PTA (p=0.052). The second multiple imputation model was identical to the first but imputed separately for each randomized group. This produced an estimated difference in

the primary effectiveness endpoint of 10.0% (95% CI 0.4%, 18.5%); with individual rates of 73.8% in DCB vs. 63.8% in PTA (p=0.024). While this second model was post-hoc and has not been reviewed by FDA, it suggests the potential for missing data to be related to the potential outcomes. This raises questions about the longer-term results where there were increasing levels of missing data and a difference in amounts of missing data between the randomized groups.

9.4.3 Sensitivity Analysis by Site and Treatment Group

The final sensitivity analysis assessed the primary effectiveness endpoint by site and treatment group using a mixed effects logistic model with fixed effect for treatment group study site, and the interaction of treatment group and site in the ITT population. The model also included a random effect for individual to accommodate the potential for correlation between observations for patients with two treated flow pathways. There was no evidence of a statistically significant interaction effect with a p-value of > 0.15.

9.4.4 Covariate Analysis of the 6-Month Primary Effectiveness Endpoint

A logistic regression model using pre-identified covariates along with treatment group helped examine any potential impact on the study results and to account for chance imbalances between randomized groups. This covariate effectiveness analysis is included as **Table 14-10** in Appendix **Section 14.6.**

There was no statistically significant difference in the 6-month primary effectiveness endpoint by protocol version (1-7 vs. 8-12), geography (US vs. OUS or US vs. Japan vs. Europe), sex, smoking status, obesity, diabetes, pathways (1 vs. 2), Rutherford Category, prior intervention, lesion length, baseline percent stenosis, reference vessel diameter, calcification, or TASC score (p-value for interaction term was > 0.15 for these covariates). In sum, the primary effectiveness endpoint results in the DCB and PTA arms did not appear to be significantly related to a variety of baseline factors.

Procedural angiographic findings (final residual stenosis) were unrelated to effectiveness, with one exception. A residual stenosis of ≤50% after pre-dilation was associated with primary effectiveness in 129/166 (77.7%) and 69/94 (73.4%) in the DCB and PTA arms, respectively, compared with 58/83 (69.9%) and 11/32 (34.4%) in the DCB and PTA arms when the residual stenosis was >50% after pre-dilation (p-value for interaction 0.031). In other words, pathways with a suboptimal technical result after pre-dilation appeared to do worse when treated with PTA compared with DCB. Of note, bailout stents were used in only 3 DCB and 1 PTA pathways, precluding a meaningful analysis of their effect.

9.5 Secondary Effectiveness Endpoints

Secondary endpoints assessed through the 36-month follow-up period are presented below, including the composite of limb salvage and primary patency (the primary effectiveness endpoint), primary patency as a single endpoint, clinically driven TLR (freedom from and total number), major and minor amputations, wound status including healing, infection, and gangrene, quality of life (EQ-5D), and Rutherford Category.[c]

9.5.1 Primary Effectiveness Endpoint Through 36 Months (By Pathway)

The primary effectiveness endpoint (composite of limb salvage and primary patency) is shown in **Figure 9-2** as a Kaplan-Meier plot through 36 months. While treatment with DCB was favorable in comparison to PTA through 6 months, the rates converged thereafter and crossed at 12 months. The amount of missing data at later time points suggests there is uncertainty with respect to longer term results.

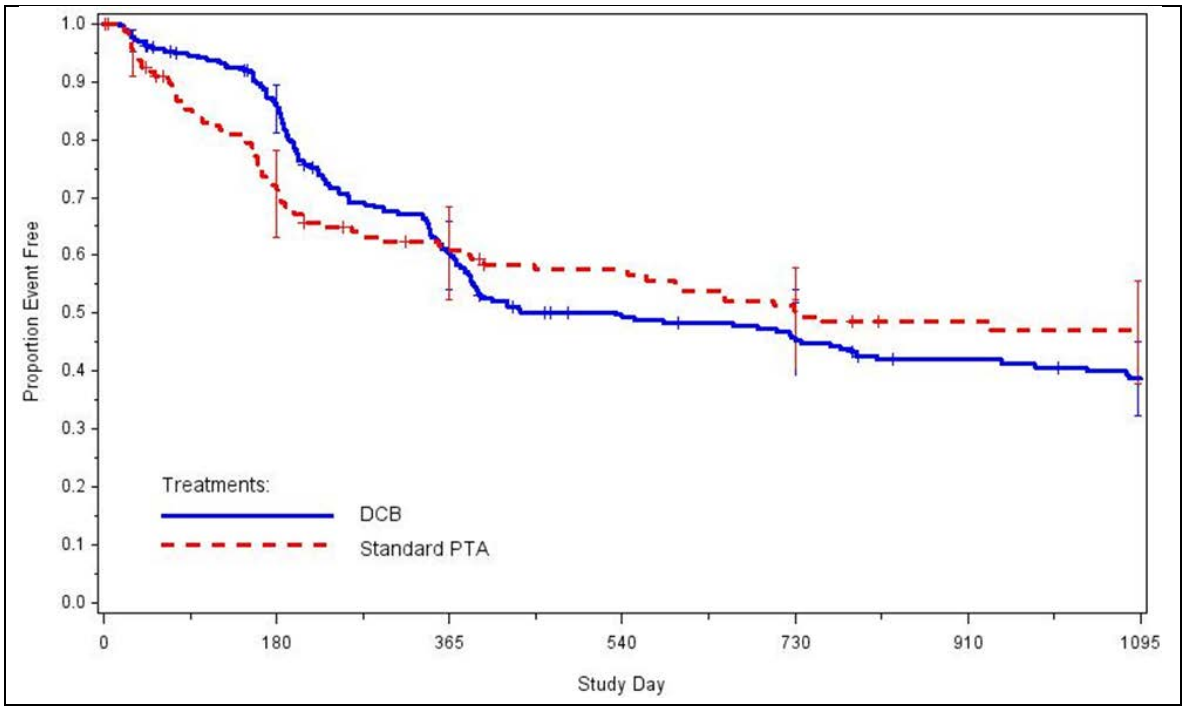

Figure 9-2. Kaplan-Meier Plot of Primary Effectiveness

[c] Not all secondary endpoints are reported in this document. The Clinical Study Report has a more complete analysis of the secondary endpoints specified in the study protocol (see Sections 6.5.6 and 6.5.7).

Group	Time Point	Primary Effectiveness (95% CI)*	Cumulative Events	Cumulative Pathways Censored	Pathways Left†	Difference (95% CI)
DCB	Day 1	100.0% (NA, NA)	0	22	301	
	Day 30	97.7% (95.2%, 98.9%)	7	22	294	2.0% (-1.4, 5.8%)
	Day 44	96.3% (93.5%, 98.0%)	11	42	270	3.8% (-0.7, 9.0%)
	Day 180	85.8% (81.1%, 89.4%)	40	48	235	14.4% (5.4, 23.5%)
	Day 210	75.6% (70.1%, 80.2%)	68	66	189	10.0% (0.2, 19.9%)
	Day 365	60.3% (54.1%, 65.9%)	106	67	150	-0.6% (-10.8,
	Day 395	53.1% (46.8%, 58.9%)	124	88	111	10.1%)
	Day 730	45.7% (39.3%, 51.8%)	139	93	91	-6.2% (-16.7, 4.6%)
	Day 790	43.2% (36.8%, 49.4%)	144	110	69	-3.7% (-14.9, 7.5%)
	Day 1095	38.7% (32.2%, 45.1%)	151	113	59	-5.3% (-16.5, 5.7%)
	Day 1155	38.0% (31.5%, 44.5%)	152	171	0	-8.3% (-19.7, 3.1%)
						-7.4% (-19.1, 4.3%)
PTA	Day 1	100.0% (NA, NA)	0	21	163	
	Day 30	95.6% (91.0%, 97.9%)	7	24	153	
	Day 44	92.5% (87.2%, 95.7%)	12	43	129	
	Day 180	71.4% (63.2%, 78.1%)	41	45	98	
	Day 210	65.6% (57.1%, 72.8%)	49	50	85	
	Day 365	60.9% (52.2%, 68.4%)	55	52	77	
	Day 395	59.3% (50.6%, 67.0%)	57	60	67	
	Day 730	49.4% (40.5%, 57.7%)	68	61	55	
	Day 790	48.5% (39.6%, 56.9%)	69	82	33	
	Day 1095	47.0% (37.8%, 55.6%)	70	84	30	
	Day 1155	45.4% (36.1%, 54.2%)	71	107	6	

**Kaplan-Meier estimate of proportion of pathways without a composite failure event at the visit day.*

†Pathways ongoing without an event at the visit day

Confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

As assessed as a binary endpoint, the 36-month rate of the primary effectiveness endpoint was 27.6% (95% CI 21.7%, 34.2%) in the DCB pathways and 29.0% (95% CI 20.4%, 38.9%) in the PTA pathways; a difference of -1.4% (95% CI -11.6%, 11.3%). The response rate of the primary effectiveness endpoint all timepoints through 36 months is summarized in **Table 9-4.**

Table 9-4. Primary Effectiveness Endpoint Through 36 Months (Analyzed as a Binary Endpoint by Pathway)

Visit	DCB Pathways		PTA Pathways		Difference (95% CI)
	Response Rate	95% CI	Response Rate	95% CI	
30 Days	283 / 294 (96.3%)	(93.4%, 98.1%)	144 / 156 (92.3%)	(86.9%, 96.0%)	4.0% (-1.0%, 7.9%)
6 Months	201 / 269 (74.7%)	(69.1%, 79.8%)	88 / 137 (64.2%)	(55.6%, 72.2%)	10.5% (0.3%, 18.7%)
12 Months	128 / 251 (51.0%)	(44.6%, 57.3%)	75 / 132 (56.8%)	(47.9%, 65.4%)	-5.8% (-17.0%, 5.2%)
24 Months	84 / 228 (36.8%)	(30.6%, 43.5%)	54 / 123 (43.9%)	(35.0%, 53.1%)	-7.1% (-17.5%, 4.5%)
36 Months	58 / 210 (27.6%)	(21.7%, 34.2%)	29 / 100 (29.0%)	(20.4%, 38.9%)	-1.4% (-11.6%, 11.3%)
Confidence intervals not adjusted for multiple comparisons					

9.5.2 Target Lesion Reinterventions (By Pathway)

All reinterventions for failure of the index procedure excluded the use of the LUTONIX DCB study device; use of the study device was restricted to the index procedure alone. **Table 9-5** shows the secondary interventions by type. At each timepoint, the most common type of reintervention in both the DCB and PTA arms was PTA with uncoated balloons.

With study randomization of 2:1 (DCB:PTA), at 6 months the PTA arm had two times the number of interventions compared to the DCB arm; 37 for DCB and 37 for PTA. Reinterventions to maintain secondary patency were also more frequent in the PTA arm through 12 months; 71 vs. 49 in the 2:1 randomized DCB:PTA arms, respectively.

Table 9-5. Types of TLRs for Pathways through 36 Months

Description	DCB TLR Pathways with Secondary Patency* (N=287)	PTA TLR Pathways with Secondary Patency* (N=155)
All Interventions by Type to 30 Days, n/N (%)		
Laser	1 (16.7%)	0 (0.0%)
PTA	4 (66.7%)	5 (100.0%)
Stent	1 (16.7%)	0 (0.0%)
Total Interventions (N)	6	5

Table 9-5. Types of TLRs for Pathways through 36 Months

Description	DCB TLR Pathways with Secondary Patency* (N=287)	PTA TLR Pathways with Secondary Patency* (N=155)
All Interventions by Type to 6 Months, n/N (%)		
Atherectomy	6 (16.2%)	3 (8.1%)
Bypass Graft	1 (2.7%)	0 (0.0%)
PTA	24 (64.9%)	28 (75.7%)
Stent	6 (16.2%)	4 (10.8%)
Thrombectomy/Thrombolysis	0 (0.0%)	2 (5.4%)
Total Interventions (N)	37	37
All Interventions by Type to 12 Months, n/N (%)		
Atherectomy	12 (16.9%)	5 (10.2%)
Bypass Graft	1 (1.4%)	0 (0.0%)
Laser	1 (1.4%)	1 (2.0%)
PTA	50 (70.4%)	32 (65.3%)
Stent	6 (8.5%)	8 (16.3%)
Thrombectomy/Thrombolysis	1 (1.4%)	3 (6.1%)
Total Interventions (N)	71	49
All Interventions by Type to 24 Months, n/N (%)		
Atherectomy	16 (17.2%)	6 (12.0%)
Laser	2 (2.2%)	0 (0.0%)
PTA	66 (71.0%)	39 (78.0%)
Stent	6 (6.5%)	4 (8.0%)
Thrombectomy/Thrombolysis	3 (3.2%)	1 (2.0%)
Total Interventions (N)	93	50
All Interventions by Type to 36 Months, n/N (%)		
Atherectomy	12 (13.8%)	4 (12.9%)
Laser	1 (1.1%)	0 (0.0%)
PTA	65 (74.7%)	24 (77.4%)
Stent	5 (5.7%)	3 (9.7%)
Thrombectomy/Thrombolysis	4 (4.6%)	0 (0.0%)
Total Interventions (N)	87	31

**Secondary patency of a target lesion is defined as the absence of total occlusion (100% diameter stenosis) based on angiography or ultrasound and is independent of whether patency was reestablished with an endovascular procedure.*

9.5.3 Primary Patency Through 36 Months(By Pathway)Primary patency was defined as freedom from occlusion and clinically driven TLR. The angiographic Core Lab determined presence of occlusion. The CEC adjudicated clinically driven TLR. Primary patency was analyzed based on pathways, using Kaplan-Meier methodology (**Figure 9-3**) as well as a binary outcome (**Table 9-6**). As for the primary effectiveness endpoint, primary patency for the DCB arm was favorable in comparison to PTA through 6 months. Thereafter, the rates converged and crossed at 12 months.

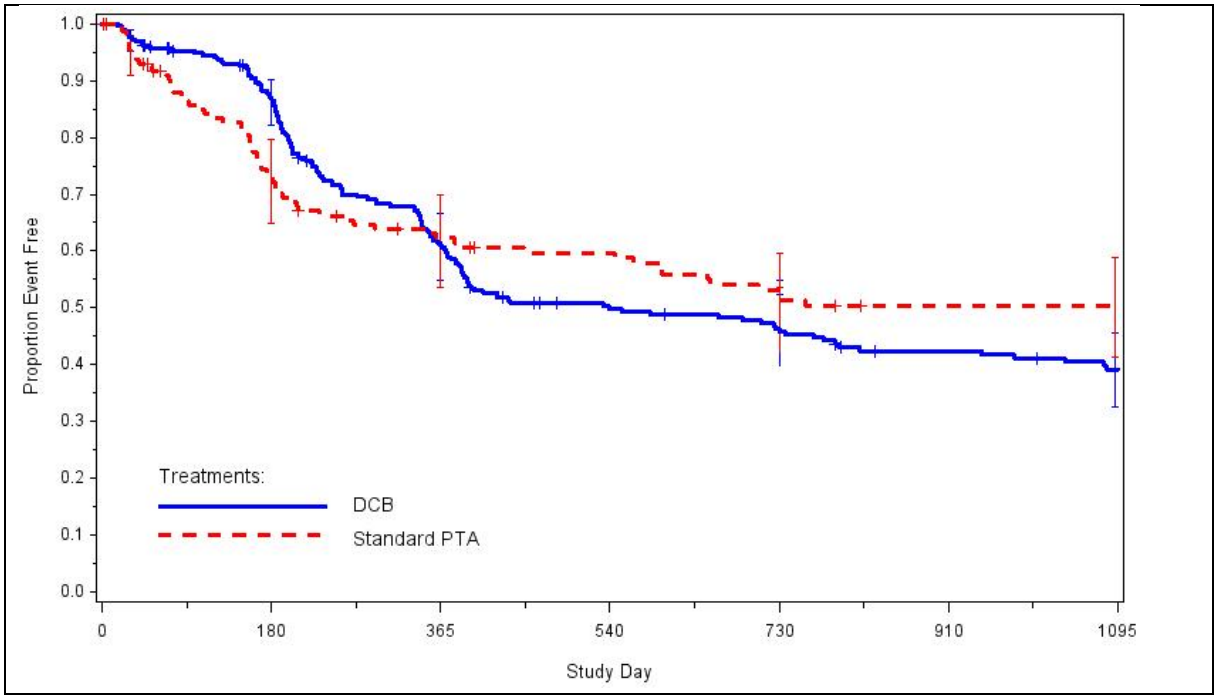

Figure 9-3. Kaplan-Meier Plot of Primary Patency (By Pathway)

Group	Time Point	Primary Patency (95% CI)*	Cumulative Events	Cumulative Pathways Censored	Pathways Left†	Difference (95% CI)
DCB	Day 1	100.0% (NA, NA)	0	23	300	
	Day 30	97.7% (95.2%, 98.9%)	7	23	293	2.1% (-1.4, 5.8%)
	Day 44	96.3% (93.5%, 98.0%)	11	44	268	3.3% (-1.2, 8.2%)
	Day 180	86.8% (82.2%, 90.2%)	37	51	235	13.8% (4.9, 22.8%)
	Day 210	76.4% (71.0%, 81.0%)	65	69	189	9.4% (-0.5, 19.2%)
	Day 365	61.0% (54.8%, 66.6%)	103	70	150	-1.2% (-12.0, 9.4%)
	Day 395	53.7% (47.4%, 59.6%)	121	91	111	-7.0% (-18.0, 3.7%)
	Day 730	46.2% (39.8%, 52.4%)	136	96	91	-5.1% (-16.6, 6.1%)
	Day 790	43.7% (37.2%, 49.9%)	141	113	69	-6.7% (-18.3, 4.7%)
	Day 1095	39.1% (32.6%, 45.6%)	148	116	59	-11.3% (-22.8, 0.3%)
	Day 1155	38.4% (31.9%, 44.9%)	149	174	0	-10.2% (-22.1, 1.5%)
PTA	Day 1	100.0% (NA, NA)	0	22	162	
	Day 30	95.6% (91.0%, 97.9%)	7	25	152	
	Day 44	93.1% (87.9%, 96.1%)	11	45	128	
	Day 180	73.0% (64.8%, 79.6%)	38	48	98	
	Day 210	67.0% (58.5%, 74.2%)	46	53	85	
	Day 365	62.2% (53.5%, 69.8%)	52	55	77	
	Day 395	60.6% (51.8%, 68.3%)	54	64	66	
	Day 730	51.3% (42.2%, 59.7%)	64	65	55	
	Day 790	50.4% (41.3%, 58.8%)	65	87	32	
	Day 1095	50.4% (41.3%, 58.8%)	65	89	30	
	Day 1155	48.7% (39.3%, 57.4%)	66	112	6	

**Kaplan-Meier estimate of proportion of pathways without a composite failure event at the visit day.*

† Pathways ongoing without an event at the visit day

Confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 9-6. Primary Patency Through 36 Months as a Binary Endpoint (by Pathway)

Visit	DCB Pathways		PTA Pathways		Difference (95% CI)
	Response Rate	95% CI	Response Rate	95% CI	
30 Days	283 / 294 (96.3%)	(93.4%, 98.1%)	144 / 155 (92.9%)	(87.7%, 96.4%)	3.4% (-1.8%, 7.1%)
6 Months	201 / 266 (75.6%)	(69.9%, 80.6%)	88 / 134 (65.7%)	(57.0%, 73.7%)	9.9% (-0.4%, 18.1%)
12 Months	128 / 248 (51.6%)	(45.2%, 58.0%)	75 / 129 (58.1%)	(49.1%, 66.8%)	-6.5% (-17.9%, 4.6%)
24 Months	84 / 225 (37.3%)	(31.0%, 44.0%)	54 / 119 (45.4%)	(36.2%, 54.8%)	-8.0% (-18.7%, 3.7%)
36 Months	58 / 207 (28.0%)	(22.0%, 34.7%)	29 / 95 (30.5%)	(21.5%, 40.8%)	-2.5% (-12.8%, 10.4%)

Confidence intervals not adjusted for multiple comparisons

9.5.4 Clinically Driven Target Lesion Revascularization (By Pathway)

Clinically driven TLR as adjudicated by the CEC is shown in **Figure 9-4.** The 6-month Kaplan-Meier estimate of freedom from CD-TLR was 93.8% in the DCB arm and 85.6% in the PTA arm. The CD-TLR Kaplan-Meier estimates at 36 months were similar in both treatment arms; 67.3% for DCB and 70.3% for PTA. As a binary endpoint, the proportion-based analysis showed a higher response rate in DCB with 90.8% vs. 82.6% PTA at 6 months, with convergence of the rates thereafter (**Table 9-7**).

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 73.7 days (95% CI -12, 159 days) for DCB.

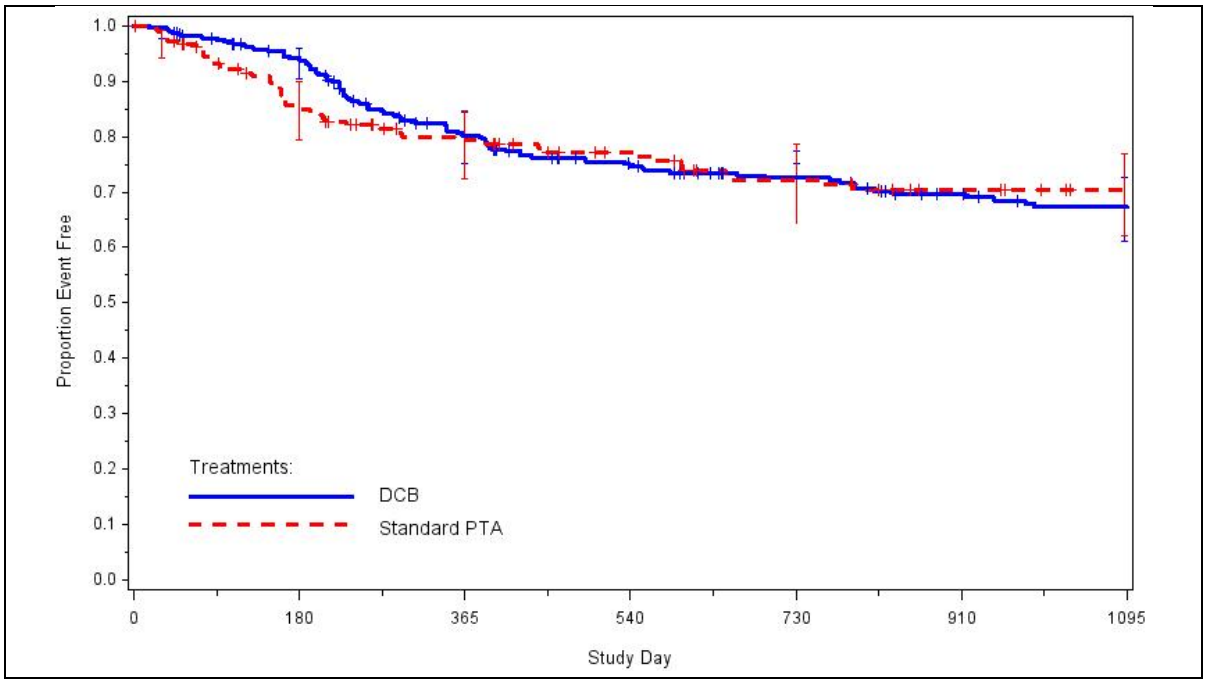

Figure 9-4. Kaplan-Meier Plot of Freedom from Clinically Driven TLR

Group	Time Point	Freedom from CD-TLR (95% CI)*	Cumulative Events	Cumulative Pathways Censored	Pathways Left†	Difference (95% CI)
DCB	Day 1	100.0% (NA, NA)	0	2	321	
	Day 30	99.7% (97.8%, 100.0%)	1	2	320	1.9% (-0.1, 4.3%)
	Day 44	98.8% (96.7%, 99.5%)	4	10	309	1.5% (-1.0, 4.4%)
	Day 180	93.8% (90.5%, 96.0%)	19	20	284	8.2% (2.1, 14.8%)
	Day 210	90.9% (87.0%, 93.6%)	28	31	264	8.2% (1.3, 15.3%)
	Day 365	80.3% (75.2%, 84.4%)	58	42	223	0.9% (-7.1, 9.0%)
	Day 395	77.8% (72.5%, 82.1%)	65	51	207	-0.9% (-9.2, 7.5%)
	Day 730	72.6% (66.9%, 77.4%)	78	74	171	0.3% (-9.2, 10.0%)
	Day 790	71.7% (66.0%, 76.6%)	80	107	136	0.3% (-9.2, 10.0%)
	Day 1095	67.3% (61.1%, 72.7%)	88	120	115	-3.0% (-13.2, 7.4%)
	Day 1155	67.3% (61.1%, 72.7%)	88	218	17	-1.6% (-12.0, 9.0%)
PTA	Day 1	100.0% (NA, NA)	0	1	183	
	Day 30	97.8% (94.3%, 99.2%)	4	1	179	
	Day 44	97.3% (93.6%, 98.9%)	5	6	173	
	Day 180	85.6% (79.5%, 90.1%)	25	13	146	
	Day 210	82.7% (76.2%, 87.6%)	30	21	133	
	Day 365	79.4% (72.4%, 84.7%)	35	33	116	
	Day 395	78.7% (71.6%, 84.2%)	36	40	108	
	Day 730	72.3% (64.4%, 78.7%)	44	54	86	
	Day 790	71.4% (63.4%, 77.9%)	45	75	64	
	Day 1095	70.3% (62.1%, 77.0%)	46	85	53	
	Day 1155	69.0% (60.5%, 76.0%)	47	125	12	

**Kaplan-Meier estimate of proportion of pathways without a composite failure event at the visit day.*

† Pathways ongoing without an event at the visit day

‡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 patients. Confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 9-7. Freedom from Clinically Driven TLR as Binary Endpoint Through 36 Months

Visit	DCB Pathways (N=323)		PTA Pathways (N=184)		Difference (95% CI)
	Response Rate	95% CI[1]	Response Rate	95% CI[1]	
30 Days	317 / 321 (98.8%)	(96.8%, 99.7%)	179 / 184 (97.3%)	(93.8%, 99.1%)	1.5% (-2.0%, 4.1%)
6 Months	275 / 303 (90.8%)	(86.9%, 93.8%)	142 / 172 (82.6%)	(76.0%, 87.9%)	8.2% (1.5%, 13.3%)
12 Months	216 / 281 (76.9%)	(71.5%, 81.7%)	116 / 152 (76.3%)	(68.7%, 82.8%)	0.6% (-9.8%, 8.5%)

Table 9-7. Freedom from Clinically Driven TLR as Binary Endpoint Through 36 Months

Visit	DCB Pathways (N=323)		PTA Pathways (N=184)		Difference (95% CI)
	Response Rate	95% CI[1]	Response Rate	95% CI[1]	
24 Months	169 / 249 (67.9%)	(61.7%, 73.6%)	85 / 130 (65.4%)	(56.5%, 73.5%)	2.5% (-9.2%, 12.4%)
36 Months	115 / 203 (56.7%)	(49.5%, 63.6%)	52 / 99 (52.5%)	(42.2%, 62.7%)	4.1% (-9.4%, 16.8%)
Confidence interval not adjusted for multiple comparisons					

9.5.5 Clinically Driven Target Vessel Revascularization (By Pathway)

The findings for clinically driven Target Vessel Revascularization (TVR) are displayed in **Figure 9-5**. The Kaplan-Meier estimate of freedom from TVR was higher in the DCB group compared with the PTA arm, 93.8% versus 85.1%, respectively, at 6 months. This difference persisted through 210 days, 90.9% versus 82.1%, respectively, after which the curves converged such that there was no difference at 36 months (67.0% DCB, 66.9% PTA).

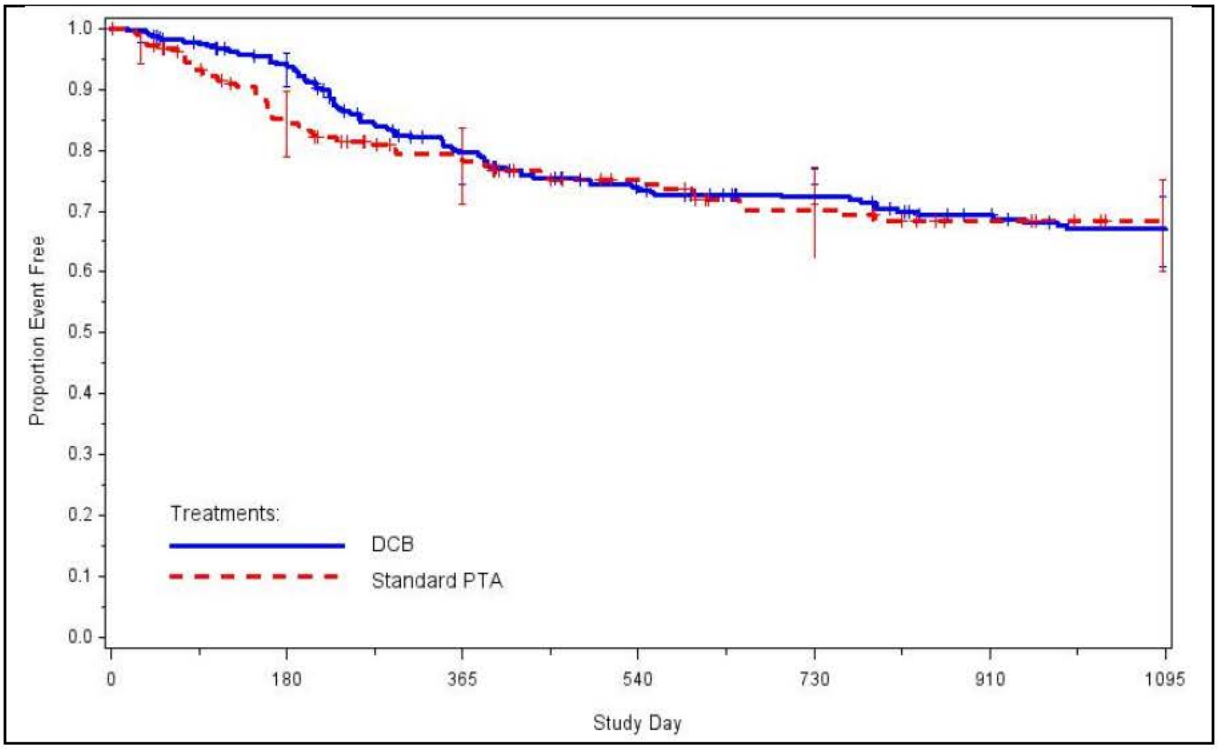

Figure 9-5. Kaplan-Meier Plot of Clinically Driven Target Vessel Revascularization

Group	Time Point	Freedom from CD TVR (95% CI)*	Cumulative Events	Cumulative Pathways Censored	Pathways Left†	Difference (95% CI)
DCB	Day 1	100.0% (NA, NA)	0	2	321	
	Day 30	99.7% (97.8%, 100.0%)	1	2	320	1.9% (-0.1, 4.3%)
	Day 44	98.8% (96.7%, 99.5%)	4	10	309	1.5% (-1.0, 4.3%)
	Day 180	93.8% (90.5%, 96.0%)	19	20	284	8.8% (2.4, 15.4%)
	Day 210	90.9% (87.0%, 93.6%)	28	31	264	8.7% (1.7, 15.8%)
	Day 365	79.6% (74.5%, 83.8%)	60	42	221	1.5% (-6.7, 9.8%)
	Day 395	77.1% (71.8%, 81.5%)	67	51	205	0.3% (-8.2, 9.1%)
	Day 730	72.3% (66.6%, 77.1%)	79	74	170	2.0% (-7.7, 11.7%)
	Day 790	71.4% (65.7%, 76.4%)	81	107	135	2.0% (-7.8, 11.8%)
	Day 1095	67.0% (60.8%, 72.4%)	89	120	114	-1.3% (-11.4, 9.1%)
	Day 1155	67.0% (60.8%, 72.4%)	89	217	17	0.1% (-10.5, 10.7%)
PTA	Day 1	100.0% (NA, NA)	0	1	183	
	Day 30	97.8% (94.3%, 99.2%)	4	1	179	
	Day 44	97.3% (93.6%, 98.9%)	5	6	173	
	Day 180	85.1% (78.8%, 89.6%)	26	13	145	
	Day 210	82.1% (75.6%, 87.1%)	31	21	132	
	Day 365	78.1% (71.0%, 83.6%)	37	33	114	
	Day 395	76.7% (69.5%, 82.5%)	39	40	105	
	Day 730	70.3% (62.3%, 76.9%)	47	54	83	
	Day 790	69.4% (61.3%, 76.1%)	48	74	62	
	Day 1095	68.3% (60.0%, 75.2%)	49	84	51	
	Day 1155	66.9% (58.4%, 74.1%)	50	123	11	

**Kaplan-Meier estimate of proportion of pathways without a composite failure event at the visit day.*

† Pathways ongoing without an event at the visit day

Confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

As a binary endpoint, freedom from clinically driven TVR at 6 months in the DCB group at 6 months, 90.8% versus 81.9% in the PTA group (by pathway). The difference became less marked over time, although the advantage in the DCB group persisted such that the binary rates at 36 months were 56.2% DCB versus 50.0% PTA (difference 6.2% 95% CI -5.8%, 18.1%) (**Table 9-8**).

Table 9-8: Freedom from Clinically Driven TVR as Binary Endpoint Through 36 Months

Visit	DCB Pathways (N=323)		PTA Pathways (N=184)		Difference (95% CI)[1]
	Response Rate	95% CI	Response Rate	95% CI	
30 Days	317 / 321 (98.8%)	(96.8%, 99.7%)	178 / 183 (97.3%)	(93.7%, 99.1%)	1.5% (-1.2%, 4.1%)
6 Months	275 / 303 (90.8%)	(86.9%, 93.8%)	140 / 171 (81.9%)	(75.3%, 87.3%)	8.9% (2.3%, 15.5%)

Table 9-8: Freedom from Clinically Driven TVR as Binary Endpoint Through 36 Months

Visit	DCB Pathways (N=323)		PTA Pathways (N=184)		Difference (95% CI)[1]
	Response Rate	95% CI	Response Rate	95% CI	
12 Months	214 / 281 (76.2%)	(70.7%, 81.0%)	112 / 151 (74.2%)	(66.4%, 80.9%)	2.0% (-6.6%, 10.6%)
24 Months	168 / 249 (67.5%)	(61.3%, 73.3%)	82 / 130 (63.1%)	(54.2%, 71.4%)	4.4% (-5.7%, 14.5%)
36 Months	114 / 203 (56.2%)	(49.0%, 63.1%)	50 / 100 (50.0%)	(39.8%, 60.2%)	6.2% (-5.8%, 18.1%)
Confidence intervals not adjusted for multiple comparisons					

9.5.6 Overall Burden of BTK Reinterventions (By Patient)

While Kaplan-Meier and binary endpoint analyses specify the number of pathways with one or more events, patients may have more than one reintervention. The cumulative number of TLRs and TVRs over time is an indication of the overall burden of reinterventions.

The incidence of TLRs favored the DCB arm at most time points, with DCB patients having a lower rate. In later time points, it was not expected that paclitaxel would show long term benefits. The average TLRs/year was 0.24 for DCB and 0.42 for PTA through 6 months. This difference did not persist, however, and through 36 months the TLR rates were 0.27/year in the DCB group and 0.23/year in the PTA group (**Table 9-9**).

Table 9-9. Cumulative TLRs and TLRs per Year

(By Patient)

Timepoint (through)	DCB (N=287)		PTA (N=155)	
	Cumulative TLRs	TLR/Year	Cumulative TLRs	TLR/Year
30 Days	5	0.14	6	0.32
6 Months	36	0.24	36	0.42
12 Months	101	0.35	53	0.35
24 Months	151	0.29	71	0.26
36 Months	170	0.27	75	0.23

The findings were similar for TVRs. Through 6 months, the rate of TVRs averaged 0.24/year in the DCB arm versus 0.44/year in the PTA arm, but the TVR rates converged thereafter such that the 36-month rates were 0.27/year and 0.24/year in the DCB and PTA arms, respectively.

9.5.7 Area Under the Curve Analysis for TLR (Post-Hoc Analysis)

To further evaluate the continued effect beyond six months, a post-hoc assessment was performed for TLR. **Table 9-10** summarizes a comparison of the area under the curve (AUC) for TLR; an index of the benefit in the avoidance of interventions that a patient would accrue with DCB or PTA. The benefit for the DCB group in freedom from clinically driven TLR was evident at day 180. While the curves converged over time, an advantage of DCB persisted through the 36-month follow-up period.

Table 9-10. Area Under the Curve Analysis for CD-TLR (Post-Hoc Analysis)

Timepoint	DCB Pathways		PTA Pathways		Difference in AUC (Positive values favor DCB)	
	Area under the Curve	SE	Area under the Curve	SE	Difference	SE
Study Day 180	175.3	1.29	168.8	2.54	6.5	2.85
Study Day 210	203.1	1.64	194.2	3.23	8.9	3.62
Study Day 365	333.8	4.26	319.9	7.41	14.0	8.55
Study Day 395	357.7	4.87	343.6	8.28	14.1	9.60
Study Day 730	607.6	12.61	596.6	18.58	11.0	22.45
Study Day 790	651.0	14.10	639.7	20.54	11.3	24.92
Study Day 1095	860.6	21.88	854.1	31.09	6.5	38.01
Study Day 1155	901.0	23.49	895.7	33.22	5.2	40.69

9.5.8 Wound Status

The number of patients with one or more wounds at baseline was similar in both treatment arms; 56.5% in the DCB arm and 56.1% in the PTA arm. The proportion of patients with open wounds is displayed in graphical form in **Figure 9-6** through 36 months. The wound assessment data underlying this graph appear in **Table 9-11.** The proportion of patients with wounds was similar in the two treatment arms at all timepoints, decreasing to 29.7% and 25.9% at 12 months in the DCB and PTA patients, respectively.

The proportion of healed wounds at 6 months was 36.7% in the DCB arm and 54.9% in the PTA arm; at the 12-month follow-up visit 40.8% of DCB patients and 30.9% of PTA patients had healed their wounds. The proportion of wounds that healed was similar between treatment arms at 36 months, observed in approximately 60% of each group.

While there was the intention to assess any difference in wound healing between the study arms, ultimately it was not possible due to several factors:

- Patients with the most severe wounds were deliberately excluded from the trial.
- Wound healing in patients with CLI is confounded by variables such as diabetes management, wound management procedures, and patient compliance.
- After trial initiation, standard criteria such as the Wound, Ischemia, and foot Infection classification system, known as WIfI, was published in 2014 and subsequently adopted.
- The standards for measuring and achieving wound healing in clinical trials – and in practice – are still evolving.

Wound care principles include improving perfusion into the limb, treating infection, avoiding pressure on a wound, debridement, and adequate nutrition. Debridement of devitalized or infected tissue by scalpel, collagenases, or even maggots promote wound healing. Antibiotics may be required to treat infection to prevent osteomyelitis. Avoiding pressure on the wound (e.g., off-loading the foot) also assists wound healing. The local temperature of the limb can be increased using sheepskin (Rooke) boots and may improve superficial collateral flow to help perfuse a limb. Negative pressure dressings (e.g., vacuum-assisted) increase capillary flow and help drain wounds. Hyperbaric oxygen therapy offers no advantages for amputation prevention but may improve the more subjective end point of wound healing in diabetes mellitus. All these factors were not standardized during the trial.[11]

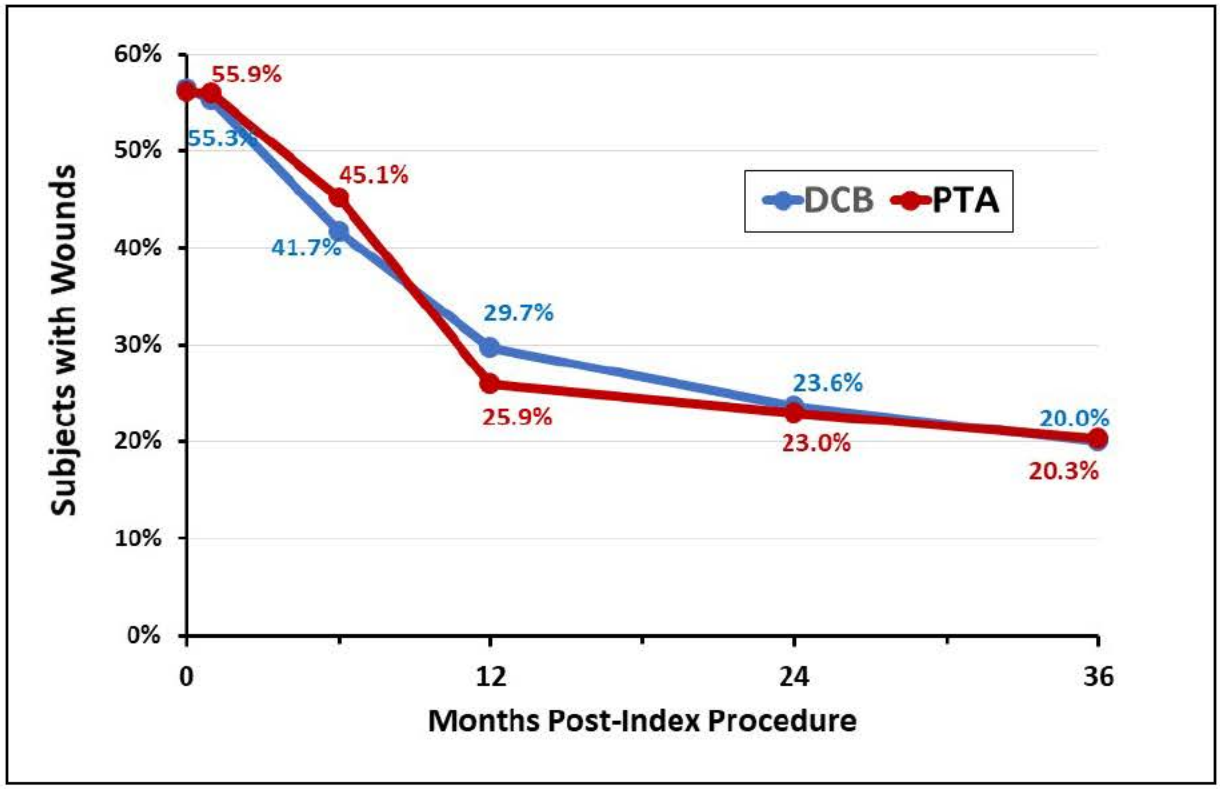

Figure 9-6. Wound Healing Through 36 Months

Table 9-11. Wound Assessments through 36 Months

	Baseline	30 Days	6 Months	12 Months	24 Months	36 Months
DCB Patients						
Assessed for Wounds	285	262	242	212	174	130
Wound Present, n/N (%) (95% CI)	161/285 (56.5%) (50.5%, 62.3%)	145/262 (55.3%) (49.1%, 61.5%)	101/242 (41.7%) (35.5%, 48.2%)	63/212 (29.7%) (23.7%, 36.4%)	41/174 (23.6%) (17.5%, 30.6%)	26/130 (20.0%) (13.5%, 27.9%)
PTA Patients						
Assessed for Wounds	155	143	122	108	87	59
Wound Present, n/N (%) (95% CI)	87/155 (56.1%) (47.9%, 64.1%)	80/143 (55.9%) (47.4%, 64.2%)	55/122 (45.1%) (36.1%, 54.3%)	28/108 (25.9%) (18.0%, 35.2%)	20/87 (23.0%) (14.6%, 33.2%)	12/59 (20.3%) (11.0%, 32.8%)

n/N, % and 95% exact confidence intervals, not adjusted for multiple comparisons

9.5.9 Infection and Gangrene

Infection and gangrene are elements of end-stage CLI. Infection was reported in 25.9% in DCB and 26.5% in PTA patients at baseline, prior to the index procedure. Gangrene was present at baseline in 22.0% and 21.2% of DCB and PTA patients, respectively **Table 9-12**.

The rate of infection is displayed graphically through follow-up in **Figure 9-7** (left panel). At 6 months the infection rate decreased to 5.4% of DCB patients and 16.0% of PTA patients. The decrease in infection rates as well as the difference between treatment groups was maintained at 12 months, with 3.9% of DCB patients and 9.3% of PTA patients reporting an infection at this time point. By 24 months the number of patients with infection rate was zero in both groups. In summary, while the rate of infection appeared to dimmish quicker in the DCB arm, both DCB and PTA resulted in resolution of infection by the two-year follow-up timepoint.

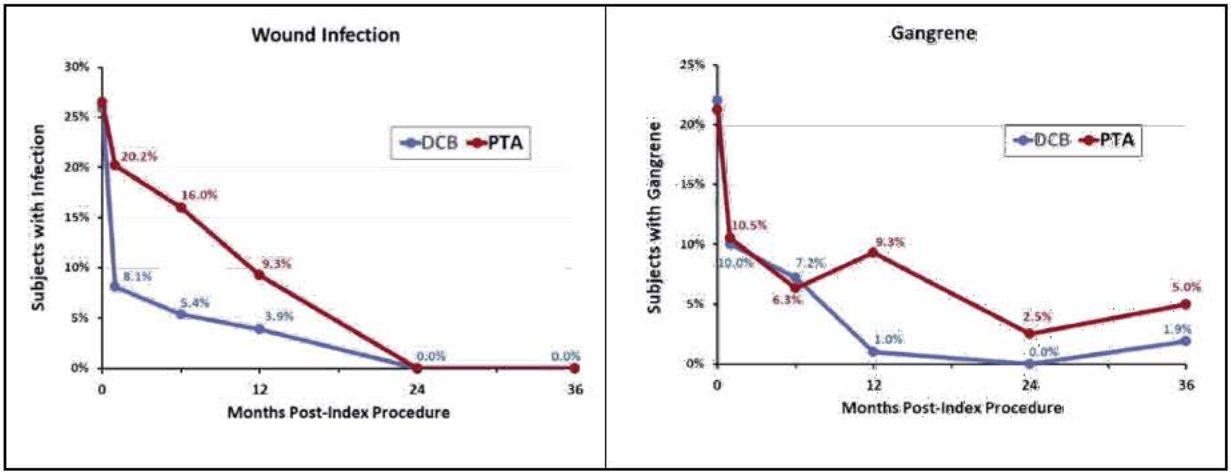

Figure 9-7. Infection and Gangrene Through 36 Months

Table 9-12. Infection and Gangrene, Baseline Through 36 Months

	Baseline	30 Days	6 Months	12 Months	24 Months	36 Months
Wound Infection						
DCB	60/232, 25.9% (20.4%, 32.0%)	17/211, 8.1% (4.8%, 12.6%)	9/166, 5.4% (2.5%, 10.0%)	4/103, 3.9% (1.1%, 9.6%)	0/73, 0.0% (0.0%, 4.9%)	0/54, 0.0% (0.0%, 6.6%)
PTA	30/113, 26.5% (18.7%, 35.7%)	23/114, 20.2% (13.2%, 28.7%)	13/81, 16.0% (8.8%, 25,9%)	5/54, 9.3% (3.1%, 20.3%)	0/40, 0.0% (0.0%, 8.8%)	0/20, 0.0% (0.0%, 16.8%)
Gangrene						
DCB	51/232, 22.0% (16.8%, 27.9%)	21/211, 10.0% (6.3%, 14.8%)	12/166, 7.2% (3.8%, 12.3%)	1/103, 1.0% (0.0%, 5.3%)	0/73, 0.0% (0.0%, 4.9%)	1/54, 1.9% (0.0%, 9.9%)

PTA	24/113, 21.2% (14.1%, 29.9%)	12/114, 10.5% (5.6%, 17.7%)	5/80, 6.3% (2.1%, 14.0%)	5/54, 9.3% (3.1%, 20.3%)	1/40, 2.5% (0.1%, 13.2%)	1/20, 5.0% (0.1%, 24.9%)
n/N, % and 95% exact confidence intervals, not adjusted for multiple comparisons						

Gangrene followed a similar pattern as infection, with resolution in both treatment arms, depicted graphically in **Figure 9-7** (right panel) and summarized numerically in **Table 9-12**. Gangrene was present in 22.0% of DCB patients and 21.2% of PTA patients at baseline. By 6 months, the proportions of patients with gangrene decreased to 7.2% and 6.3% in the DCB and PTA arms, respectively. At 12 months, the proportion of patients with gangrene was lower in the DCB arm, 1.0% versus 9.3%, but gangrene resolved in all but one patient in each group at 24 months and beyond.

9.5.10 Quality of Life Indices and Walking Impairment

There were no differences between DCB and PTA with respect to the EQ-5D or the Walking Impairment Questionnaire (WIQ). The average change in EQ-5D from baseline at 6 months for index score was similar in both treatment arms: 0.07 ± 0.3 in DCB arm vs. 0.05 ± 0.30 in PTA arm. Similar scores between treatment arms were also observed at 36 months; 0.08 ± 0.29 for DCB and 0.11 ± 0.29 for PTA.

Table 9-13. Pain/Discomfort and Mobility Components of EQ-5D and WIQ

Index	6 Months	12 Months	24 Months	36 Months
EQ-5D Pain/Discomfort Component (% Improved from Baseline)				
DCB	39.5%	39.0%	39.7%	38.1%
PTA	36.4%	44.5%	38.5%	45.9%
EQ-5D Mobility Component (% Improved from Baseline)				
DCB	26.1%	27.5%	26.3%	25.2%
PTA	25.6%	26.4%	23.1%	36.1%
WIQ (Mean + SD)				
DCB	34 ± 22	33 ± 21	33 ± 24	31 ± 22
PTA	35 ± 22	34 ± 21	34 ± 22	37 ± 22

Focusing on improvement in pain/discomfort and mobility components of the EQ-5D, 83.1% of the DCB patients and 78.4% of the PTA patients reported moderate or extreme pain/discomfort at baseline prior to treatment. For mobility, 81.0% of the DCB patients and

80.4% of the PTA patients reported walking problems (**Table 9-13).** The Walking Impairment Questionnaire (WIQ) was administered at each follow-up time point prior to the Investigator's clinical assessment. Although not a secondary endpoint, the instrument was used to assess quality of life at specific points in time in patients enrolled in the trial. There was no difference in the WIQ between the two treatment arms over time. Further, there was little change from baseline in the two arms, most likely reflecting the lower relevance of walking improvements in patients who primarily present with complaints of rest pain, ulcer, or gangrene (Rutherford Category ≥ 4, comprising the majority patients in this study) compared to other studies and therapies directed at claudicants (Rutherford Category ≤ 3).

Alabi and colleagues reviewed the available evidence from 11 studies and over 5,000 patients concerning physician and patient-centered outcomes after surgical or endovascular intervention for patients with CLI, provided here directly from the article.[42] They noted that vascular reconstruction outcomes have traditionally been measured by objective clinical measures such as primary patency, limb salvage, and survival. In the 1990s, reports on CLI cohorts demonstrated a shift towards patient-reported measures of postsurgical revascularization functional or ambulatory status, or both. The paradigm continued to evolve toward the use of validated QoL instruments to evaluate other patient-centered outcomes, such as perceived pain, emotional and physical role functioning, vitality, mental health and other HR-QoL domains, after surgical or endovascular revascularization.

However, in this patient population with multiple chronic and often debilitating comorbid conditions and high mortality rates, few reports have evaluated all these outcomes after surgical bypass, endovascular interventions, or major amputation. And certainly, to date, no study has been fashioned to directly compare these groups using validated QoL instruments. Although no strong conclusions can be made to guide clinical practice, it does appear that despite optimal limb salvage and revascularization patency rates, a reasonable functional status after intervention, and the ability to live and function independently after the procedure, patients do not always experience significant nor sustained gains in their health related QoL. It does, however, appear that repeat procedures, whether open surgical or endovascular, likely adversely affect QoL.

No revascularization type can be favored over another toward the goal of improved QoL in CLI patients, based on the literature currently available. Validated predictive models for assessing QoL in the CLI patient after revascularization are sorely needed to help guide treatment in this vulnerable population so that both physician-centered and patient-centered goals and outcomes can be attained.

9.5.11 Rutherford Category

The baseline Rutherford Category was similar in the two treatment arms. Most patients were Rutherford Category 4 (rest pain) and 5 (tissue loss), with only 9.1% of the DCB group and 10.3% of the PTA group classified as Rutherford Category 3.

The Rutherford Category improved from baseline to 30 days in 61.2% and 57.6% of the DCB and PTA treatment arms, respectively (**Figure 9-8**, **Table 9-14**). Improvement over baseline was reported in 73.7% and 81.7%, respectively at 6 months. The improvement persisted through 36 months in both groups.

Rutherford Category is a relatively coarse measure of benefit. While both treatment arms had substantial improvement in Rutherford Category after treatment, the absence of a difference between the two arms is consistent with prior studies that have found the measure to lack the precision necessary to identify changes between different modalities.[36] It should also be noted that.[43] have shown that primary patency and improvement in Rutherford Category have no relationship in CLI patients. Therefore, it is not unexpected that, while both treatment arms showed improvement in Rutherford Category, the measure is not precise enough to identify differences between groups.

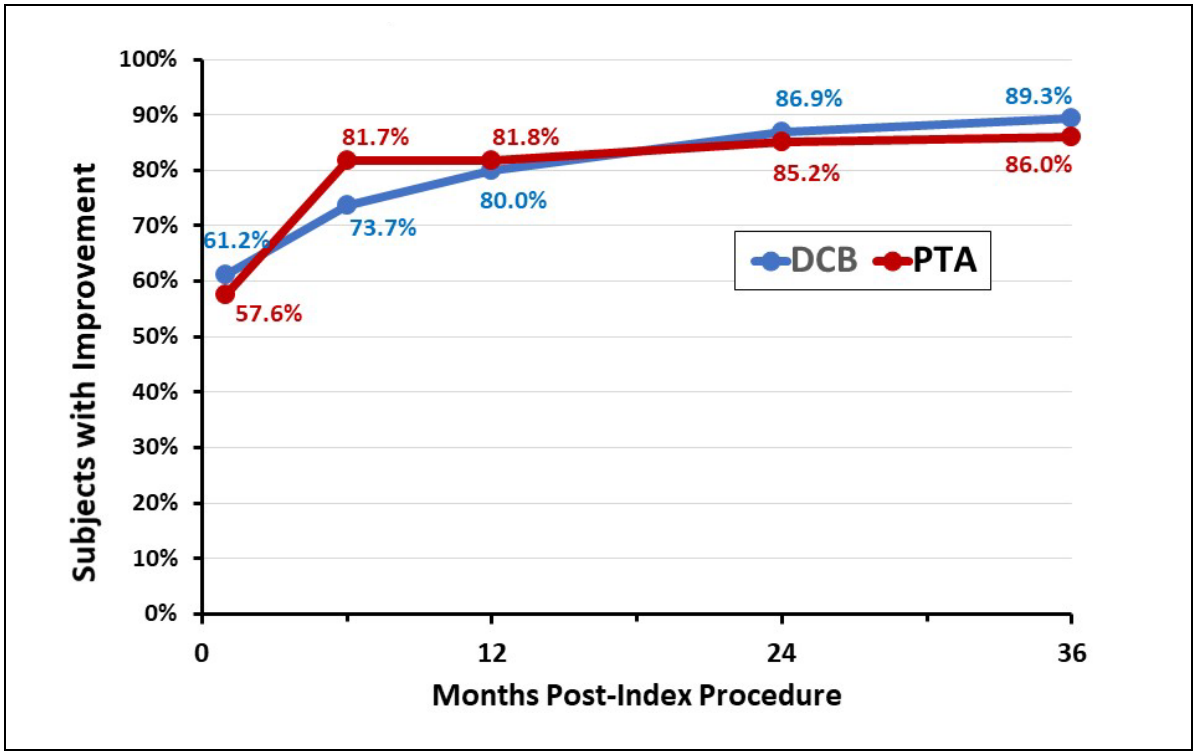

Figure 9-8. Improvement in Rutherford Category through 36 Months

Table 9-14. Improvement in Rutherford Category through 36 Months

	30 Days	6 Months	12 Months	24 Months	36 Months
DCB Patients	161/263, 61.2% (55.0%, 67.1%)	179/243, 73.7% (67.7%, 79.1%)	176/220, 80.0% (74.1%, 85.1%)	152/175, 86.9% (80.1%, 91.5%)	117/131, 89.3% (82.7%, 94.0%)
PTA Patients	83/144, 57.6% (49.1%, 65.8%)	98/120, 81.7% (73.6%, 88.1%)	90/110, 81.8% (73.3%, 88.5%)	75/88, 85.2% (76.1%, 91.9%)	49/57, 86.0% (74.2%, 93.7%)
All numbers n/N, % and 95% confidence interval without adjustment for multiple comparisons.					

9.6 Summary of Effectiveness Observations

The findings from the LUTONIX DCB trial suggest a benefit for effectiveness of DCB over PTA, but the effect was limited to 6-month endpoint. That said, the improvement was coincident with the specified 6-month primary effectiveness endpoint, with freedom from CD-TLR, occlusion, or major amputation in 74.7% (201/269) DCB pathways compared with 64.2% (88/137) PTA pathways (p = 0.0222, threshold of 0.0085).

Secondary and post-hoc analyses corroborated the early benefit of DCB, with a reduced rate of CD-TLR, measured as:

- The point estimate of CD-TLR as a binary endpoint; 90.8% (275/303) versus 82.6% (142/172) in the DCB and PTA arms respectively (difference 8.2%, 95% DI 1.5%, 13.3%),
- The number of reinterventions through 6 months was lower in the DCB arm; 36 DCB and 36 PTA, with 2:1 randomization for DCB:PTA, and
- The days to first reintervention, averaging 73.7 days longer in the DCB arm (95% CI -12, 159 days).

Effectiveness did not persist beyond 12 months for many of the measures, with similar findings in both groups beyond the first year. This observation is consistent with the duration of drug persistence within the arterial wall,[44] as well as the protocol-specified prohibition against reintervention with a paclitaxel device. Reinterventions in both groups were performed without paclitaxel coated balloons, most commonly with standard, uncoated PTA.

Differences in QoL measures were not observed in the trial, both groups improved over time. The study was not powered to detect differences in QoL measures over time, nor are such measures precise enough to resolve differences in two treatments for CLI.

In conclusion, DCB appeared to offer benefit to patients with CLI, advantages most prominent in the early (<1 year) follow-up period, with convergence of outcomes thereafter.

10 LIMITATIONS OF THE STUDY

10.1 Inherent Limitations

In considering the totality of the data for safety and effectiveness of the LUTONIX BTK IDE Trial, it is important to note the study limitations that are both inherent in the trial design and that presented throughout the course of the trial.

10.2 Changes to the Trial Design

Although necessary as more knowledge from outside the study was gained, the changes to the clinical investigational protocol created limitations in the trial. In particular, the primary endpoint was changed from 12 months to 6 months, and the implementation of adaptive design and the introduction of a proximal segment analysis resulted in a primary effectiveness endpoint threshold of p-value 0.0085. These changes were not based on interim study results.

10.3 Limitations Due to Slow Enrollment

The trial was terminated prior to completion of planned enrollment. There were two interim analysis performed according to the interim analysis plan. Formal stopping boundaries were not crossed. However, BD made the business decision to stop enrollment. This results in a more limited data set than intended which reduces study power and can create difficulties in data analysis. The limited enrollment of patients in the trial is compounded by the number of patients that were lost to follow-up.

10.3.1 Lost to Follow-Up

Due to the high number of patients that were lost to follow-up by 12 months, the data at the 1-year timepoint have wider confidence intervals than at the 6-month timepoint. Additionally, there was differential attrition rates between the treatment arms: a greater number of patients were lost to follow-up from the PTA arm of the trial than from the DCB arm.

10.4 Long Term Data

In this patient population, there were high rates of missing data beyond 12 months due to high rates of mortality and study discontinuation in both randomized groups. Discontinuation rates did appear to vary by randomized groups and did appear to depend on baseline characteristics, suggesting longer term results may be difficult to interpret.

10.5 Secondary Endpoints

There are important points to note about the secondary endpoints:

1. The study sample size was based only on power for the primary endpoints.
2. Several secondary endpoints have many factors potentially altering their course.

In the example of wound healing, there was no standardization of wound care or of wound data collection and analysis. There was no control over wound photographs, and the photographs did not undergo third party analysis, making the data hard to interpret. Although wound healing is an important outcome for patients, due to the complex nature of the wound healing process, it is difficult to eliminate confounding factors in order to interpret wound healing data as an endpoint. Patients in both arms of the study benefited from improved wound healing, but the multifactorial characteristics of wound healing make it complicated to attribute the outcomes to the treatment differences between the trial arms.

The literature has reported the lack of relationship between primary patency and endpoints such as improvement in Rutherford Category and QoL questionnaires.[24,42]

11 SUPPORTIVE DATA FROM REAL-WORLD EXPERIENCE AND PUBLISHED LITERATURE

Summary

- CLI patients treated off-label with the LUTONIX DCB in the VQI Registry were compared to PTA and demonstrated a trend for improvement in both TLR and primary patency rates through 12 months with hazard ratios of 0.703 (95% CI: 0.367, 1.345) and 0.760 (95% CI: 0.451, 1.281) for freedom from TLR and primary patency, respectively.
- Data from a multicenter, single arm real-world registry of the LUTONIX DCB for treatment of BTK arteries were pooled with DCB data from the BTK IDE pivotal study and propensity adjusted to compare to the PTA data from the BTK IDE pivotal trial. Freedom from CD-TLR was improved in the combined DCB cohort compared with the PTA cohort, with DCB vs. PTA rates of 93.3% vs. 82.0% (6 months), 81.1% vs. 74.2% (12 months) and 75.0% vs. 67.2% (24 months), respectively.
- Data from a randomized, prospective study evaluating the DCB vs. PTA treatment of CLI in hemodialysis patients. The composite effectiveness endpoint of 6-month limb salvage and primary patency was 70.0% for the DCB vs. 38.9% for PTA (by pathway).

A discussion of the information and data which supports the safety and effectiveness of the LUTONIX DCB in the treatment of native popliteal, tibial, and peroneal arteries is provided below. More complete summaries are included in Appendix **Section 14.6**. These studies represent clinical results from over 650 infrapopliteal patients treated with the LUTONIX 035 DCB (i.e., 4 mm balloon diameter) and were conducted, or else evaluated, to address feedback from the FDA regarding the need for additional data. As FDA's questions centered around effectiveness, safety data were not captured from all sources.

11.1 Real-World Effectiveness Data from the Society of Vascular Surgery Vascular Quality Initiative (VQI) Registry

The Society of Vascular Surgery (SVS) Vascular Quality Initiative (VQI) registry contains data collected from real-world clinical trials from vascular procedures intended to treat peripheral artery occlusive disease in the US and Canada and represents the largest real-world dataset of

patients with CLI treated off-label with the LUTONIX 035 DCB (848 devices) (see Appendix **Section 14.8.1** for further details on the VQI registry). Notably, BTK arteries typically require treatment with a balloon diameter < 4 mm; given the smallest LUTONIX 035 device size has a 4 mm balloon diameter, its use in treating BTK arteries is limited which is reflected by the relatively small number of off-label cases available in VQI.

To collect all available clinical data associated with the LUTONIX DCB, a prospectively designed retrospective analysis of the VQI registry was conducted. A total of 167 DCB and 397 PTA patients from VQI were independently selected in a consecutive manner between January 2016 and May 2019. Analyses were based on the use of propensity scores to adjust for imbalances in the patient baseline disease status and comorbidities between treatment groups. Because the unequal distribution of patients within several of the propensity score strata made it difficult to interpret the differences between treatment groups, the inverse probability weight (IPW) event-free survival estimate was reported.

The LUTONIX DCB patients in VQI demonstrated a trend for improvement in both TLR and primary patency rates through 12 months. This trend was consistent across time through 12 months with hazard ratios of 0.703 (95% CI: 0.367, 1.345) and 0.760 (95% CI: 0.451, 1.281) for TLR-free and primary patency survival. Although these failed to reach statistical significance, the lack of a significant or a more pronounced treatment effect may also relate to the severity of comorbidities in this CLI population as evidenced by the high mortality rate in both groups and the more limited patient selection based on the LUTONIX 035 balloon size of 4.0 mm.

11.3 Real-World Data from the LUTONIX Global BTK Registry

The LUTONIX Global BTK Registry is a multicenter, single arm real-world registry designed to evaluate the safety and assess the clinical use outcomes of the commercially available LUTONIX 014 DCB in the European Union (EU) for treatment of BTK arteries in a heterogeneous patient population in real-world use. The LUTONIX DCB data from the BTK IDE Trial and the Global BTK Registry were pooled and propensity adjusted to compare to the PTA data from the LUTONIX BTK IDE Trial (see Appendix **Section 14.8.2**).

The objective of this prospectively designed retrospective analysis was to provide additional supportive information on the 6-, 12-, and 24-month performance of the LUTONIX DCB. A total of 658 pooled and propensity adjusted Global BTK Registry and BTK IDE DCB patients (with 727 total flow pathways) were compared to 155 PTA patients (with 184 total flow pathways) from the LUTONIX BTK IDE Trial. Analyses were based on the use of propensity scores to adjust for imbalances in the patient baseline disease status and comorbidities between treatment

groups. Because the unequal distribution of patients within several of the propensity score strata made it difficult to interpret the differences between treatment groups, the IPW event-free survival estimate was reported.

An analysis of the primary effectiveness endpoint, or freedom from failure based on IPW, at 6 months reached statistical significance (DCB 76.4% and PTA 60.6%, p<0.001). Freedom from CD-TLR also demonstrated continuous improvement of the combined DCB cohort compared to the IDE PTA cohort with DCB vs. PTA rates of 93.3% vs. 82.0% (6 months), 81.1% vs. 74.2% (12 months) and 75.0% vs. 67.2% (24 months). Primary patency also demonstrated an advantage for the DCB cohort compared to the IDE PTA cohort with DCB vs. PTA rates of 87.7% vs. 68.6% (6 months), 65.2% vs. 57.2% (12 months) and 53.1% vs. 46.0% (24 months). An analysis of the primary safety endpoint through two years also confirms no safety issues were uncovered when combining the data sets; freedom from primary safety at 24 months was 92.6% (DCB) and 88.1% (PTA). In conclusion, the LUTONIX DCB demonstrated a continuous efficacy benefit when adding more patients to the IDE cohort via propensity score adjustment with the Global BTK Registry data, including at 12 months.

11.4 Japanese Hemodialysis Randomized Control Trial Data

The Japanese hemodialysis (HD) RCT was designed to evaluate the effectiveness and safety of the LUTONIX 014 DCB in Japanese HD patients with BTK disease. The study enrolled a total of 36 patients (19 DCB and 17 PTA with 23 and 21 flow pathways, respectively).

The first key effectiveness 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. At 12 months, the event-free rate for DCB was higher than PTA (47.1% vs. 35.3%). The second key effectiveness endpoint was limb salvage at 6 months; all Japan HD patients had limb salvage at that time point. At 12 months there was only 1 major amputation (in the PTA group), leading to a 7.1% treatment difference (95% CI -17.9%, 33.8%). In the HD DCB group, 100% of patients were free from BTK MALE+POD compared to 94.1% of patients in the HD PTA group for a treatment difference of 5.9% (95% CI -13.5%, 29.5%). In summary, the results of the Japanese HD RCT confirmed the safety and effectiveness of the LUTONIX DCB for the treatment of BTK disease in hemodialysis patients, with a benefit of DCB over PTA for the composite of limb salvage and primary patency at 6 and 12 months.

11.5 Summary of Relevant Published Literature

In addition to the registry analyses and Japanese HD RCT discussed in the preceding sections, a search of the peer-reviewed literature using well established databases (e.g., PubMed,

Embase) was conducted and produced three single-center, retrospective studies detailing the use of the LUTONIX 014 DCB in BTK arteries, summarized in **Table 11-1**. While there are limitations associated with these retrospective studies, they do provide additional safety and effectiveness information on over 680 LUTONIX DCBs used in 284 patients.

Table 11-1. Summary of Relevant Published Literature

Publication	Number of Patients/Devices	Patient Demographics	Follow-up	Safety	Freedom from TLR	Other
Micari et al. Ital J Vasc Endovasc. 2016;23:1-4.[45]	55 patients (retrospective), ~127 devices	Rutherford class > 3; 70% total occlusions	182 days median follow-up	96.4% freedom from amputation; no deaths reported	Not specified; 78.2% freedom from TVR at a median of 6 months	Ulcer size/depth reduction in 89.1% of patients
Steiner et al. J Endovasc Ther. 2016;23:417-423[46]	208 patients (retrospective), 510 devices	61.4% CLI patients; 63.6% total occlusions	9-month median follow-up	93.4% freedom from death or major amputation at 6 months and 89.5% at 12 months	84.1% at a median of 9 months	Complete wound healing in 68/89 (76.4%); 59.1% improved by at least 1 Rutherford class by 12 months
Palena et al. Cardiovasc Revasc Med. 2018, 19:83-87[47]	21 patients (retrospective), ~46 devices	95.2% Rutherford class 5-6; 100% diabetic	356.5 days mean follow-up	0% MALE; no major amputations; 100% limb salvage; 2 deaths	Not specified;83.8 % freedom from CD-TLR at 390 days	Ulcer size/depth reduction in 19/21 (90.4%); 87.5% demonstrated a 1 category shift in Rutherford class at 12 months

12 POST-APPROVAL STUDY PROPOSAL

12.1 Post-Approval Study (not previously reviewed by FDA)

As described in other sections of this document, there is evidence to support the safety and effectiveness of the LTX 014 during the critical timepoint of 6 months. BD acknowledges the trial design limitations of the IDE dataset and propose post-approval study to confirm the continued safety and effectiveness of the device in a least burdensome approach.[48]

As previously communicated to FDA, BD has extended follow-up of the IDE patients for 5 years for vital status and will report to FDA through the IDE annual reports. The extended vital status follow-up is currently in progress with existing IDE sites. In addition, BD has committed to the continued evaluation of this product post-market and therefore proposes a post approval study using Vascular Quality Initiative (VQI) to prospectively collect clinical data on the effectiveness of the LTX 014 through 1 year and vital status through 5 years. The use of Real World Evidence (RWE) has become an efficient method of collecting data prospectively in a post-market setting in order to meet PAS requirements.[49]

Details of the VQI proposal are in **Table 12-1** below. BD believes data collected in the current proposal will provide post-market confirmatory evidence of the continued safety and effectiveness of the LTX 014 for treatment of obstructive de novo or non-stented restenotic lesions in the native popliteal, tibial, and peroneal arteries.

BD is committed to working with FDA and the panel members to refine the proposal further.

Table 12-1. VQI Post-Approval Study Protocol Synopsis

Objectives	The objective of this project is to conduct long term post-market surveillance of the safety and effectiveness of the LUTONIX 014 Drug Coated Balloon PTA catheter for treatment of obstructive de novo or non-stented restenotic lesions in the native popliteal, tibial, and peroneal arteries.
Design	This is a prospective observational study using VQI PVI module to evaluate consecutive patients treated with the LUTONIX 014 Drug Coated Balloon PTA catheter for treatment of obstructive de novo or non-stented restenotic lesions in the native popliteal, tibial, and peroneal arteries. Data collection will be through the existing VQI PVI Registry. Patient information will be collected according to standard care through 12-months post-index procedure and vital status information will be collected through 60-months post-index procedure.

Device	The commercially available LUTONIX 014 Drug Coated Balloon PTA catheter. Consult IFU for device specific information and sizing.
Enrollment	All eligible patients (a minimum of 196) will be treated with the LUTONIX 014 Drug Coated Balloon PTA in the VQI PVI Registry in popliteal, tibial, and peroneal artery lesions.
Registry Sites	VQI PVI Registry centers in the United States that agree to participate in this data collection proposal. There are currently 228 centers participating in the VQI PVI Registry.
Surveillance Population	All eligible patients with symptomatic de novo or restenotic lesions in popliteal, tibial, and peroneal arteries.
Primary Post Approval Surveillance Project Endpoints (as assessed by a performance goal)	**Effectiveness:** Freedom from Target Lesion Revascularization (TLR) at 12-months post-index procedure. **Safety:** Freedom from Major Adverse Events (MAE) defined as device and/or procedure-related death or target limb(s) major amputation through 12-months post-index procedure.

13 BENEFIT-RISK CONCLUSIONS

13.1 Indications for Use

Per the FDA guidance document, *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* (Benefit-Risk Guidance), the indications for use statement is a key consideration for whether the evidence supports a finding of benefit. The proposed indication for use statement for the LUTONIX DCB is:

> 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.

Although this statement does not specifically state that the device is to be used in patients with CLI, BTK vascular procedures are intended for these patients. As presented in **Section 2.4**, there is an unmet need for devices purposely designed for use in BTK lesions to aid in the treatment of this debilitating disease.

13.2 Assessment of Benefit

There is evidence of clinical benefit for use of the LUTONIX DCB in patients with CLI as summarized in **Table 13-1,** with the primary endpoint at 6 months. Per the Benefit-Risk Guidance, "benefit should be considered based on the assessment of the data, whether or not the results are statistically significant." Additionally, "benefit may be considered in terms of how a patient feels, functions, survives, or an acceptable surrogate." For the LUTONIX DCB Trial, the surrogate is the reduced rate of reinterventions through 6 months and the longer time to first reintervention.

Table 13-1. Evidence of Clinical Benefit

FDA Guidance	LUTONIX DCB Study Results
Was there a favorable change in at least one clinical assessment that is equal to or greater than seen in the control group?	• There was a clinically meaningful difference (point estimate 10.5%, 14.4% KM estimate) in freedom from the composite of above-ankle amputation, target lesion occlusion, and CD-TLR through 6 months in favor of DCB. • There was a reduced reintervention rate in the DCB arm through 6 months (36 TLRs in the DCB arm and 36 TLRs in the PTA arm, with 2:1 randomization for DCB:PTA). Further, there were an additional 73.7 days to the first TLR for the DCB group. • Convergence of these measures was observed at 12 months, suggesting that the drug is a contributing factor for improving blood flow within the first year after use of the DCB. • Benefit for CD-TLR was observed in supportive data sets (VQI registry, Global BTK registry, and the Japanese HD RCT).

The Benefit-Risk Guidance recognizes that some extent of uncertainty always exists. The sources of uncertainty for the benefits are presented in **Table 13-4**.

Table 13-2. Uncertainty Around Clinical Benefit

FDA Guidance	LUTONIX DCB Study	Comment
What is the extent of uncertainty for the benefits?	• Difference in the primary effectiveness endpoint outcomes did not reach statistical significance. • Clinically meaningful difference in the composite primary endpoint was not sustained at later follow-up intervals. • There were missing data at all timepoints, increasing during later follow-up intervals. Rates varied by arm, and missing patients differed from non-missing patients on several baseline characteristics. • Although patients in both study groups showed improvement, differences were not demonstrated in infection rate, major amputations, wound healing, or quality of life based on measurement tools through the duration of the study.	• The lack of statistical significance was not due to wide confidence intervals. • The DCB could not be used for reinterventions. • Other trials in the CLI population have similar missing data.[33-35] In addition, the study design assumed an attrition rate of 15%. • The study sample size was based only on power for the primary endpoints. It would talk a very large study of the enrolled population to show a difference in the secondary endpoints. In addition, some of these endpoints are based on multiple factors (e.g., wound care, footwear).

In summary, there was a clinically meaningful benefit for the DCB arm measured at 6 months, an appropriate interval given the aggressive nature of CLI. These benefits gradually diminished such that there was not a difference at the 12-month timepoint. It is likely that a patient would benefit from use of the balloon. The presence of the drug on the balloon is likely to provide benefit in extending the time to the first reintervention and in the rate of reinterventions within the first 6 months. The level of uncertainty is not unexpected for a degenerative disease such as CLI.

The Benefit-Risk Guidance acknowledges that it is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits. The LUTONIX DCB is a novel device as it is the first to provide an ancillary drug effect with mechanical dilatation. CLI is an irreversibly debilitating human disease and there is an unmet need for more effective treatments

in restoring blood flow BTK. Although the benefit was not statistically significant, the guidance further states that "FDA may determine the novel device to be reasonably safe and effective even though the sponsor demonstrates a relatively small probable benefit." This statement suggests that the clinically meaningful benefit observed in the LUTONIX DCB Trial exceeds the minimal expectations for a device intended to address an unmet need.

13.3 Assessment of Risks

The information relevant to the risks associated with the LUTONIX DCB are presented in **Table 13-3**, with the primary endpoint at 30 days.

Table 13-3. Known/Probable Risks

FDA Guidance	LUTONIX DCB Study Results
What are the adverse events AEs or outcomes related to the device itself?	• The proportion of patients that did not have a safety event through Day 30 was 99.3% in the DCB arm, and 99.4% in the PTA arm (p<0.0001 single-sided). • Major Adverse Cardiovascular Event (MACE) was defined as any myocardial infarction, stroke, or all-cause death. All MACE events through 12 months have been adjudicated by the CEC. MACE rates were low in both treatment arms and similar through 36 months: 7.9% DCB vs. 6.0% PTA at 6 months, 11.1% DCB vs. 10.0% PTA at 12 months, 18.8% DCB vs. 15.2% PTA at 24 months, and 27.5% DCB vs. 26.3% PTA at 36 months.
What are the AEs or outcomes related to the use of the device or procedure to use the device?	
Are there adverse events or outcomes, not seen in the study, but probable based on "class effect" or events known to occur with similar technologies?	• Though not "probable," there is a potential for increased risk of mortality associated with paclitaxel based on ATK studies. In the LUTONIX DCB Trial there was no mortality signal for the LUTONIX DCB in BTK lesions out to 3 years.

The Benefit-Risk Guidance recognizes that some extent of uncertainty always exists. The sources of uncertainty for the risks are presented in **Table 13-4**.

Table 13-4. Uncertainty Around Risks

FDA Guidance	LUTONIX DCB Study	Comment
What is the extent of uncertainty for the risks?	There were missing data at all timepoints, increasing during later follow-up intervals.	Other trials in the CLI population have similar missing data.[33-35]

In summary, the risks associated with the LUTONIX DCB are consistent with those for PTA. The presence of the drug on the balloon is not associated with an increased risk during the evaluation period. The level of uncertainty is not unexpected for a study of patients with a degenerative disease such as CLI.

13.4 Additional Considerations

The Benefit-Risk Guidance provides direction for consideration of additional factors that can impact the Benefit-Risk assessment. The relevant additional factors for the LUTONIX DCB Trial are presented in **Table 13-5.**

The LUTONIX DCB would fill an unmet need for a more effective treatment of CLI by providing a greater clinically meaningful benefit than existing therapy, while posing similar risks to PTA. This unmet need is evidenced by the off-label use of ATK DCBs, as well as the FDA's granting of several Breakthrough Designation Requests for devices intended to treat CLI. It would not be feasible to repeat this study.

13.5 Assessment of Benefit-Risk

The purpose of balloon angioplasty is to restore blood flow. The data suggest that the LUTONIX DCB provides improved blood flow at 6 months compared with PTA; an effect which gradually diminishes such that there is not a difference at the 1-year timepoint. Although the performance of the device was evaluated through 36 months, a longer-term patency benefit was not expected due to the complexity of the patient population and the transition to standard of care for reinterventions (i.e., the DCB could only be used for the index intervention and reinterventions were performed with PTA or other non-DCB modalities).

Table 13-5. Additional Considerations

Considerations from FDA Guidance	Comment
The device fills an unmet medical need or niche for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease/conditions	• CLI is an irreversibly debilitating human disease. The LUTONIX DCB offers advantages over PTA including the time to first reintervention and the rate of reinterventions at 6 months as compared to PTA. The benefit is most notable at 6 months and extends to 12 months.
Understanding how the size of the patient population impacts feasibility of conducting large trials and affects public health need for both rare and common diseases or conditions	• Although the number of patients with CLI is high, many patients had to be screened to achieve the final number of enrolled patients (442). This observation was the result of the complex patient population and the need for somewhat strict eligibility criteria to limit attrition through follow-up.
Understanding of patient willingness or unwillingness to accept a large extent of uncertainty in the benefits and/or risks	• CLI patients are expected to be willing to accept uncertainty regarding their potential for obtaining benefit as compared to having treatment with PTA, especially since the LUTONIX DCB has been demonstrated to be as safe as PTA.
The study is a first of a kind (robustness of the analysis)	• Much was learned during the conduct of the clinical study which prompted changes in the study with associated statistical penalties. • To date, this is the only US IDE pivotal study on BTK angioplasty.

Currently DCBs are being used off-label to treat BTK lesions. Approval of the LUTONIX DCB will provide a device specifically designed and evaluated for this challenging anatomy, addressing an unmet need for patients with CLI. The instructions for use will describe the data and the limitations of the LUTONIX BTK IDE TRIAL which will allow for informed decisions regarding patient selection and device use. Continued evaluation of the LUTONIX DCB under a post-approval study will further the understanding of the patients most likely to benefit from the use of this device. (See **Section 12**).

Because the device was shown to be as safe as PTA during the evaluation period, the benefits outweigh the risks.

14 APPENDICES

APPENDICES ARE INCLUDED ON THE FOLLOWING PAGES

14.1 Demographics and Baseline Characteristics

Table 14-1. Medical History

Characteristic	DCB Patients (N=287)	PTA Patients (N=155)	Total Patients (N=442)
BMI (kg/m²):			
N	287	155	442
Mean (SD)	28.4 (6.31)	28.0 (5.65)	28.2 (6.08)
Median	28.0	27.4	27.7
Min, Max	14.1, 69.9	16.7, 51.6	14.1, 69.9
Rutherford Category, (%)			
N	287	155	442
3	9.1%	10.3%	9.5%
4	34.8%	33.5%	34.4%
5	56.1%	56.1%	56.1%
History of Risk Factors, (%)	99.3%	100.0%	99.5%
Diabetes	71.1%	68.4%	70.1%
Dyslipidemia	78.4%	74.8%	77.1%
Hypertension	92.0%	95.5%	93.2%
Cigarette Smoking	59.2%	57.4%	58.6%
Current	15.0%	12.3%	14.0%
Former	44.3%	45.2%	44.6%
Cardiac Disease, (%)	65.9%	71.0%	67.6%
Angina Pectoris	10.8%	12.9%	11.5%
Arrhythmia (Other Than A-Fib)	8.0%	8.4%	8.1%
Atrial Fibrillation (A-Fib)	20.6%	23.9%	21.7%
Cardiomyopathy	9.4%	13.5%	10.9%
Coronary Artery Disease (CAD)	47.0%	54.8%	49.8%
Heart Failure	11.8%	10.3%	11.3%
Ischemic Heart Disease	4.2%	9.7%	6.1%
Myocardial Infarction (MI)	22.3%	20.0%	21.5%
Valvular Heart Disease	9.8%	11.6%	10.4%
Other	18.8%	17.4%	18.3%
Respiratory Illness, (%)	27.5%	34.2%	29.9%
Asthma	4.9%	3.9%	4.5%
Bronchitis	3.8%	3.2%	3.6%
Chronic Obstructive Pulmonary Disease	10.5%	17.4%	12.9%
Other	15.7%	20.6%	17.4%
Vascular Disease, (%)	67.9%	72.3%	69.5%
AAA	3.8%	7.1%	5.0%
Aortic Disease	4.2%	2.6%	3.6%
Aorto-Iliac Occlusive Disease	1.0%	0.0%	0.7%

Table 14-1. Medical History

Characteristic	DCB Patients (N=287)	PTA Patients (N=155)	Total Patients (N=442)
Deep Vein Thrombosis (DVT)	5.2%	5.2%	5.2%
Iliac Artery Aneurysm	1.0%	1.3%	1.1%
Stroke	12.2%	11.0%	11.8%
Thrombolysis	0.3%	0.6%	0.5%
Transient Ischemic Attack (TIA)	8.4%	6.5%	7.7%
Vasculitis	0.0%	1.3%	0.5%
Venous Insufficiency	7.0%	9.0%	7.7%
Other	52.6%	54.8%	53.4%
Other Disease, (%)	88.9%	85.2%	87.8%
Active Infection	5.6%	4.5%	5.2%
Active Inflammatory Wounds	4.2%	5.2%	4.5%
Bleeding Disorder	2.1%	1.3%	1.8%
Cancer	17.4%	16.8%	17.2%
Gastrointestinal Bleeding	4.2%	2.6%	3.6%
Hepatic Insufficiency	0.0%	0.6%	0.2%
Immunosuppressed	0.3%	0.0%	0.2%
Liver Disease	2.1%	3.9%	2.7%
Osteomyelitis	9.8%	3.9%	7.7%
Renal Failure	23.7%	16.8%	21.3%
Systemic Lupus Erythematosus	0.3%	1.3%	0.7%
Ulcers	47.4%	47.1%	47.5%
Other	70.7%	74.2%	71.9%

Table 14-2. Previous and Planned Interventions

	DCB Patients (N=287)	PTA Patients (N=155)	Total Patients (N=442)
Any intervention by patient[1]	72.8%	74.8%	73.5%
Any coronary intervention	42.2%	45.2%	43.2%
Prior stent in target limb	14.6%	14.8%	14.7%
Prior peripheral vascular intervention	53.7%	54.2%	53.8%
Planned intervention ≤ 30 days	7.3%	5.8%	6.8%
Target limb interventions			
0	59.2%	61.3%	60.0%
1	18.8%	12.3%	16.5%
2	9.4%	12.9%	10.6%
3	4.9%	7.1%	5.7%

Table 14-2. Previous and Planned Interventions

	DCB Patients (N=287)	PTA Patients (N=155)	Total Patients (N=442)
4	3.8%	2.6%	3.4%
5	1.0%	1.3%	1.1%
6	0.7%	0.6%	0.7%
7	1.4%	0.6%	1.1%
9	0.3%	0.0%	0.2%
10	0.3%	0.0%	0.2%
>10	0.0%	1.3%	0.5%
Target limb interventions[2]			
Amputation	12.2%	10.3%	11.5%
Atherectomy	7.0%	3.9%	5.9%
Cutting/Scoring Balloon	1.4%	1.3%	1.4%
DCB	3.1%	3.9%	3.4%
Other	8.7%	9.0%	8.8%
Peripheral Bypass	0.3%	1.9%	0.9%
Peripheral PTA	16.7%	20.6%	18.1%
Stenting	10.1%	11.0%	10.4%
Vascular Bypass	0.7%	0.0%	0.5%
Total interventions by patient			
0	26.5%	25.2%	26.0%
1	21.6%	14.2%	19.0%
2	17.1%	19.4%	17.9%
3	10.1%	14.8%	11.8%
4	6.3%	8.4%	7.0%
5	7.0%	7.1%	7.0%
6	2.4%	1.3%	2.0%
7	1.4%	1.3%	1.4%
8	2.1%	1.3%	1.8%
9	2.8%	4.5%	3.4%
10	0.7%	0.6%	0.7%
11	0.3%	0.0%	0.2%
12	0.7%	0.6%	0.7%
13	0.7%	0.0%	0.5%
18	0.0%	0.6%	0.2%
22	0.0%	0.6%	0.2%
25	0.3%	0.0%	0.2%
All limb interventions[3]			
AAA Repair	0.7%	0.6%	0.7%
Amputation	18.8%	16.8%	18.1%
Atherectomy	11.1%	9.7%	10.6%
Cardiac PTCA/Stent	17.4%	19.4%	18.1%

Table 14-2. Previous and Planned Interventions

	DCB Patients (N=287)	PTA Patients (N=155)	Total Patients (N=442)
Carotid Endarterectomy/Stent	2.4%	3.2%	2.7%
Coronary Artery Bypass Graft	19.9%	23.2%	21.0%
Cryoplasty	0.3%	0.0%	0.2%
Cutting/Scoring Balloon(s)	2.8%	1.3%	2.3%
DCB	6.3%	4.5%	5.7%
Other	18.1%	18.1%	18.1%
Pacemaker Implantation	5.9%	7.1%	6.3%
Peripheral Bypass	0.7%	3.2%	1.6%
Peripheral PTA	29.3%	34.2%	31.0%
Stenting	17.4%	20.0%	18.3%
Valvuloplasty/Valve Replacement	2.8%	4.5%	3.4%
Vascular Bypass	1.7%	1.3%	1.6%
Vascular Iliac Graft	0.3%	0.0%	0.2%

[1]*Patients indicated any coronary intervention, stent in target limb, previous peripheral vascular intervention, or planned intervention*
[2]*Patients may appear in more than one category but are only counted once in each category*

Table 14-3. Angiographic (Core Lab) Target Lesion Characteristics, by Lesion

	Treated Lesions		
	DCB (N=352)	PTA (N=213)	P-value[2]
Lesion Type, N	352	212	0.694
Distal 1/3, n (%)	17 (4.8%)	14 (6.6%)	
Proximal 2/3, n (%)	194 (55.1%)	121 (57.1%)	
Split across 2/3 reference line, n (%)	126 (35.8%)	70 (33.0%)	
Unknown/NA, n (%)	15 (4.3%)	7 (3.3%)	
Target Lesion Length (mm), n	349	206	0.034
Mean	111.8	94.7	
SD	92.64	85.36	
Min - Max	6 - 340	7 - 361	
Initial % Stenosis, n	352	212	0.090
Mean	86.7	84.8	
SD	14.51	14.45	
Min - Max	38 - 100	32 - 100	
MLD (mm), n	352	212	0.124
Mean	0.5	0.4	
SD	2.10	0.41	
Min - Max	0.0 - 39.0	0.0 - 2.0	

Table 14-3. Angiographic (Core Lab) Target Lesion Characteristics, by Lesion

	Treated Lesions		
	DCB (N=352)	PTA (N=213)	P-value[2]
RVD (mm), n	350	212	0.164
Mean	2.5	2.6	
SD	0.61	0.62	
Min - Max	0.0 - 4.7	1.3 - 5.3	
Run-off Present through Foot, n/N (%)	310/328 (94.5%)	192/202 (95.0%)	0.787
Run-off Vessels[1], N	284	181	0.455
Anterior Tibial, n (%)	128 (45.1%)	88 (48.6%)	0.339
Posterior Tibial, n (%)	102 (35.9%)	73 (40.3%)	0.988
Peroneal, n (%)	212 (74.6%)	135 (74.6%)	
Pedal Arch, N	305	185	0.882
Complete, n (%)	115 (37.7%)	71 (38.4%)	
Incomplete, n (%)	190 (62.3%)	114 (61.6%)	
Any Calcification, n/N (%)	211/352 (59.9%)	115/212 (54.2%)	0.185
Severe Calcification, n/N (%)	53/352 (15.1%)	28/212 (13.2%)	0.542
TASC Lesion Type, N	351	209	0.072
A, n (%)	182 (51.9%)	131 (62.7%)	
B, n (%)	61 (17.4%)	32 (15.3%)	
C, n (%)	62 (17.7%)	28 (13.4%)	
D, n (%)	46 (13.1%)	18 (8.6%)	
Aneurysm, n/N (%)	0/351 (0.0%)	0/212 (0.0%)	NA
Thrombus, n/N (%)	3/351 (0.9%)	1/212 (0.5%)	0.589
Eccentric Lesion, n/N (%)	6/351 (1.7%)	3/212 (1.4%)	0.786
Ulcerated Plaque, n/N (%)	1/351 (0.3%)	0/212 (0.0%)	0.331
AV Fistula, n/N (%)	2/351 (0.6%)	0/212 (0.0%)	0.169

[1] *Patients may have more than one location indicated.*
[2] *Wilcoxon Rank-Sum test and Likelihood Ratio Chi-Square test*

14.2 Evolution of the Clinical Trial Design

Table 14-4. LUTONIX BTK IDE Trial Major Protocol Changes

CIP Version	Endpoint-related	Incl/Excl-related	Procedural-related	Statistical-related
v.2 to v.4			Clarified medication regimen.	
v.4 to v.6		Allowed inclusion of superficial ischemic ulcers that extended past the digit-metatarsal skin crease by 4cm. Allowed inclusion of patients with acute infection.	Changed the ABI/TBI and Duplex Ultrasound assessment from the discharge time point to anytime within the 30-day visit window. Clarified that wound photographs are required at baseline and each time point, if wound(s) are present.	
v. 6 to v.7		Removed the hemodynamic inclusion criterion.		

Table 14-4. LUTONIX BTK IDE Trial Major Protocol Changes

CIP Version	Endpoint-related	Incl/Excl-related	Procedural-related	Statistical-related
v. 7 to v.8	Decreased the percent (%) residual stenosis for technical and procedural success from <50% to <30%.	Allowed inclusion of Rutherford 3 patients. Allowed inclusion of patients with major amputations on the contralateral limb.	Allowed atherectomy during inflow treatment in conjunction with a distal protection device. Removed the requirement for stent use in lesions > 40mm. Changed the balloon diameter difference between the reference vessel diameter and a pre-dilatation balloon from < 0.5 to the site's standard of care. Decreased the minimum residual stenosis post pre-dilatation from <75% to <50%. Removed the requirement for additional balloon treatment for patients randomized to the control cohort. Removed the requirement for angiogram assessment at the 12-month follow-up visit. Removed the requirement for blood analyses with the exception of a pregnancy test.	
v.8 to v.9			Changed the minimum inflation time required for the DCB to 2 minutes to ensure both adequate drug release and a good angioplasty outcome.	Updated the Statistical Analysis Plan to account for an increase in sample size (up to 840 randomized pathways) based on an adaptive design and added interim analyses.
v. 9 to v.11	Changed the time point of the primary endpoint assessment from 12 months to 6 months.		Reduced the follow-up duration from 5 years to 3 years.	Changed to a repeated measures primary effectiveness analysis approach to account for the possibility of multiple pathways per patient and to aid in the evaluation of the

Table 14-4. LUTONIX BTK IDE Trial Major Protocol Changes

CIP Version	Endpoint-related	Incl/Excl-related	Procedural-related	Statistical-related
				site/treatment interaction.
v. 11 to v. 12	Added the inclusion of the proximal segment, as a primary effectiveness endpoint. Added the following secondary endpoint: Primary Patency with exclusion of early mechanical recoil (freedom from occlusion without clinically driven TLR events > 30 days).	Added a proximal vessel arm in case enrollment needed to continue following the interim analyses.		Added a secondary endpoint analysis for exclusion of early mechanical recoil events. Updated endpoint testing to account for the proximal vessel analysis.
v. 12 to v. 13	Separated hypothesis tested secondary endpoints into safety and effectiveness endpoints for testing based on success of the respective primary endpoint (as opposed to success of both primary endpoints) to allow secondary endpoint hypothesis testing based on success of the respective primary endpoint success only. Added wound healing as a hypothesis tested secondary endpoint due to the importance of this endpoint.			Added 48-month and 60-month time points for all-cause death Removed separate secondary endpoint analyses of the amputation free survival cohort to simplify analyses. Changed analysis of the major amputation secondary endpoint from a superiority test to a non-inferiority test to show equivalence in this safety event to PTA.

14.3 BTK IDE Trial Design: Eligibility Criteria and Analysis Populations

Eligible patients had to meet each of the inclusion and exclusion criteria to be enrolled in the study, as follows:

14.3.2 Inclusion Criteria

Clinical Inclusion Criteria

- Male or non-pregnant, non-breastfeeding female ≥ 18 years of age;
- Rutherford Clinical Category 3, 4 or 5. Patients categorized as a Rutherford Clinical Category 3 must have failed medical management per physician discretion.
- Life expectancy ≥ 1 year;
- Patient is willing to provide informed consent, is geographically stable, and is willing to comply with the protocol-required follow up visits, testing schedule and medication regimen;
- No other prior surgical or vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment, but the following are allowed within 2 weeks prior or within 30 days after the procedure:
    - Planned transmetatarsal or lower minor amputations;
    - Index limb inflow-lesion treatment;
    - Contralateral iliac treatment;
    - Wound debridement;

Except for allowed iliac treatment (noted above), contralateral limb lesion(s) could not have been treated during the index procedure or within 2 weeks before and/or planned 30 days after in order to avoid confounding complications.

Angiographic Inclusion Criteria

- Significant stenosis (≥ 70%) or occlusion of one or two native artery(s) below the tibial plateau and above the tibiotalar joint appropriate for angioplasty per operator visual assessment.

  NOTE: One or two flow pathways are allowed as artery(s); i.e., peroneal or posterior tibial arteries may involve tibioperoneal trunk lesions and tibial arteries may involve popliteal lesions;

- Cumulative length of target lesion(s) ≤ 320 mm;
- Target lesion(s) not previously stented and at least 20 mm from any previous stent;
- A patent inflow artery from the aorta to the target lesion free from significant (≥ 50%) stenosis as confirmed by angiography;

- Target vessel(s) diameter between 2 and 4 mm and able to be treated with available device size matrix;
- Successful antegrade pre-dilatation of the target lesion with standard PTA catheter 236.+0appropriate size for the reference vessel diameter;
- Target vessel(s) 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);
- Additional inclusion criteria applicable only if continued enrollment of "proximal segment only" arm is required per adaptive study design: Target lesion is located entirely within the proximal two-thirds of the leg between the tibial plateau and tibiotalar joint.

14.3.3 Exclusion Criteria

- Any severe medical comorbidities (untreated CAD/CHF, severe COPD, metastatic malignancy, etc.) that would preclude compliance with the study protocol or currently receiving immune-suppressive, chemotherapeutic, or radiation therapy;
- Patient is currently participating in an investigational drug or device study or previously randomized or a roll-in patient in this study
- History of stroke within 3 months;
- History of MI, thrombolysis or angina within 30 days of enrollment;
- Gangrene extending proximal to the digit-metatarsal skin crease (target limb);
- Ischemic ulceration that extends more than 4 cm proximal to digit-metatarsal skin crease (target limb);
- Neurotropic ulcer or heel pressure ulcer or ulcer potentially involving calcaneus (target limb);
- Evidence of osteomyelitis in a bone not intended for resection (target limb);
- Signs and symptoms of systemic infection (temperature of ≥ 38.0° Celsius and/ or WBC of ≥12,000 cells/ μL) at the time of assessment;
- Planned major amputation (of either leg);
- Prior major amputation if amputation occurred less than one year prior to enrollment and if patient is not independently ambulating;
- GFR ≤ 30 ml/min/1.73m^2;

- Allergy to contrast or known allergy to contrast, taxols or polysorbates that cannot be adequately managed with pre- and post-procedure medication;
- Hemodynamically significant aortic or CFA occlusive disease (concurrent aortic and common femoral artery treatment not allowed);
- Intended use of adjunctive primary treatment modalities (e.g., atherectomy, laser, cutting balloons, radiation therapy, stents) in below-the-knee vessels;
- Acute limb ischemia (symptom onset within 2 weeks);
- In-stent restenosis of target lesion;
- Presence of thrombus in the target vessel.

14.3.4 Analysis Populations

All safety and effectiveness analyses were performed on an Intent-to-Treat (ITT) basis. In addition, the primary safety and effectiveness analyses were performed on the AT, PP, and Japanese ITT populations as sensitivity analyses.

The definitions of the analysis populations are as follows:

Intent-to-Treat (ITT)	Includes all randomized patients or flow pathways analyzed according to their randomized treatment group.
As Treated (AT)	Includes all patients or flow pathways analyzed according to the actual treatment received. Patients who receive DCB in at least one flow pathway will be included in the AT population at the patient level and flow pathways may be DCB or PTA within the same patient. Any flow pathway that did not receive DCB will be considered standard PTA.
Per Protocol (PP)	Includes all randomized patients or flow pathways that are characterized by appropriate exposure to treatment (procedurally correct as prespecified), and the absence of major protocol violations including violations of entry criteria. The protocol deviations that are considered to have a “major” grade were defined a priori in the analysis plan.

Standard Practice (SP)	Population includes all patients that did not meet post-pre-dilatation criteria and not randomized and treated per standard practice.
Japan ITT (JITT)	Includes all Japanese ITT patients and flow pathways.
Roll-in	Patients who were included to allow investigators to treat patients outside the randomization.

14.3.5 Proximal Segment Subgroup Analyses

It is now known that elastic recoil can lead to acute failure of infrapopliteal angioplasty. This information of the different pathophysiology of BTK vessels became known after trial initiation. In brief, the investigators were concerned that the new data at that time suggested that there may be two distinctly different, heterogeneous, restenosis pathologies in below the knee arteries, based on differences in location, concentration and morphology of calcium observed in these vessels.[27,28] Therefore, the Statistical Analysis Plan (v.2) was updated with an additional subgroup of lesions; namely lesions in the proximal segment of the BTK anatomy, was added as a separate study population for the effectiveness analysis. The Proximal Segment analysis population was defined by the extent of the target lesions, as assessed by the core laboratory. The Proximal Segment population comprised those flow pathways that were entirely within the proximal 2/3 segment of the target flow pathway boundary or are split across the 2/3 cut-off.

With this update, the primary analysis data set was predefined on a hierarchical basis for analysis on 1) a per vessel pathway basis or 2) a per lesion basis of proximal segment lesions only. The first primary effectiveness analysis was based on the total number of randomized flow pathways. The second primary effectiveness analysis was based on the total number of randomized flow pathways that include at least one or a portion of a lesion in the proximal segment of flow pathway. The analysis method and cut-offs were the same for the entire flow pathway and proximal-segment analyses. The study was considered to have demonstrated primary effectiveness if either of the analyses (all flow pathway analysis or proximal-segment only analysis) reached statistical significance.

Although this is a Trial Design appendix, for ease of review, a summary of the results of this subgroup analysis is described here. The Proximal Segment population made up 95% of the overall BTK IDE study population (95.1% DCB / 94.8% PTA). The primary effectiveness endpoint was freedom from the composite of above-ankle amputation, target lesion occlusion,

and clinically driven target lesion revascularization through 6 months. Success was defined as a treated flow pathway (rather than patient) with no failure event on or before Day 210. A total of 388 ITT flow pathways had data available for analysis. The 6-month success rate was 76.2% for the DCB arm and 64.4% for the Control arm (11.8% difference) and did not meet the primary effectiveness endpoint for superiority (p-value=0.0139, single sided). The preponderance of Proximal Segment lesions explains the absence of large differences between these results and those of the analysis of the All Flow Pathways population.

For the purposes of this panel meeting, BD will not be addressing proximal segment further.

14.4 Additional All-Cause Mortality Data Through 60 Months

The database cut for the LUTONIX BTK IDE Clinical Study Report used in support of (b) (4) occurred on October 17, 2019, which was prior to FDA approval on December 20, 2019 of version 13 (25Sep2019) of the study protocol which extended the study from 3 to 5 years, for collection of vital status only.

The sponsor conducted an additional data cut on June 17, 2020 to show the 60-month survival rate of treatment arms using 48-month and 60-month data that have been entered by investigational sites. The Kaplan-Meier curve and analysis are shown below and there continues to be no difference in mortality between the groups out to 60 months. The amount of data available at 48 and 60 months remains still limited, as observed in the number of censored patients. The sponsor is continuing to diligently contact sites to track and record 48-month and 60-month vital status for patients who have completed the original 36-months and need to be re-contacted to allow for additional follow-up.

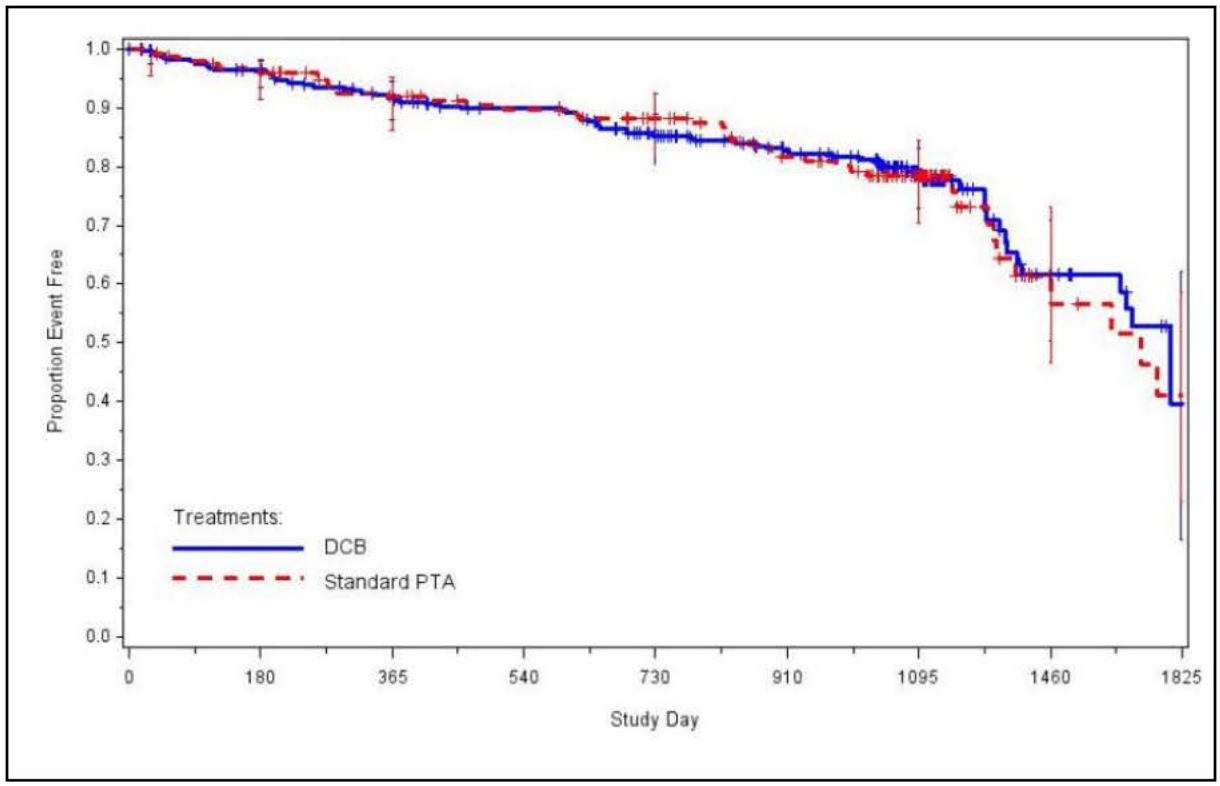

Figure 14-1. All-Cause Mortality Rate Through 60 Months.

Group	Time Point	Freedom From MALE+POD*	Cumulative Patients with Events	Cumulative Patients Censored	Patients Left†	Overall Median Survival (Day), 95% CI
DCB	Day 1	100.0% (NA, NA)	0	1	286	1792 (1655, NA)
	Day 30	99.6% (97.5%, 100.0%)	1	4	282	
	Day 44	98.9% (96.8%, 99.7%)	3	4	280	
	Day 180	96.5% (93.5%, 98.1%)	10	7	270	
	Day 210	94.7% (91.3%, 96.8%)	15	9	263	
	Day 365	91.8% (87.8%, 94.4%)	23	14	250	
	Day 395	91.0% (87.0%, 93.8%)	25	17	245	
	Day 730	85.3% (80.4%, 89.0%)	40	36	211	
	Day 790	84.4% (79.5%, 88.2%)	42	49	196	
	Day 1095	78.6% (72.8%, 83.2%)	54	117	116	
	Day 1155	77.8% (71.8%, 82.6%)	55	177	55	
	Day 1460	61.5% (50.3%, 70.9%)	64	196	27	
	Day 1520	61.5% (50.3%, 70.9%)	64	201	22	
	Day 1825	39.6% (16.5%, 62.1%)	68	216	3	

Group	Time Point	Freedom From MALE+POD*	Cumulative Patients with Events	Cumulative Patients Censored	Patients Left†	Overall Median Survival (Day), 95% CI
PTA	Day 1	100.0% (NA, NA)	0	0	155	1710 (1362. NA)
	Day 30	99.4% (95.5%, 99.9%)	1	1	153	
	Day 44	99.4% (95.5%, 99.9%)	1	2	152	
	Day 180	96.1% (91.4%, 98.2%)	6	6	143	
	Day 210	96.1% (91.4%, 98.2%)	6	9	140	
	Day 365	91.9% (86.2%, 95.3%)	12	12	131	
	Day 395	91.9% (86.2%, 95.3%)	12	14	129	
	Day 730	88.3% (81.8%, 92.5%)	17	22	116	
	Day 790	87.5% (80.8%, 91.9%)	18	27	110	
	Day 1095	78.4% (70.3%, 84.5%)	29	57	69	
	Day 1155	78.4% (70.3%, 84.5%)	29	88	38	
	Day 1460	61.3% (46.6%, 73.1%)	35	107	13	
	Day 1520	56.6% (40.2%, 70.1%)	36	107	12	
	Day 1825	41.2% (22.9%, 58.6%)	39	115	1	

** Kaplan-Meier estimate of proportion of patients without a key safety event at the visit day (95% CI).*
† Patients ongoing without an event at the visit day.
Confidence intervals not adjusted for multiple comparisons.

14.5 Adverse Event Tables

Table 14-5. Device-Related AEs by Body System and Preferred Term through 36 Months

Body System Preferred Term	DCB Patients (N=287)		PTA Patients (N=155)	
	Site Reported	Adjudicated	Site Reported	Adjudicated
Total Device Related Adverse Event[1]	64	40	24	18
Sent for Adjudication	60		22	
Patients with at least one Device Related AE	44 (15.3%)	33 (11.5%)	17 (11.0%)	15 (9.7%)
General Disorders/ Administration Site Conditions	1 (0.3%)	0	0	0
Disease Progression	1 (0.3%)	0	0	0
Infections And Infestations	1 (0.3%)	1 (0.3%)	1 (0.6%)	1 (0.6%)
Cellulitis	1 (0.3%)	0	0	0
Gangrene	0	1 (0.3%)	1 (0.6%)	0
Osteomyelitis	0	0	1 (0.6%)	1 (0.6%)
Injury, Poisoning And Procedural Complications	20 (7.0%)	8 (2.8%)	12 (7.7%)	8 (5.2%)
Peripheral Arterial Reocclusion	11 (3.8%)	3 (1.0%)	3 (1.9%)	3 (1.9%)
Peripheral Artery Restenosis	8 (2.8%)	4 (1.4%)	9 (5.8%)	5 (3.2%)
Procedural Pain	1 (0.3%)	1 (0.3%)	0	0
Wound	1 (0.3%)	0	1 (0.6%)	0
Wound Necrosis	0	0	1 (0.6%)	0
Musculoskeletal And Connective Tissue Disorders	1 (0.3%)	0	0	1 (0.6%)
Arthralgia	0	0	0	1 (0.6%)
Pain In Extremity	1 (0.3%)	0	0	0
Nervous System Disorders	0	1 (0.3%)	0	0
Hypoaesthesia	0	1 (0.3%)	0	0
Skin And Subcutaneous Tissue Disorders	1 (0.3%)	0	0	0
Skin Ulcer	1 (0.3%)	0	0	0
Vascular Disorders	30 (10.5%)	26 (9.1%)	4 (2.6%)	7 (4.5%)
Embolism Arterial	4 (1.4%)	6 (2.1%)	0	1 (0.6%)
Peripheral Arterial Occlusive Disease	9 (3.1%)	6 (2.1%)	2 (1.3%)	1 (0.6%)
Peripheral Artery Dissection	8 (2.8%)	6 (2.1%)	1 (0.6%)	1 (0.6%)
Peripheral Artery Stenosis	1 (0.3%)	1 (0.3%)	1 (0.6%)	1 (0.6%)
Peripheral Artery Thrombosis	1 (0.3%)	1 (0.3%)	0	1 (0.6%)
Vasospasm	10 (3.5%)	8 (2.8%)	0	3 (1.9%)
Uncoded Adverse Event	0	0	1 (0.6%)	0
Uncoded: Worsening Peripheral Artery Disease	0	0	1 (0.6%)	0

**Related includes: Definitely Related, Highly Probably Related, and Possibly Related*

Table 14-6. Procedure-Related AEs by Body System and Preferred Term through 36 Months

Body System and Preferred Term	DCB Patients (N=287)		PTA Patients (N=155)	
	Site Reported	Adjudicated	Site Reported	Adjudicated
Total Procedure Related Adverse Events[1]	130	94	47	36
Sent for Adjudication	110		45	
Patients with at least one Procedure Related AE	88 (30.7%)	73 (25.4%)	32 (20.6%)	30 (19.4%)
Blood And Lymphatic System Disorders	2 (0.7%)	1 (0.3%)	0	0
Anaemia	2 (0.7%)	1 (0.3%)	0	0
Cardiac Disorders	2 (0.7%)	4 (1.4%)	0	1 (0.6%)
Acute Myocardial Infarction	1 (0.3%)	2 (0.7%)	0	1 (0.6%)
Atrial Fibrillation	1 (0.3%)	1 (0.3%)	0	0
Myocardial Infarction	0	1 (0.3%)	0	0
Gastrointestinal Disorders	2 (0.7%)	1 (0.3%)	0	0
Gastritis	1 (0.3%)	0	0	0
Retroperitoneal Haematoma	1 (0.3%)	1 (0.3%)	0	0
General Disorders/Administration Site Conditions	19 (6.6%)	12 (4.2%)	5 (3.2%)	5 (3.2%)
Disease Progression	1 (0.3%)	0	0	0
Local Swelling	1 (0.3%)	1 (0.3%)	1 (0.6%)	0
Oedema Peripheral	3 (1.0%)	2 (0.7%)	1 (0.6%)	1 (0.6%)
Puncture Site Haemorrhage	2 (0.7%)	2 (0.7%)	0	0
Pyrexia	1 (0.3%)	0	1 (0.6%)	1 (0.6%)
Stent Malfunction	0	0	1 (0.6%)	1 (0.6%)
Vessel Puncture Site Haematoma	11 (3.8%)	7 (2.4%)	1 (0.6%)	2 (1.3%)
Immune System Disorders	1 (0.3%)	0	0	0
Drug Hypersensitivity	1 (0.3%)	0	0	0
Infections And Infestations	3 (1.0%)	6 (2.1%)	1 (0.6%)	2 (1.3%)
Arthritis Bacterial	0	1 (0.3%)	0	0
Cellulitis	2 (0.7%)	2 (0.7%)	0	0
Gangrene	0	1 (0.3%)	1 (0.6%)	1 (0.6%)
Infected Skin Ulcer	1 (0.3%)	0	0	0
Localised Infection	0	1 (0.3%)	0	0
Osteomyelitis	0	2 (0.7%)	1 (0.6%)	1 (0.6%)
Injury, Poisoning And Procedural Complications	28 (9.8%)	16 (5.6%)	18 (11.6%)	12 (7.7%)
Incision Site Complication	2 (0.7%)	2 (0.7%)	0	0
Peripheral Arterial Reocclusion	12 (4.2%)	3 (1.0%)	3 (1.9%)	2 (1.3%)
Peripheral Artery Restenosis	6 (2.1%)	3 (1.0%)	11 (7.1%)	4 (2.6%)
Post Procedural Discomfort	1 (0.3%)	0	0	0
Procedural Pain	2 (0.7%)	1 (0.3%)	0	0
Scrotal Haematoma	1 (0.3%)	1 (0.3%)	0	0

Table 14-6. Procedure-Related AEs by Body System and Preferred Term through 36 Months

Body System and Preferred Term	DCB Patients (N=287)		PTA Patients (N=155)	
	Site Reported	Adjudicated	Site Reported	Adjudicated
Subcutaneous Haematoma	1 (0.3%)	1 (0.3%)	0	0
Vascular Pseudoaneurysm	4 (1.4%)	5 (1.7%)	3 (1.9%)	3 (1.9%)
Wound	1 (0.3%)	0	1 (0.6%)	3 (1.9%)
Wound Necrosis	0	0	1 (0.6%)	0
Investigations	2 (0.7%)	2 (0.7%)	0	0
Haemoglobin Decreased	1 (0.3%)	1 (0.3%)	0	0
Urine Analysis Abnormal	1 (0.3%)	1 (0.3%)	0	0
Musculoskeletal/ Connective Tissue Disorders	0	0	0	1 (0.6%)
Arthralgia	0	0	0	1 (0.6%)
Nervous System Disorders	0	1 (0.3%)	0	1 (0.6%)
Hypoaesthesia	0	1 (0.3%)	0	1 (0.6%)
Psychiatric Disorders	1 (0.3%)	1 (0.3%)	0	0
Delirium	1 (0.3%)	1 (0.3%)	0	0
Renal And Urinary Disorders	3 (1.0%)	3 (1.0%)	0	0
Haematuria	1 (0.3%)	1 (0.3%)	0	0
Nephropathy Toxic	1 (0.3%)	1 (0.3%)	0	0
Renal Failure	1 (0.3%)	1 (0.3%)	0	0
Skin And Subcutaneous Tissue Disorders	2 (0.7%)	2 (0.7%)	0	0
Blister	0	1 (0.3%)	0	0
Rash	0	1 (0.3%)	0	0
Skin Ulcer	2 (0.7%)	0	0	0
Vascular Disorders	49 (17.1%)	36 (12.5%)	13 (8.4%)	13 (8.4%)
Arteriovenous Fistula	0	0	1 (0.6%)	1 (0.6%)
Embolism Arterial	4 (1.4%)	6 (2.1%)	1 (0.6%)	1 (0.6%)
Haematoma	5 (1.7%)	4 (1.4%)	0	0
Haemorrhage	0	0	1 (0.6%)	1 (0.6%)
Hypertension	1 (0.3%)	0	0	0
Hypertensive Crisis	0	0	1 (0.6%)	1 (0.6%)
Hypotension	1 (0.3%)	0	1 (0.6%)	1 (0.6%)
Peripheral Arterial Occlusive Disease	13 (4.5%)	7 (2.4%)	3 (1.9%)	1 (0.6%)
Peripheral Artery Aneurysm	0	0	1 (0.6%)	0
Peripheral Artery Dissection	13 (4.5%)	10 (3.5%)	2 (1.3%)	2 (1.3%)
Peripheral Artery Stenosis	0	1 (0.3%)	1 (0.6%)	1 (0.6%)
Peripheral Artery Thrombosis	1 (0.3%)	1 (0.3%)	2 (1.3%)	1 (0.6%)
Reperfusion Injury	1 (0.3%)	0	0	0
Vasospasm	17 (5.9%)	11 (3.8%)	4 (2.6%)	4 (2.6%)
Vessel Perforation	1 (0.3%)	1 (0.3%)	0	0
Uncoded Adverse Event	0	0	1 (0.6%)	0
Uncoded: Worsening Peripheral Artery Disease	0	0	1 (0.6%)	0

Table 14-6. Procedure-Related AEs by Body System and Preferred Term through 36 Months

Body System and Preferred Term	DCB Patients (N=287)		PTA Patients (N=155)	
	Site Reported	Adjudicated	Site Reported	Adjudicated
Related includes: Definitely Related, High Probable Related, and Possibly Related.				

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
Patients 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
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
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%)
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
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
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
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%)
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
Renal Impairment	1 (0.3%)	0
Ureteric Stenosis	1 (0.3%)	0
Urinary Retention	1 (0.3%)	1 (0.6%)
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%)

Table 14-7. Serious Adverse Events by Body System and Preferred Term through 36 Months, Site-reported

Body System and Preferred Term	DCB Patients (N=287) n (%)	PTA Patients (N=155) n (%)
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

Table 14-8. Serious Device-Related or Procedure-Related AEs by Body System and Preferred Terms through 36 Months, CEC adjudicated

Body System and Preferred Term	DCB Patients (N=287)		PTA Patients (N=155)	
	Device Related* n (%)	Procedure Related* n (%)	Device Related* n (%)	Procedure Related* n (%)
Patients with at least one Related Serious Adverse Event	18 (6.3%)	29 (10.1%)	11 (7.1%)	18 (11.6%)
Cardiac Disorders	0	3 (1.0%)	0	1 (0.6%)
Acute Myocardial Infarction	0	2 (0.7%)	0	1 (0.6%)
Myocardial Infarction	0	1 (0.3%)	0	0

Table 14-8. Serious Device-Related or Procedure-Related AEs by Body System and Preferred Terms through 36 Months, CEC adjudicated

Body System and Preferred Term	DCB Patients (N=287)		PTA Patients (N=155)	
	Device Related* n (%)	Procedure Related* n (%)	Device Related* n (%)	Procedure Related* n (%)
Gastrointestinal Disorders	0	1 (0.3%)	0	0
Retroperitoneal Haematoma	0	1 (0.3%)	0	0
General Disorders And Administration Site Conditions	0	1 (0.3%)	0	1 (0.6%)
Local Swelling	0	1 (0.3%)	0	0
Pyrexia	0	0	0	1 (0.6%)
Infections And Infestations	1 (0.3%)	5 (1.7%)	0	1 (0.6%)
Arthritis Bacterial	0	1 (0.3%)	0	0
Cellulitis	0	1 (0.3%)	0	0
Gangrene	1 (0.3%)	1 (0.3%)	0	1 (0.6%)
Localised Infection	0	1 (0.3%)	0	0
Osteomyelitis	0	2 (0.7%)	0	0
Injury, Poisoning And Procedural Complications	5 (1.7%)	6 (2.1%)	7 (4.5%)	7 (4.5%)
Peripheral Arterial Reocclusion	3 (1.0%)	2 (0.7%)	3 (1.9%)	2 (1.3%)
Peripheral Artery Restenosis	2 (0.7%)	0	4 (2.6%)	3 (1.9%)
Subcutaneous Haematoma	0	1 (0.3%)	0	0
Vascular Pseudoaneurysm	0	3 (1.0%)	0	0
Wound	0	0	0	2 (1.3%)
Investigations	0	1 (0.3%)	0	0
Haemoglobin Decreased	0	1 (0.3%)	0	0
Renal And Urinary Disorders	0	1 (0.3%)	0	0
Nephropathy Toxic	0	1 (0.3%)	0	0
Vascular Disorders	15 (5.2%)	17 (5.9%)	5 (3.2%)	9 (5.8%)
Embolism Arterial	3 (1.0%)	3 (1.0%)	1 (0.6%)	1 (0.6%)
Haemorrhage	0	0	0	1 (0.6%)
Hypertensive Crisis	0	0	0	1 (0.6%)
Hypotension	0	0	0	1 (0.6%)
Peripheral Arterial Occlusive Disease	5 (1.7%)	6 (2.1%)	1 (0.6%)	1 (0.6%)
Peripheral Artery Dissection	4 (1.4%)	4 (1.4%)	0	1 (0.6%)
Peripheral Artery Stenosis	1 (0.3%)	1 (0.3%)	1 (0.6%)	1 (0.6%)
Peripheral Artery Thrombosis	1 (0.3%)	1 (0.3%)	1 (0.6%)	1 (0.6%)
Vasospasm	2 (0.7%)	2 (0.7%)	1 (0.6%)	1 (0.6%)
Vessel Perforation	0	1 (0.3%)	0	0

**Related includes: Definitely Related, Highly Probable Related, and Possibly Related*

Table 14-9. Listing of Deaths (All Patients)

Treatment Arm	Age	Sex	Days (Index Procedure to Death)	Primary Cause of Death*
DCB	66	M	18	Diastolic heart failure
Standard PTA	70	F	20	Exacerbation of COPD
DCB	86	F	31	Respiratory failure
DCB	85	F	37	Non index limb gangrene. Refused treatment. Home care with hospice until cardiovascular event leading to death. Cause on death certificate listed as CAD
DCB	81	M	47	Pulmonary embolism
DCB	74	M	53	Cardiac arrest.
Standard PTA	74	M	53	Acute heart failure
Standard PTA	72	M	68	Respiratory failure
DCB	96	F	84	Hypertensive emergency
Standard PTA	63	M	105	Congestive heart failure
DCB	81	M	107	Fulminant pneumonia
DCB	85	M	109	Acute exacerbation of chronic CHF
DCB	81	M	117	Respiratory insufficiency by known COPD
Standard PTA	77	F	123	Due to clostridium difficile diarrhea
Standard PTA	73	F	162	Congestion pneumonia caused by an hospitalization due to shoulder fracture
DCB	84	M	186	Cardiac issues
DCB	94	M	194	Unknown at this time
DCB	85	F	197	Pancreatic cancer with metastases to liver and lung
DCB	77	M	199	Global heart dilatation
DCB	79	M	204	Coronary insufficiency
DCB	66	F	219	Intracerebral hemorrhage
DCB	83	M	241	Heart failure
DCB	79	M	254	Cardiac arrest
Standard PTA	78	M	260	Death in follow of a cardiopulmonary insufficiency
Standard PTA	70	F	262	End stage heart disease
Standard PTA	84	F	274	Colon carcinoma with liver metastasis
Standard PTA	82	F	288	Valvular aortic stenosis

Table 14-9. Listing of Deaths (All Patients)

Treatment Arm	Age	Sex	Days (Index Procedure to Death)	Primary Cause of Death*
DCB	73	M	298	Unknown cause of death - no contact with patient or family
DCB	70	M	310	Unknown
DCB	57	M	322	Immediate cause of death was peripheral vascular disease, secondary condition contributing to death was diabetes mellitus per certificate of death.
DCB	79	M	341	Congestive heart failure
Standard PTA	81	M	341	Cardiopulmonary arrest.
DCB	83	M	367	Immediate cause- respiratory failure d/t systolic heart failure d/t ischemic cardiomyopathy d/t coronary artery disease
DCB	79	M	373	Fall that resulted in subdural hematoma.
DCB	78	M	411	Lung cancer
Standard PTA	76	M	416	Sick sinus syndrome
DCB	59	F	428	Unknown. No med recs found at local hospital
DCB	78	M	457	Unknown - information to follow
Standard PTA	85	F	464	Unknown at this time.
Standard PTA	83	M	513	Complications of heart failure
DCB	58	M	596	Cardiac arrest secondary to septic shock.
DCB	84	F	602	Unknown
Standard PTA	90	M	615	Rectal cancer
DCB	84	M	617	Lung cancer
Standard PTA	81	F	618	Renal failure
DCB	50	M	633	Massive heart attack. Will update as soon as i know more information.
DCB	83	M	644	Oral cancer
DCB	73	M	646	NSTEMI in the setting of CHF exacerbation and renal failure
DCB	82	F	650	Coronary artery disease. Recent NSTEMI
DCB	82	M	688	Paralytic ileus
DCB	57	M	689	Died during sleep - cardiocirculatory arrest
DCB	83	M	725	Acute renal failure
DCB	79	F	776	Pancreatic cancer. Noted death in electronic medical record review done 8/31/2018

Table 14-9. Listing of Deaths (All Patients)

Treatment Arm	Age	Sex	Days (Index Procedure to Death)	Primary Cause of Death*
DCB	71	M	782	Respiratory failure secondary pneumonia
Standard PTA	75	F	822	Septic shock
Standard PTA	81	M	825	Cerebrovascular disease
Standard PTA	83	M	827	Epicarditis
Standard PTA	74	M	835	Myocardial infarction
DCB	48	M	839	Cause of death is unknown at this time.
Standard PTA	80	F	864	Heart failure / cardiomyopathy
DCB	59	F	883	Metastatic colon cancer
Standard PTA	77	M	889	Hemorrhage
DCB	65	F	905	Cardiac/PEA arrest
DCB	61	M	912	CHF, COPD
Standard PTA	67	F	935	Cardiac arrest due to multiple cardiac co-morbidities
DCB	79	M	973	Severe heart disease
Standard PTA	64	F	999	Cardiac arrest
DCB	50	M	1010	Unknown
DCB	65	M	1037	Lung cancer
DCB	76	M	1093	Pancreas carcinoma
DCB	67	M	1105	Congestive heart failure
Standard PTA	59	F	1199	Respiratory arrest
DCB	69	M	1291	Global heart dilatation
DCB	64	M	1341	Cardiac and respiratory decompensation

**Terms are corrected for spelling and grammar.*

14.6 Covariate Analysis for Primary Effectiveness

Table 14-10 (below) is a covariate analysis of baseline covariates and their effect on the primary effectiveness endpoint. A logistic regression model using pre-identified covariates along with treatment group examined any potential impact on the study results and to account for chance imbalances between randomized groups. Quartiles were used to help summarize binary success rates of the continuous variables. There were no statistically significant differences (p-value

for interaction terms >0.15). in the primary effectiveness endpoint by geography or any of the baseline characteristics except age (the response with DCB was greater in patients below 70 years of age). There were no lesion characteristics associated with a significant interaction and the only procedural characteristics with an effect were the maximum residual stenosis after pre-dilatation in preparation for use of the study device (PTA or DCB). When the residual stenosis after lesion prep was more than 50%, patients did better with DCB compared with PTA. The same was evident when the residual stenosis after lesion prep was more than 75%; these patients tended to do better with DCB.

Table 14-10. Covariate Analysis for Primary Effectiveness (By Pathway)

Factor	Level	Response by Level of Factor		Logistic Model Type 3 Test P-values
		DCB (N=269[1]) Response Rate (95% CI)[2]	PTA (N=137[1]) Response Rate (95% CI)[2]	
Geographic Location	US	126 / 164 (76.8%) (69.6%, 83.1%)	56 / 87 (64.4%) (53.4%, 74.4%)	Treatment: 0.064 Factor: 0.573 Interaction: 0.581
	OUS	75 / 105 (71.4%) (61.8%, 79.8%)	32 / 50 (64.0%) (49.2%, 77.1%)	
Age (Years)	<70 Years	72 / 99 (72.7%) (62.9%, 81.2%)	24 / 47 (51.1%) (36.1%, 65.9%)	Treatment: 0.024 Factor: 0.040 Interaction: 0.173
	≥70 Years	129 / 170 (75.9%) (68.7%, 82.1%)	64 / 90 (71.1%) (60.6%, 80.2%)	
Gender	Female	60 / 78 (76.9%) (66.0%, 85.7%)	29 / 42 (69.0%) (52.9%, 82.4%)	Treatment: 0.089 Factor: 0.351 Interaction: 0.767
	Male	141 / 191 (73.8%) (67.0%, 79.9%)	59 / 95 (62.1%) (51.6%, 71.9%)	
Smoking Status	Current	32 / 44 (72.7%) (57.2%, 85.0%)	8 / 14 (57.1%) (28.9%, 82.3%)	Treatment: 0.058 Factor: 0.497 Interaction: 0.948
	Former	98 / 127 (77.2%) (68.9%, 84.1%)	46 / 68 (67.6%) (55.2%, 78.5%)	
	Never	71 / 98 (72.4%) (62.5%, 81.0%)	34 / 55 (61.8%) (47.7%, 74.6%)	
Obesity (BMI ≥30)	No	125 / 172 (72.7%) (65.4%, 79.2%)	57 / 87 (65.5%) (54.6%, 75.4%)	Treatment: 0.031 Factor: 0.743 Interaction: 0.368
	Yes	76 / 97 (78.4%) (68.8%, 86.1%)	31 / 50 (62.0%) (47.2%, 75.3%)	
Dyslipidemia	No	37 / 53 (69.8%) (55.7%, 81.7%)	13 / 30 (43.3%) (25.5%, 62.6%)	Treatment: 0.020 Factor: 0.015 Interaction: 0.162

Table 14-10. Covariate Analysis for Primary Effectiveness (By Pathway)

Factor	Level	Response by Level of Factor		Logistic Model Type 3 Test P-values
		DCB (N=269[1]) Response Rate (95% CI)[2]	PTA (N=137[1]) Response Rate (95% CI)[2]	
	Yes	164 / 216 (75.9%) (69.7%, 81.5%)	75 / 107 (70.1%) (60.5%, 78.6%)	
Hypertension	No	15 / 21 (71.4%) (47.8%, 88.7%)	2 / 6 (33.3%) (4.3%, 77.7%)	Treatment: 0.061 Factor: 0.156 Interaction: 0.280
	Yes	186 / 248 (75.0%) (69.1%, 80.3%)	86 / 131 (65.6%) (56.9%, 73.7%)	
Diabetes	No	63 / 77 (81.8%) (71.4%, 89.7%)	29 / 39 (74.4%) (57.9%, 87.0%)	Treatment: 0.099 Factor: 0.036 Interaction: 0.870
	Yes	138 / 192 (71.9%) (64.9%, 78.1%)	59 / 98 (60.2%) (49.8%, 70.0%)	
Total Pathways	1	159 / 218 (72.9%) (66.5%, 78.7%)	68 / 106 (64.2%) (54.3%, 73.2%)	Treatment: 0.037 Factor: 0.348 Interaction: 0.405
	2	42 / 51 (82.4%) (69.1%, 91.6%)	20 / 31 (64.5%) (45.4%, 80.8%)	
Rutherford Category[4]	3	27 / 29 (93.1%) (77.2%, 99.2%)	12 / 12 (100.0%) (0.0%, 26.5%)	Treatment: 0.979 Factor: 0.003 Interaction: 0.781
	4	87 / 104 (83.7%) (75.1%, 90.2%)	32 / 45 (71.1%) (55.7%, 83.6%)	
	5	87 / 136 (64.0%) (55.3%, 72.0%)	44 / 80 (55.0%) (43.5%, 66.2%)	
Previous Intervention	No	51 / 69 (73.9%) (61.9%, 83.7%)	24 / 37 (64.9%) (47.5%, 79.8%)	Treatment: 0.091 Factor: 0.995 Interaction: 0.849
	Yes	150 / 200 (75.0%) (68.4%, 80.8%)	64 / 100 (64.0%) (53.8%, 73.4%)	
Baseline Target Limb Hemodynamics	Poor Flow[3]	88 / 125 (70.4%) (61.6%, 78.2%)	36 / 63 (57.1%) (44.0%, 69.5%)	Treatment: 0.043 Factor: 0.040 Interaction: 0.752
	Good Flow	113 / 144 (78.5%) (70.9%, 84.9%)	52 / 74 (70.3%) (58.5%, 80.3%)	
Baseline Stenosis (%)	32 - <= 78	56 / 66 (84.8%) (73.9%, 92.5%)	24 / 32 (75.0%) (56.6%, 88.5%)	Treatment: 0.082 Factor: <.001 Interaction: 0.971
	78 < - <= 92	61 / 71 (85.9%) (75.6%, 93.0%)	26 / 33 (78.8%) (61.1%, 91.0%)	
	92 < - <= 100	84 / 132 (63.6%) (54.8%, 71.8%)	38 / 72 (52.8%) (40.7%, 64.7%)	

Table 14-10. Covariate Analysis for Primary Effectiveness (By Pathway)

Factor	Level	Response by Level of Factor		Logistic Model Type 3 Test P-values
		DCB (N=269[1]) Response Rate (95% CI)[2]	PTA (N=137[1]) Response Rate (95% CI)[2]	
Final Residual Stenosis (%)	0 - <= 22	62 / 74 (83.8%) (73.4%, 91.3%)	27 / 33 (81.8%) (64.5%, 93.0%)	Treatment: 0.070 Factor: 0.008 Interaction: 0.328
	22 < - <= 30	56 / 78 (71.8%) (60.5%, 81.4%)	30 / 49 (61.2%) (46.2%, 74.8%)	
	30 < - <= 36	35 / 48 (72.9%) (58.2%, 84.7%)	21 / 29 (72.4%) (52.8%, 87.3%)	
	36 < - <= 100	48 / 69 (69.6%) (57.3%, 80.1%)	10 / 26 (38.5%) (20.2%, 59.4%)	
Final Residual Stenosis	<= 20%	53 / 64 (82.8%) (71.3%, 91.1%)	21 / 26 (80.8%) (60.6%, 93.4%)	Treatment: 0.327 Factor: 0.020 Interaction: 0.566
	> 20%	148 / 205 (72.2%) (65.5%, 78.2%)	67 / 111 (60.4%) (50.6%, 69.5%)	
Maximum Post Pre-Dilatation Residual Stenosis	1 - <= 35	42 / 56 (75.0%) (61.6%, 85.6%)	34 / 43 (79.1%) (64.0%, 90.0%)	Treatment: 0.027 Factor: 0.028 Interaction: 0.108
	35 < - <= 43	52 / 66 (78.8%) (67.0%, 87.9%)	17 / 25 (68.0%) (46.5%, 85.1%)	
	43 < - <= 53	47 / 63 (74.6%) (62.1%, 84.7%)	20 / 31 (64.5%) (45.4%, 80.8%)	
	53 < - <= 100	46 / 64 (71.9%) (59.2%, 82.4%)	9 / 27 (33.3%) (16.5%, 54.0%)	
Max Post Pre-Dilatation Residual Stenosis <= 50%	No	58 / 83 (69.9%) (58.8%, 79.5%)	11 / 32 (34.4%) (18.6%, 53.2%)	Treatment: 0.004 Factor: <.001 Interaction: 0.031
	Yes	129 / 166 (77.7%) (70.6%, 83.8%)	69 / 94 (73.4%) (63.3%, 82.0%)	
Max Post Pre-Dilatation Residual Stenosis <= 75%	No	5 / 7 (71.4%) (29.0%, 96.3%)	0 / 1 (0.0%) (0.0%, 97.5%)	Treatment: NA Factor: NA Interaction: NA
	Yes	182 / 242 (75.2%) (69.3%, 80.5%)	80 / 125 (64.0%) (54.9%, 72.4%)	
Any Dissection	No	114 / 154 (74.0%) (66.4%, 80.8%)	49 / 75 (65.3%) (53.5%, 76.0%)	Treatment: 0.042 Factor: 0.975 Interaction: 0.669
	Yes	87 / 115 (75.7%) (66.8%, 83.2%)	39 / 62 (62.9%) (49.7%, 74.8%)	
Any Grade D Dissection	No	197 / 264 (74.6%) (68.9%, 79.8%)	87 / 135 (64.4%) (55.8%, 72.5%)	Treatment: 0.334 Factor: 0.872 Interaction: 0.638

Table 14-10. Covariate Analysis for Primary Effectiveness (By Pathway)

Factor	Level	Response by Level of Factor		Logistic Model Type 3 Test P-values
		DCB (N=269[1]) Response Rate (95% CI)[2]	PTA (N=137[1]) Response Rate (95% CI)[2]	
	Yes	4 / 5 (80.0%) (28.4%, 99.5%)	1 / 2 (50.0%) (1.3%, 98.7%)	
Max. Dissection Grade[4]	A	56 / 76 (73.7%) (62.3%, 83.1%)	24 / 41 (58.5%) (42.1%, 73.7%)	Treatment: 0.491 Factor: 0.749 Interaction: 0.949
	B	20 / 25 (80.0%) (59.3%, 93.2%)	10 / 14 (71.4%) (41.9%, 91.6%)	
	C	7 / 9 (77.8%) (40.0%, 97.2%)	4 / 5 (80.0%) (28.4%, 99.5%)	
	D	2 / 3 (66.7%) (9.4%, 99.2%)	1 / 2 (50.0%) (1.3%, 98.7%)	
	F	2 / 2 (100.0%) (0.0%, 84.2%)	0 / 0	
Any Outflow to the Foot (Core Lab)	No	1 / 1 (100.0%) (0.0%, 97.5%)	1 / 1 (100.0%) (0.0%, 97.5%)	Treatment: NA Factor: NA Interaction: NA
	Yes	194 / 261 (74.3%) (68.6%, 79.5%)	84 / 132 (63.6%) (54.8%, 71.8%)	
Lesion Location	Tibioperoneal Trunk Alone	24 / 24 (100.0%) (0.0%, 14.2%)	14 / 16 (87.5%) (61.7%, 98.4%)	Treatment: NA Factor: NA Interaction: NA
	Anterior Tibial Alone	72 / 98 (73.5%) (63.6%, 81.9%)	28 / 42 (66.7%) (50.5%, 80.4%)	
	Posterior Tibial Alone	25 / 45 (55.6%) (40.0%, 70.4%)	13 / 27 (48.1%) (28.7%, 68.1%)	
	Peroneal Alone	26 / 35 (74.3%) (56.7%, 87.5%)	9 / 16 (56.3%) (29.9%, 80.2%)	
	T. Trunk and Ant. or Post. Tibial	10 / 14 (71.4%) (41.9%, 91.6%)	7 / 11 (63.6%) (30.8%, 89.1%)	
	T. Trunk and Peroneal	19 / 26 (73.1%) (52.2%, 88.4%)	9 / 11 (81.8%) (48.2%, 97.7%)	
	Popliteal Alone or with Other Location	24 / 26 (92.3%) (74.9%, 99.1%)	8 / 13 (61.5%) (31.6%, 86.1%)	

Table 14-10. Covariate Analysis for Primary Effectiveness (By Pathway)

Factor	Level	Response by Level of Factor		Logistic Model Type 3 Test P-values
		DCB (N=269[1]) Response Rate (95% CI)[2]	PTA (N=137[1]) Response Rate (95% CI)[2]	
Site Location	Europe	53 / 78 (67.9%) (56.4%, 78.1%)	24 / 35 (68.6%) (50.7%, 83.1%)	Treatment: 0.048 Factor: 0.908 Interaction: 0.263
	Japan	22 / 27 (81.5%) (61.9%, 93.7%)	8 / 15 (53.3%) (26.6%, 78.7%)	
	US	126 / 164 (76.8%) (69.6%, 83.1%)	56 / 87 (64.4%) (53.4%, 74.4%)	
Protocol Version	Version 1-7	125 / 174 (71.8%) (64.5%, 78.4%)	47 / 82 (57.3%) (45.9%, 68.2%)	Treatment: 0.072 Factor: 0.018 Interaction: 0.521
	Version 8-12	76 / 95 (80.0%) (70.5%, 87.5%)	41 / 55 (74.5%) (61.0%, 85.3%)	
Any Calcification	No	84 / 108 (77.8%) (68.8%, 85.2%)	30 / 46 (65.2%) (49.8%, 78.6%)	Treatment: 0.048 Factor: 0.481 Interaction: 0.672
	Yes	117 / 161 (72.7%) (65.1%, 79.4%)	58 / 91 (63.7%) (53.0%, 73.6%)	
Any Severe Calcification	No	179 / 232 (77.2%) (71.2%, 82.4%)	79 / 112 (70.5%) (61.2%, 78.8%)	Treatment: 0.043 Factor: <.001 Interaction: 0.313
	Yes	22 / 37 (59.5%) (42.1%, 75.2%)	9 / 25 (36.0%) (18.0%, 57.5%)	
TASC Score	A	113 / 129 (87.6%) (80.6%, 92.7%)	56 / 73 (76.7%) (65.4%, 85.8%)	Treatment: 0.016 Factor: <.001 Interaction: 0.666
	B	31 / 48 (64.6%) (49.5%, 77.8%)	14 / 23 (60.9%) (38.5%, 80.3%)	
	C	34 / 58 (58.6%) (44.9%, 71.4%)	10 / 23 (43.5%) (23.2%, 65.5%)	
	D	23 / 34 (67.6%) (49.5%, 82.6%)	6 / 16 (37.5%) (15.2%, 64.6%)	
Total Lesion Length by 50mm Intervals	<=50 mm	74 / 81 (91.4%) (83.0%, 96.5%)	31 / 41 (75.6%) (59.7%, 87.6%)	Treatment: 0.012 Factor: <.001 Interaction: 0.330
	>50 - <= 100 mm	48 / 59 (81.4%) (69.1%, 90.3%)	27 / 36 (75.0%) (57.8%, 87.9%)	
	>100 - <= 150 mm	21 / 36 (58.3%) (40.8%, 74.5%)	7 / 14 (50.0%) (23.0%, 77.0%)	
	>150 - <= 200 mm	15 / 27 (55.6%) (35.3%, 74.5%)	9 / 14 (64.3%) (35.1%, 87.2%)	

Table 14-10. Covariate Analysis for Primary Effectiveness (By Pathway)

Factor	Level	Response by Level of Factor		Logistic Model Type 3 Test P-values
		DCB (N=269[1]) Response Rate (95% CI)[2]	PTA (N=137[1]) Response Rate (95% CI)[2]	
	>200 - <= 250 mm	16 / 28 (57.1%) (37.2%, 75.5%)	1 / 8 (12.5%) (0.3%, 52.7%)	
	>250 mm	26 / 37 (70.3%) (53.0%, 84.1%)	8 / 19 (42.1%) (20.3%, 66.5%)	
RVD (mm)	0.0 - <= 2.1	46 / 67 (68.7%) (56.2%, 79.4%)	14 / 30 (46.7%) (28.3%, 65.7%)	Treatment: 0.013 Factor: 0.004 Interaction: 0.232
	2.1 < - <= 2.4	44 / 70 (62.9%) (50.5%, 74.1%)	15 / 24 (62.5%) (40.6%, 81.2%)	
	2.4 < - <= 2.9	47 / 63 (74.6%) (62.1%, 84.7%)	29 / 42 (69.0%) (52.9%, 82.4%)	
	2.9 < - <= 5.3	63 / 68 (92.6%) (83.7%, 97.6%)	30 / 41 (73.2%) (57.1%, 85.8%)	
Average Patient Transit Time (sec)	2 - <= 20	49 / 68 (72.1%) (59.9%, 82.3%)		Factor: 0.614
	20 < - <= 35	47 / 66 (71.2%) (58.7%, 81.7%)		
	35 < - <= 60	56 / 70 (80.0%) (68.7%, 88.6%)		
	60 < - <= 219	49 / 63 (77.8%) (65.5%, 87.3%)		

1 N represents the number of pathways with an outcome in the 6-month primary analysis.

2 Exact 95% CI based on exact binomial distribution.

3 Poor flow indicates ankle pressure <= 70 mm Hg or toe pressure or TCPO2 <= 50 mm Hg.

4 Patient as a random effect not included in the model.

5 95% CI for difference based on observed data without adjustment for random effects.

6 Two-sided p-value for paired difference obtained from logistic model.

7 Two-sided p-value for paired difference obtained from normal approximation without adjustment for random effects.

14.7 Missingness Analysis for Covariates at Each Timepoint (By Pathway)

The following table summarizes missing and non-missing values for the primary effectiveness endpoint at the 30-day, 6, 12, 24, and 36-month timepoints. Each row lists the value of the particular risk factor at each timepoint, with the missing values in red font and the non-missing data in green font.

Table 14-11. Baseline Covariates for Missing and Non-Missing Effectiveness Endpoints at Each Follow-Up Timepoint

Risk Factor	Arm	Baseline	Missing / Non-Missing Balance of Effectiveness Datapoints over Follow-Up				
			30 Days	6 Months	12 Months	24 Months	36 Months
Age (Years)	DCB	72.9	72.2 / 73.0	75.4 / 72.4	76.3 / 72.0	75.2 / 72.0	75.1 / 71.7
	PTA	73.3	75.3 / 73.0	75.9 / 72.5	76.0 / 72.3	75.9 / 72.1	75.1 / 71.9
Female Sex	DCB	29%	17% / 30%	30% / 29%	32% / 28%	24% / 31%	24% / 32%
	PTA	34%	50% / 31%	45% / 31%	46% / 30%	41% / 31%	40% / 29%
Smoking (Ever)	DCB	60%	59% / 61%	44% / 64%	42% / 66%	53% / 64%	54% / 64%
	PTA	58%	43% / 61%	53% / 60%	52% / 61%	52% / 61%	58% / 58%
Diabetes Mellitus	DCB	71%	72% / 71%	70% / 71%	64% / 73%	63% / 75%	62% / 76%
	PTA	68%	68% / 69%	60% / 72%	62% / 71%	59% / 73%	58% / 77%
Coronary Disease	DCB	46%	31% / 48%	50% / 46%	47% / 46%	47% / 46%	48% / 46%
	PTA	54%	46% / 55%	53% / 54%	50% / 55%	52% / 54%	58% / 50%
Renal Failure	DCB	24%	28% / 24%	35% / 22%	38% / 20%	29% / 22%	28% / 22%
	PTA	17%	25% / 15%	23% / 15%	27% / 13%	25% / 13%	23% / 12%
Malignancy	DCB	17%	31% / 16%	28% / 15%	26% / 15%	23% / 15%	25% / 13%
	PTA	17%	29% / 15%	13% / 18%	17% / 17%	18% / 16%	19% / 15%
Dyslipidemia	DCB	79%	69% / 80%	72% / 80%	76% / 80%	77% / 80%	80% / 79%
	PTA	75%	46% / 80%	66% / 78%	63% / 80%	67% / 79%	76% / 74%
TASC B, C, D*	DCB	52%	59% / 51%	52% / 52%	54% / 51%	48% / 54%	46% / 55%
	PTA	43%	43% / 46%	40% / 47%	40% / 47%	36% / 50%	37% / 52%
Rutherford 5†	DCB	55%	90% / 52%	80% / 51%	72% / 51%	63% / 52%	56% / 55%
	PTA	57%	68% / 55%	51% / 58%	52% / 58%	48% / 61%	46% / 65%
CTO	DCB	42%	52% / 41%	41% / 42%	42% / 42%	38% / 43%	37% / 44%
	PTA	42%	39% / 43%	32% / 46%	35% / 45%	32% / 48%	33% / 50%
Lesion Calcium	DCB	63%	55% / 62%	69% / 60%	64% / 61%	63% / 61%	59% / 62%
	PTA	58%	38% / 61%	32% / 66%	37% / 66%	43% / 65%	49% / 65%
Lesion Length (mm)	DCB	122	137 / 121	117 / 123	121 / 122	117 / 124	115 / 126
	PTA	112	107 / 112	96 / 117	106 / 114	101 / 116	100 / 120
RVD (mm)	DCB	2.5	2.2 / 2.5	2.4 / 2.5	2.4 / 2.5	2.5 / 2.5	2.5 / 2.5
	PTA	2.6	2.4 / 2.6	2.4 / 2.7	2.5 / 2.7	2.6 / 2.6	2.6 / 2.6

Table 14-11. Baseline Covariates for Missing and Non-Missing Effectiveness Endpoints at Each Follow-Up Timepoint

Risk Factor	Arm	Baseline	Missing / Non-Missing Balance of Effectiveness Datapoints over Follow-Up				
			30 Days	6 Months	12 Months	24 Months	36 Months
**TASC B, C, D vs. TASC A*							
†Rutherford 5 vs. Rutherford Category 3, 4							
CTO- Chronic total occlusion. RVD- Reference vessel diameter							

14.8 Supportive Data from Real-World Experience and Published Literature

A discussion of the information and data which supports device effectiveness and the quality-of-life benefits associated with the LUTONIX DCB in the treatment of native popliteal, tibial, and peroneal arteries is provided below. These studies represent clinical results from over 650 infrapopliteal patients treated with the LUTONIX DCB and were conducted, or else evaluated, to address feedback from the Agency regarding the need for additional data.

14.8.1 Real-World Data from the Society of Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry

14.8.1.1 VQI Introduction

The SVS VQI registry contains data collected from real-world use from vascular procedures intended to treat peripheral artery occlusive disease in the US and Canada. Each registry record includes information from the patient's initial hospitalization and at 1-year follow-up.

14.8.1.2 Analysis Design

To present real-world data on the off-label use of the commercially available LUTONIX 035 DCB in treating infrapopliteal arteries, BD collaborated with SVS VQI to generate a data analysis protocol, which was approved by FDA. A synopsis of the analysis design is given in **Table 14-12**.

Table 14-12. VQI Registry Analysis Design

Title	An Analysis of VQI Peripheral Vascular Intervention (PVI) Registry Primary Effectiveness Results for the use of the LUTONIX 035 DCB in BTK Real-World Patients
Analysis Population	Peripheral vascular intervention patients from the VQI registry database with at least one BTK artery treated. Patients were independently and consecutively selected from the registry by VQI between January 2016 – May 2019.

Analysis Purpose	To evaluate the safety and effectiveness of the LUTONIX 035 DCB in treating BTK lesions as compared to the PTA from the VQI Registry.
Analysis Design	Prospectively designed retrospective analysis.
Sample Size	Patients: The original sample size was calculated to be 200 LUTONIX 035 DCB patients and 200 PTA patients, for a total of 400 patients from the VQI PVI Registry database. The actual analysis included fewer DCB (167) and some additional PTA (397) patients based on the patients with complete, relevant data available. Flow Pathways: Not specified.
Sample Size Calculation	A total of 200 LUTONIX 035 DCB cases and 200 PTA cases would provide at least 80% power, for a difference of 11% in the TLR free rate at 6 months based on a binary outcome comparison (chi-square test). This assessment was based on the assumption that follow-up for the endpoint was at least 90% at 6 months (sample size of 180 per group), DCB patients had at least a 90% response rate (consistent with the BTK IDE Trial), and PTA patients had a response rate of 79%.
Clinical Sites	200 total clinical sites (and 750 treating physicians) across the US and Canada.
Inclusion Criteria	• At least one below the knee (BTK) artery treated (anterior tibial, posterior tibial, peroneal or tibial-peroneal trunk) during the procedure • Procedure date from January 2016 through May 2019 • At least one long-term follow-up visit • Key variables (pre-treatment symptoms and primary outcomes) available • Balloon diameter in control PTA cases = 4.0 mm to match LUTONIX balloon diameter
Exclusion Criteria	• Treatment of dorsal pedal or plantar arteries during same procedure • Bilateral treatment of BTK arteries during the same procedure • BTK artery treated with atherectomy or primary stenting in addition to LUTONIX or PTA
Primary Endpoints	The primary performance measure for this analysis was freedom from clinically driven target lesion revascularization (CD-TLR) evaluated at 6 months.
Secondary Endpoints	• Primary Patency Survival • Overall Survival (Freedom from All-Cause Mortality) • Freedom from Amputation • Freedom from Major Amputation • Rutherford Class
Propensity Scoring Methodology	Analyses were based on the use of propensity scores to adjust for imbalances in the patient baseline disease status and comorbidities. The propensity scores were obtained as a first step, separate from the analysis of the outcome data. An independent statistician who did not receive the outcome data was provided with the baseline variables and treatment groups. This independent statistician was not involved in the analysis of the outcome data.

	Propensity scores were generated based on the time of interest in the analysis; scores were calculated based on the limbs available for analysis at a given time point. The propensity scores were used to stratify the population into eight strata for a propensity adjusted comparison. The strata were selected to provide similar propensity scores and similar distributions of modeling factors across the two treatment groups. The inverse probability weight (IPW) was created based on the inverse of the probability weighting. Because the unequal distribution of patients within several of the propensity score strata made it difficult to interpret the differences between treatment groups, the IPW event-free survival estimate was reported.

14.8.1.3 Demographics and Baseline Medical

The demographic characteristics were overall well-matched between the LUTONIX DCB and the PTA control groups. The average age of the 564 patients was 70.8 ± 11.6 years in the DCB group and 70.2 ± 11.2 years in the PTA group. Approximately 70% of patients were male in both groups (70.7% in LUTONIX DCB and 69.5% in PTA). The average BMI was similar between groups with 28.1 ± 6.27 kg/m^2 in the LUTONIX DCB group and 28.7 ± 6.12 kg/m^2 in the PTA group. The majority of patients in both groups were White (82.6% in LUTONIX DCB and 75.3% in PTA), with African American or Black being the next largest group (9.6% and 18.1% in LUTONIX DCB and PTA groups, respectively).

The expected co-morbidities for this patient population were observed, with over half (63.5% in LUTONIX DCB and 67.8% in control) of the patients being diabetic in both groups and a large majority presenting with hypertension in both groups (88.0% in LUTONIX DCB and 91.2% in control). The percentage of current or former smokers was comparable in both groups (68.3% LUTONIX DCB and 65.0% Control). There were differences in Rutherford grade distributions between the groups, where the PTA control had more Rutherford 1 patients (10.1% vs. 2.4% in the LUTONIX DCB) and LUTONIX DCB had more Rutherford 6 patients (24.0% vs. 13.4% in the control).

Although the baseline lesion characteristics of the groups were matched, the LUTONIX DCB group appeared to have more complicated lesions (as expected in real world usage). The average total target lesion length in the LUTONIX DCB group was 16.7 cm ± 17.6 cm, slightly longer than the control group (13.0 cm ± 13.3 cm). The difference in prior treatment of the lesion (restenotic lesions) was nearly triple in the LUTONIX DCB group (27.5%) compared to the control group (9.8%). In the LUTONIX DCB group, 71.9% of patients were reported as having baseline target lesion calcification vs. 47.4% in the Control group. TASC lesion types were distributed fairly evenly across the two groups; however, the LUTONIX DCB group had more TASC D lesions compared to the control group (40.4% vs 30.0%, respectively).

14.8.1.4 Effectiveness

The 6-month freedom from Target Lesion Revascularization (TLR) by Kaplan-Meier estimates was 96.1% for LUTONIX DCB and 95.2% for the PTA control group (p=0.332). The difference in the 6-month rate of freedom from TLR was 0.9% (95% CI: -3.1%, 4.8%). At 12 months the freedom from TLR was 91.8% in the LUTONIX DCB and 88.6% in the control group, with a difference of 3.3% (95% CI: -2.9%, 9.5%). The 6-month primary patency rate was 93.4% for the LUTONIX DCB group and 92.0% for the PTA control group for a difference of 1.4% (95% CI: -3.7%, 6.4%). This separation in primary patency between the two groups was present at 12 months (87.2% for LUTONIX DCB and 84.7% for control) for a difference of 2.5% (95% CI: -4.8%, 9.7%). The hazard ratios for TLR and primary patency failure both slightly favored LUTONIX DCB, with the hazard ratios of 0.703 (95% CI: 0.367, 1.345) and 0.760 (95% CI: 0.451, 1.281) respectively.

14.8.1.5 Safety

There was no meaningful difference in the overall survival rate at any time point, with the survival rate at 12 months of 86.7% in the LUTONIX DCB group and 87.5% in the control group for a difference of -0.8% (95% CI: -7.6%, 6.0%). Freedom from major amputation was slightly higher in the LUTONIX DCB group at all timepoints with a rate of 98.1% compared to 97.0% at 12 months for a difference of 1.1% (95% CI: -1.9%, 4.2%).

14.8.1.6 Summary

The LUTONIX DCB patients demonstrated a trend for improvement in both TLR and primary patency rates through 12 months. This trend was consistent across time through 12 months with hazard ratios of 0.703 (95% CI: 0.367, 1.345) and 0.760 (95% CI: 0.451, 1.281) for TLR-free and primary patency survival. Although these failed to reach statistical significance, the lack of a significant or a more pronounced treatment effect may also relate to the severity of comorbidities in this critical limb ischemia (CLI) population as evidenced by the high mortality rate in both groups and the more limited patient selection based on a balloon size of 4.0 mm.

In summary, these results in real-world below the knee patients show equivalent safety with trends toward additional clinical benefits of higher freedom from TLR and primary patency compared to standard PTA. This data further supports published data with the LUTONIX DCB in BTK arteries and demonstrates the real-world importance of the LUTONIX DCB in the underserved CLI patient population.

14.8.2 Real-World Data from the LUTONIX Global BTK Registry

14.8.2.1 Global BTK Registry Summary

The LUTONIX Global BTK Registry is a multicenter, single arm real-world registry designed to evaluate the safety and assess the clinical use outcomes of the commercially available LUTONIX 014 DCB in the European Union (EU) for treatment of BTK arteries in a heterogeneous patient population in real-world clinical practice. A total of 371 patients were enrolled at 26 sites across 11 countries. Overall, 86.5% the patients had evaluable data for the primary effectiveness endpoint at 6 months and 97.0% had evaluable data for the primary safety endpoint at 30 days. The 12-month visit was completed by 76.3% of all patients. Follow-up through 24 months is still ongoing for 8.6% of the patients.

The primary effectiveness endpoint, freedom from Target Lesion Reintervention (TLR) at 6 months, showed a rate of 90.0% by patient counts and 92.8% by Kaplan-Meier estimates. The secondary endpoint freedom from TLR at 12 and 24 months was 79.9% and 74.2%, respectively, by patient counts, and 82.3% and 78.9%, respectively, by Kaplan-Meier estimates.

Consistent with all other evaluations of the LUTONIX DCB, there are no reported safety concerns with freedom at 30 days from the composite of all-cause death, above-ankle amputation or major reintervention, of the index limb involving a below-the-knee artery was 98.3% by patient counts and 98.3% by Kaplan Meier estimates. Therefore, the Global Registry supports effectiveness for the commercially available product in the EU while also supporting safety.

14.8.2.2 Propensity Adjusted Data: LUTONIX BTK IDE and LUTONIX Global BTK Registry

The LUTONIX DCB data from the BTK IDE Trial and the Global BTK Registry were pooled and propensity adjusted to compare to the PTA data from the BTK IDE Trial. The objective of this comparative analysis was to provide additional supportive information on the 6-, 12-, and 24-month performance of the LUTONIX DCB. A synopsis of the analysis design is given in **Table 14-13.**

Table 14-13. Propensity Adjusted Global BTK Registry Analysis Design

Title	Propensity Adjusted Pooled Registry DCB with the IDE PTA Arm
Analysis Population	Patients were from the LUTONIX Global BTK Registry database and the LUTONIX BTK IDE Trial. Patients treated with the DCB across the registry and trial were pooled and propensity adjusted to compare to the PTA patients from the trial.
Analysis Purpose	To provide additional supportive information on the 6-, 12-, and 24-month performance of the LUTONIX DCB.
Analysis Design	Prospectively designed retrospective analysis.

Sample Size	Patients: 658 DCB and 155 PTA Flow Pathways: 727 DCB and 184 PTA
Geographies	US, Canada, Japan, Europe, Saudi Arabia
Primary Endpoints	The primary performance measure for this analysis was freedom from CD-TLR evaluated at 6 months.
Secondary Endpoints	Primary Patency Survival Overall Survival (Freedom from All-Cause Mortality) Freedom from Amputation Freedom from Major Amputation Rutherford Class
Propensity Scoring Methodology	Analyses were based on the use of propensity scores to adjust for imbalances in the patient baseline disease status and comorbidities. The propensity scores were obtained as a first step, separate from the analysis of the outcome data. An independent statistician who did not receive the outcome data was provided with the baseline variables and treatment groups. This independent statistician was not involved in the analysis of the outcome data. Propensity scores were generated based on the time of interest in the analysis; scores were calculated based on the limbs available for analysis at a given time point. The propensity scores were used to stratify the population into eight strata for a propensity adjusted comparison. The strata were selected to provide similar propensity scores and similar distributions of modeling factors across the two treatment groups. The inverse probability weight (IPW) was created based on the inverse of the probability weighting. Because the unequal distribution of patients within several of the propensity score strata made it difficult to interpret the differences between treatment groups, the IPW event-free survival estimate was reported.

14.8.2.3 Demographics and Baseline Comorbidities

A total of 911 treated flow pathways were analyzed. Notably, while the propensity adjusted DCB patients from the Global BTK registry tended to be healthier (lower BMI, hypertension, less prevalence of diabetes and smoking), their lesions were similar to the DCB IDE patients, in having longer lesions (mean 100.00 mm), smaller RVD (mean 2.5), and high percentage of calcification (66.8%). Baseline angiographic assessments are presented in **Table 14-14**.

Table 14-14. Baseline Angiography Assessment Pathway, ITT

Summary	DCB Registry (N==404)	DCB IDE (N=323)	PTA (N=184)
Maximum RVD (mm)			
N	402	323	181
Mean (SD)	2.9 (2.00)	2.8 (0.60)	2.9 (0.63)
Median	2.5	2.7	2.8
Min, Max	1.7, 35.0	1.6, 4.9	1.5, 6.3
Any calcification, n/N (%)	258/386 (66.8%)	195/323 (60.4%)	102/181 (56.4%)
Severe calcification, n/N (%)	80/386 (20.7%)	51/323 (15.8%)	26/181 (14.4%)
TASC lesion type, n/N (%)			
N	402	323	181
1	106 (26.4%)	159 (49.2%)	105 (58.0%)
2	100 (24.9%)	57 (17.6%)	30 (16.6%)
3	67 (16.7%)	61 (18.9%)	26 (14.4%)
4	53 (13.2%)	45 (13.9%)	17 (9.4%)
5	76 (18.9%)	1 (0.3%)	3 (1.7%)

All analyses based on logistic model using IPW scores obtained at baseline.

**One-sided null hypothesis that the DCB rate is less than or equal to the PTA rate.*

14.8.2.4 Effectiveness

An analysis of the primary effectiveness endpoint, or freedom from failure based on inverse probability weighting (IPW), at 6-months reached statistical significance (DCB 76.4% and PTA 60.6%, p<0.001), as shown in **Table 14-15**.

Table 14-15. Primary Effectiveness Success as Binary Endpoint by Time Point with Overall IPW, Registry DCB vs IDE PTA

Time Point	LS Means Estimates		Evaluation of Treatment Difference	
	DCB (95% CI)	PTA (95% CI)	Odds Ratio (95% CI)	P-value*
30 Days	92.0% (88.4%, 94.6%)	90.1% (84.0%, 94.0%)	1.27 (0.64, 2.52)	0.247
6 Months	76.4% (71.2%, 80.8%)	60.6% (52.1%, 68.4%)	2.11 (1.36, 3.25)	<0.001
12 Months	64.9% (59.0%, 70.3%)	54.5% (45.9%, 62.9%)	1.54 (1.01, 2.36)	0.024
24 Months	35.5% (28.4%, 43.4%)	41.6% (33.3%, 50.5%)	0.77 (0.47, 1.26)	0.852

All analyses based on logistic model using IPW scores obtained at baseline.

**One-sided null hypothesis that the DCB rate is less than or equal to the PTA rate.*

Freedom from CD-TLR also demonstrated continuous improvement of the combined DCB cohort compared to the IDE PTA cohort with DCB vs. PTA rates of 93.3% vs. 82.0% (6 months), 81.1% vs. 74.2% (12 months) and 75.0% vs. 67.2% (24 months), as shown in and **Figure 14-2** and **Table 14-16**.

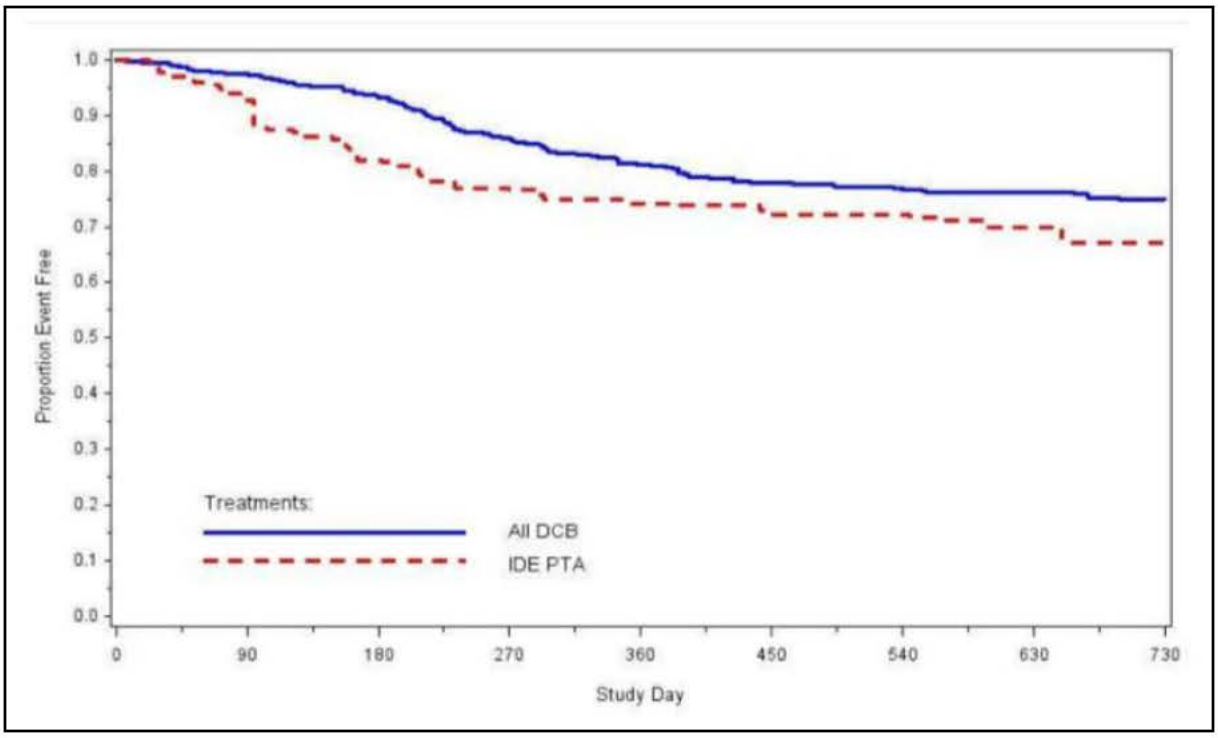

Figure 14-2. Freedom from Clinically Driven TLR Based on IPW, All DCB vs IDE PTA

Table 14-16. Freedom from Clinically Driven TLR based on IPW, All DCB vs IDE PTA

Time Point (Days)	Pathway-Level Freedom from Clinically Driven TLR				
	IPW DCB Success (%)	IPW PTA Success (%)	Difference (95% CI)	Difference P-value*	Log-Rank P-value†
0	100.0% (100.0%, 100.0%)	100.0% (100.0%, 100.0%)	NA	NA	NA
180	93.3% (91.0%, 95.0%)	82.0% (73.1%, 88.2%)	11.3% (3.6%, 19.0%)	0.002	<0.001
365	81.1% (77.7%, 84.0%)	74.2% (64.5%, 81.6%)	6.9% (-2.1%, 15.9%)	0.067	0.034
730	75.0% (71.2%, 78.4%)	67.2% (57.0%, 75.6%)	7.8% (-2.2%, 17.8%)	0.063	0.041

** One-sided null hypothesis that the success rate in DCB is less than or equal to the PTA rate.*

† IPW log-rank test with patients censored at the specified time point.

Primary patency also demonstrated an advantage for the DCB cohort compared to the IDE PTA cohort with DCB vs. PTA rates of 87.7% vs. 68.6% (6 months), 65.2% vs. 57.2% (12 months) and 53.1% vs. 46.0% (24 months), as shown in **Figure 14-3** and **Table 14-17**.

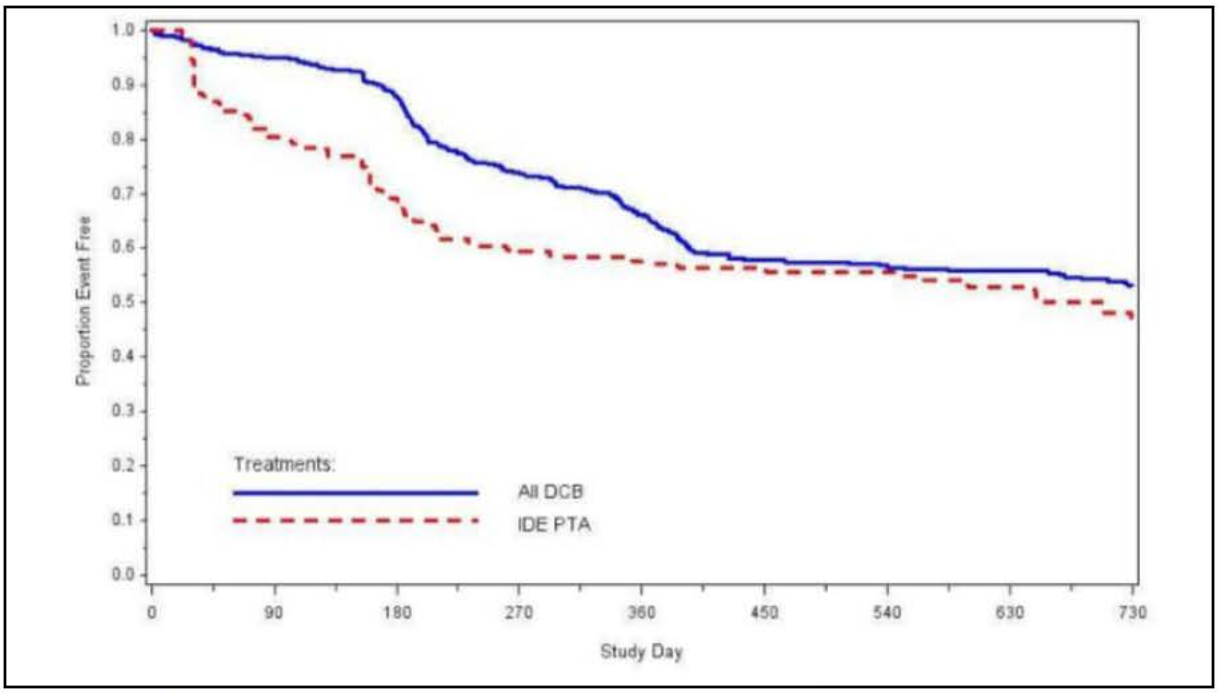

Figure 14-3. Primary Patency Based on IPW, All DCB vs IDE PTA

Table 14-17. Primary Patency Based on IPW, All DCB vs IDE PTA

Time Point (Days)	Pathway-Level Freedom from Clinically Driven TLR				
	IPW DCB Success (%)	IPW PTA Success (%)	Difference (95% CI)	Difference P-value*	Log-Rank P-value†
0	100.0% (100.0%, 100.0%)	100.0% (100.0%, 100.0%)	NA	NA	NA
180	87.7% (84.7%, 90.2%)	68.6% (58.9%, 76.4%)	19.1% (9.9%, 28.3%)	<0.001	<0.001
365	65.2% (60.9%, 69.2%)	57.2% (47.2%, 65.9%)	8.1% (-2.2%, 18.3%)	0.062	0.008
730	53.1% (48.1%, 57.9%)	46.0% (36.0%, 55.4%)	7.1% (-3.8%, 18.1%)	0.101	0.024

** One-sided null hypothesis that the success rate in DCB is less than or equal to the PTA rate.*

† IPW log-rank test with patients censored at the specified time point.

14.8.2.5 Safety

An analysis of the primary safety endpoint through two years also confirms no safety issues were uncovered when combining the data sets; freedom from a primary safety event at 24 months was 92.6% (DCB) and 88.1% (PTA), as shown in **Figure 14-4** and **Table 14-17**.

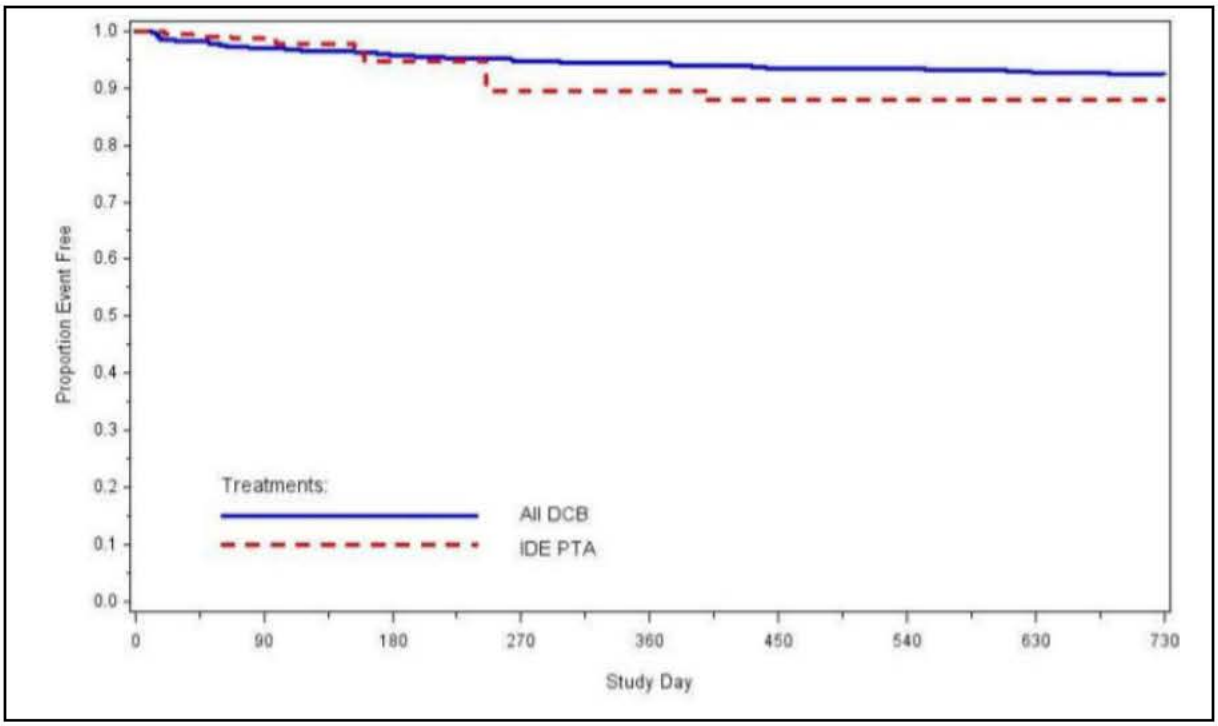

Figure 14-4. Freedom from Primary Safety Endpoint Failure Based on IPW - All DCB vs IDE PTA

Table 14-18. Primary Patency Based on IPW, All DCB vs IDE PTA

Time Point (Days)	Pathway-Level Freedom from Clinically Driven TLR				
	IPW DCB Success (%)	IPW PTA Success (%)	Difference (95% CI)	Difference P-value*	Log-Rank P-value†
0	100.0% (100.0%, 100.0%)	100.0% (100.0%, 100.0%)	NA	NA	NA
30	98.7% (97.4%, 99.3%)	99.7% (87.2%, 100.0%)	-1.0% (-2.5%, 0.5%)	<0.001	0.406
180	96.1% (94.2%, 97.4%)	95.0% (87.1%, 98.1%)	1.1% (-4.0%, 6.1%)	<0.001	0.691
365	94.6% (92.4%, 96.2%)	89.1% (79.4%, 94.4%)	5.5% (-1.8%, 12.9%)	<0.001	0.066
730	92.6% (90.0%, 94.5%)	88.1% (78.3%, 93.6%)	4.5% (-3.2%, 12.2%)	<0.001	0.151

** One-sided null hypothesis that the success rate in DCB is less than or equal to the PTA rate.*

† IPW log-rank test with patients censored at the specified time point.

14.8.2.6 ***Summary***

In conclusion, the LUTONIX DCB demonstrated continuous efficacy benefit when adding more patients to the IDE cohort via propensity score adjustment with the Global BTK Registry data, including at 12 months.

14.8.3 Japanese Hemodialysis Randomized Control Trial (RCT) Data

14.8.3.1 Introduction

The Japanese hemodialysis (HD) RCT was designed to evaluate the effectiveness and safety of the LUTONIX 014 DCB in Japanese HD patients with BTK disease. The study enrolled a total of 36 patients (19 DCB and 17 PTA). The study inclusion/exclusion criteria were the same as the LUTONIX BTK IDE Trial, with the only exception being patients on hemodialysis were included in this Japanese study and they were excluded from the IDE trial. A synopsis of the analysis design is given in **Table 14-19**.

Table 14-19. Japanese HD Analysis Design

Title	Japanese Hemodialysis Randomized Control Trial (RCT)
Analysis Population	Japanese patients undergoing chronic hemodialysis for end stage renal disease presenting with CLI (Rutherford Category 4 or 5) and an angiographically significant (≥ 70%) native artery lesion appropriate for angioplasty that was below the knee and above the ankle.
Analysis Purpose	To evaluate the safety and effectiveness of the LUTONIX 014 DCB in the special sub-population of CLI in Japanese HD patients with BTK disease in order to compare the outcome of this domestic study to the Global BTK IDE Study.
Analysis Design	RCT: After successful protocol-defined pre-dilatation, patients who met lesion and outflow angiographic criteria were stratified by Rutherford Category and then randomized 1:1 to treatment with either the LUTONIX DCB (test) or standard uncoated PTA catheter (control). All target lesion(s) in up to two target vessels were treated with the as-randomized (by patient) test DCB or control PTA devices. After the protocol-defined pre-dilatation with a standard uncoated PTA catheter step was completed and if randomized to control, treatment with an additional standard uncoated PTA catheter (control device) was at the discretion of the Investigator as long as 0-30% residual stenosis was achieved. Patients with no target vessels that met post-predilatation entry criteria were excluded (and treated per standard practice) and followed for safety for 30 days.
Sample Size	Patients: 19 DCB and 17 PTA Flow Pathways: 23 DCB and 21 PTA
Sample Size Calculation	This study was not designed to obtain any confirmatory evidence with formal statistical hypothesis tests; rather, it was projected to randomize 36 patients. The

Table 14-19. Japanese HD Analysis Design

	sample size of 36 patients (1:1 test vs. control) was based on the potential adequacy of the data to meet the study objectives and not on statistical considerations.
Inclusion Criteria	Inclusion criteria were the same as the LUTONIX BTK IDE Trial, with the exception being patients on hemodialysis were included in this study and were excluded from the trial.
Exclusion Criteria	Exclusion criteria were the same as the LUTONIX BTK IDE Trial.
Primary Endpoints	The primary effectiveness endpoint was a composite of limb salvage, CD-TLR, and target lesion occlusion evaluated at 6 months by patient and flow pathway (as a binary endpoints). The primary safety endpoint was a composite of freedom from BTK MALE + POD (post-operative death) at 30 days. This was defined as freedom from the composite of all-cause death, above ankle amputation or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy /thrombolysis) of the index limb involving a BTK artery.
Secondary Endpoints	Device Success Technical Success Procedural Success EQ-5D Surveys Device related Adverse Events through 6 months Wound Healing at 30 Da, 3, 6, and 12 Month Rutherford Scale Composite of Freedom from Above-ankle Amputation, Unhealed wound, Ischemic Rest Pain, Target Vessel Occlusion and clinically driven TVR at 30 Day, 3, 6 and 12 Month Primary Patency at 30 Day, 3, 6 and 12 Month Primary Patency with Exclusion of Early Mechanical Recoil Secondary Patency at 30 Day, 3, 6, and 12 Month Hemodynamic Outcome at 30 Day, 3, 6 and 12 Month Walking Impairment Questionnaire at 30 Daye, 3, 6, and 12 Month TLR/TVR and Amputation Adverse Events Vital Signs Laboratory Testing Activities of Daily Living Score

14.8.3.2 Effectiveness and Safety

In the HD DCB group, 100% of patients were free from BTK MALE+POD compared to 94.1% of patients in the HD PTA group for a treatment difference of 5.9% (95% CI -13.5%, 29.5%).

There were no safety events in the BTK IDE Study Japanese patients and only one event in the Japan HD study in the PTA arm.

The first key effectiveness 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. At 12 months, the event-free rate for DCB was higher than PTA (47.1% vs. 35.3%). The second key effectiveness endpoint was limb salvage at 6 months; all Japan HD patients had limb salvage at that time point. At 12 months there was only 1 major amputation (in the PTA group), leading to a 7.1% treatment difference (95% CI -17.9%, 33.8%).

14.8.3.3 Summary

In summary, the results of the Japanese HD RCT confirmed the safety and effectiveness of the LUTONIX DCB for the treatment of BTK disease in hemodialysis patients, with a benefit of DCB over PTA for the composite of limb salvage and primary patency at 6 and 12 months.

14.8.4 Summary of Relevant Published Literature

In addition to the registry analyses and Japanese HD RCT discussed in the preceding sections, a search of the peer-reviewed literature using well established databases (e.g., PubMed, Embase) was conducted and produced three single-center, retrospective studies detailing the use of the LUTONIX 014 DCB in BTK arteries, summarized in **Table 14-20** and discussed below:

Table 14-20. Summary of Relevant Published Literature

Publication	Number of Patients/Devices	Patient Demographics	Follow-up	Safety	Freedom from TLR	Other
Micari et al. Ital J Vasc Endovasc. 2016;23:1-4.[45]	55 patients (retrospective), ~127 devices	Rutherford class > 3; 70% total occlusions	182 days median follow-up	96.4% freedom from amputation; no deaths reported	Not specified; 78.2% freedom from TVR at a median of 6 months	Ulcer size/depth reduction in 89.1% of patients
Steiner et al. J Endovasc Ther. 2016;23:417-423.[46]	208 patients (retrospective), 510 devices	61.4% CLI patients; 63.6% total occlusions	9-month median follow-up	93.4% freedom from death or major amputation at 6 months and 89.5% at 12 months	84.1% at a median of 9 months	Complete wound healing in 68/89 (76.4%); 59.1% improved by at least 1 Rutherford

Table 14-20. Summary of Relevant Published Literature

Publication	Number of Patients/Devices	Patient Demographics	Follow-up	Safety	Freedom from TLR	Other
						class by 12 months
Palena et al. Cardiovasc Revasc Med. 2018, 19:83-87.[47]	21 patients (retrospective), ~46 devices	95.2% Rutherford class 5-6; 100% diabetic	356.5 days mean follow-up	0% MALE; no major amputations; 100% limb salvage; 2 deaths	Not specified;83.8 % freedom from CD-TLR at 390 days	Ulcer size/depth reduction in 19/21 (90.4%); 87.5% demonstrated a 1 category shift in Rutherford class at 12 months

While there are limitations associated with these retrospective studies, they do provide additional safety and effectiveness information on over 680 LUTONIX DCBs used in 284 patients.

14.8.4.1 Micari et al., 2016

Micari et al. retrospectively reviewed the results of a cohort of 55 patients treated at a single center in Italy with the LUTONIX 0.014 DCB for obstructive BTK lesions and symptoms of CLI (Rutherford 4 to Rutherford 6).[45] Observational data on death, amputation, reintervention, and overall clinical outcomes were collected retrospectively. Median follow-up was 182 days, with 72% of patients having greater than 6-months follow-up. Twelve patients (21.8%) underwent TVR resulting in 78.2% freedom from TVR. There were two amputations (3.6%) in Rutherford 6 patients. Wound healing information was available in 54 of 55 patients (98.2%); the authors noted a "marked reduction' in the size and depth of wounds with an observed complete wound healing of 89.1% of patients. They concluded that in this respective review no safety issues were associated with patients treated with the LUTONIX DCB and that generally these patients had favorable clinical outcomes.

14.8.4.2 Steiner et al., 2016

Steiner and colleagues retrospectively reviewed a cohort of 208 patients from a single center in Germany treated with the LUTONIX 0.014 DCB for symptomatic BTK peripheral arterial disease (Rutherford $\geq$ 3).[46] In this cohort, 61.4% of patients had symptoms of CLI, 17.8% of patients had all BTK arteries occluded, and 63.3% of target lesions were total occlusions. The median

follow-up was 9 months with 89.4% of patients having ≥6-months of follow-up. There were no peri-procedural deaths, and 22 deaths (10.6%) were reported through the follow-up period. Mortality rate amongst CLI patients was 14.8% and 3.8% in claudicants. There were no device-related deaths. The TLR rate was 15.9% (17.8% for CLI patients and 12.9% for claudicants) and 9 major above-ankle amputations were performed (6 in Rutherford 5 patients and 3 in Rutherford 6 patients). Probability of freedom from major amputation was 97% at 6 months and 96% at 12 months. Of the 108 patients who presented with wounds, 89 (82.4%) had evaluable wound data at follow-up with complete wound healing reported in 68 (76.4%). Improvement in clinical symptoms, measured by improvement of at least one Rutherford Category, was observed in 59.1% of the treated limbs at 12 months; 80% of the same limbs showed improvement in more than two Rutherford categories. Deterioration of clinical symptoms was observed in 2.7% of limbs. The authors concluded that patients with BTK peripheral arterial disease treated with the LUTONIX 014 DCB demonstrated overall favorable clinical outcomes and an acceptable TLR rate of 15.9% at a median 9-month follow-up. In addition, combined major amputation and mortality estimates were 6.6% at 6 months and 10.5% at 12 months, which they felt compared favorably to rates reported in the literature.

14.8.4.3 Palena et al., 2018

Palena et al. reported retrospective, chart-review outcomes from their center in Italy. The cohort consisted of 21 diabetic patients with CLI who underwent TLR of previously treated infrapopliteal and inframalleolar artery obstructive lesions using the LUTONIX 0.014 DCB.[47] Acute technical and procedural success were 100%. The mean study follow-up was 356.5 ±159.2 days, with 90% of patients having reached 12-month follow-up. The estimated freedom from CD-TLR (Kaplan-Meier analysis) was 83.8% at 390 days. Complete wound healing or a reduction in ulcer size and depth was reported in 19 patients (90.4%) at 12 months. Of these, 18 (87.5%) experienced a shift in Rutherford class. All patients that presented with Rutherford 6 pre-procedure shifted to Rutherford 0 at follow-up. There were no major amputations, and two deaths were reported - one at 3 months and one at 11 months. Estimated rates of major adverse limb events, major adverse cardiovascular events, and major amputation were 0%, 10%, and 0% at the mean long-term follow up of approximately 12 months. Amputation-free survival was 90%, limb salvage was 100%, and overall survival was 90%. The authors concluded that, in their hands, the LUTONIX DCB was safe to use and produced good clinical outcomes in patients with significant comorbidities and difficult, long lesions in small infrapopliteal and pedal arteries.

14.9 Literature on Coronary Drug-Eluting Stents for BTK Arterial Disease

In the absence of alternate drug-eluting or drug-coated interventions, drug-eluting stents have been used to treat CLI patients with BTK disease. A summary of studies that included DES treatment of BTK lesions follows:

14.9.1 DESTINY Trial

The DESTINY (Drug-Eluting Stents in the Critically Ischemic Lower Leg) study randomized 140 de novo CLI patients (Rutherford-Becker class 4 and 5).[33] The study evaluated patients with infra-popliteal PAD comparing coronary BMS (Multi-LinkVision, Abbott) to coronary DES (Xience V, Abbott Laboratories, Abbott Park, IL, USA). The patients who enrolled had a mean total lesion length of 18mm, and 76% had severe calcification. Over 12 months of follow-up, DES had superior patency (DES 85% versus BMS 54%, P=0.0001) and freedom from TLR (DES 91% versus BMS 66%, P=0.001).

14.9.2 YUKON-BTX Trial

The YUKON-BTX (YUKON-Drug-Eluting Stent Below the Knee) Trial randomized 161 patients with severe claudication, and CLI to IP treatment with coronary BMS or DES (Sirolimus-eluting YUKON stent, Translumina).[35] The patients who enrolled had mean total lesion length of 30mm. Primary patency at 1 year for the DES cohort was 80.6% vs. BMS 55.6% (P=0.004). At three years of follow-up there was significant clinical benefit for the DES group for event-free survival (DES 65.8% versus 44.6% for BMS, P=0.02), reduced amputation (DES 2.6% versus BMS 12.2%, P=0.03) and TLR rates (DES 9.2% versus BMS 20% (P=0.06).

14.9.3 ACHILLES Trial

The ACHILLES (Comparing Angioplasty and DES in the Treatment of Patients With Ischemic Infrapopliteal Arterial Disease) Trial randomized 200 patients with infra-popliteal PAD to PTA or DES (Cypher Select Sirolimus Eluting Stent).[50] The patients who enrolled had a mean total lesion length of 27mm. Primary patency rates at 1 year were superior for the DES cohort (DES 75% versus PTA 57.1%, P=0.025). At 6 months, there was better wound healing with DES versus PTA (95% healing versus 60% healing, P=0.048), but at 1 year, the rates of complete wound healing with DES versus PTA (72.9% versus 55.6%; P=0.088, respectively) were not different. Quality of life survey scores improved significantly up to 1 year in the DES cohort (P<0.0001), but not in the PTA group. There was a trend to increased quality of adjusted life years gained with DES compared with PTA up to 1 year after randomization. For patients with total lesion lengths below 120 mm, the 1-year restenosis rate for DES over PTA were significantly lower (22.4% versus 41.9%, P=0.019), a difference that was even more pronounced among diabetics (DES: 17.6% versus PTA: 53.2%, P<0.001) who constitute most

patients with IP PAD. There was no difference between the PTA or DES cohorts for death, amputation rates, or improved functional status.

14.9.4 PADI Trial

The PADI (Percutaneous transluminal Angioplasty versus Drug eluting stents for Infrapopliteal lesions) trial randomized 137 patients with RU >4 to paclitaxel-eluting (TAXUS Liberte, Boston Scientific) vs bare metal stents.[51] The patients who enrolled had a mean total lesion length of 22.1mm. Six-month patency rates were 48.0% for DES and 35.1% for PTA±BMS (P=0.096). The ordinal score showed significantly worse treatment failure for PTA±BMS versus DES (P=0.041). The observed major amputation rate remained lower in the DES group until 2 years post-treatment, with a trend toward significance (P=0.066). Fewer minor amputations occurred after DES until 6 months post-treatment (P=0.03).

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