FDA Executive Summary

Prepared for the February 17, 2021 Meeting of the
Cardiovascular Devices Panel
Meeting to be held Virtually

Premarket Approval (PMA) (b) (4)
Lutonix, Inc. a Subsidiary of Becton, Dickinson and Company (BD)
Lutonix 014 Drug Coated Balloon PTA Catheter

Office of Cardiovascular Device
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
Food and Drug Administration

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1 Introduction

This is FDA's Executive Summary of the premarket approval (PMA) (b) (4) application from Lutonix, Inc., a wholly owned subsidiary of Becton, Dickinson and Company (hereafter referred to as Lutonix), for the Lutonix 014 Drug Coated Balloon PTA catheter (Lutonix 014 DCB) for the treatment of 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. This document includes a clinical review of below-the-knee (BTK) critical limb ischemia (CLI), a description of the Lutonix drug-device combination product, regulatory history associated with this product, and the clinical data provided in the PMA application and subsequent amendments.

2 Summary

The Lutonix 014 DCB, if approved under PMA (b) (4), would be the first device other than percutaneous transluminal angioplasty (PTA) and atherectomy to be indicated for the treatment of BTK CLI in the US.

A clinical study was initiated in 2013 in order to assess the safety and effectiveness of the Lutonix 014 DCB vs. PTA. The primary safety endpoint was freedom from BTK major adverse limb events (MALE) and perioperative death (POD) at 30 days. In the original protocol, the primary effectiveness endpoint was a composite of limb salvage (freedom from the composite of above ankle amputation) and primary patency (freedom from target lesion occlusion or clinically-driven target lesion revascularization (CD-TLR)) at 12 months. Subsequently, however, the sponsor changed the assessment of the primary effectiveness endpoint timepoint to 6 months. Secondary endpoints included wound healing, hemodynamic outcomes, and amputation.

The study was initially approved for 480 subjects and later increased to 1000 subjects due to revised event rate assumptions. Multiple interim analyses were incorporated into the statistical analysis plan, and, from the two interim analyses that were performed, stopping criteria were not met. Trial enrollment was difficult, and several modifications were implemented to help increase enrollment. However, about 5 years after study initiation, the sponsor elected to terminate the trial with approximately half of the required sample size.

For the primary effectiveness endpoint (the composite of limb salvage and primary patency at 6 months), the Lutonix 014 DCB arm had a rate of 74.7% vs. 64.2% in the control arm, corresponding to a 10.5% absolute difference ($p = 0.0222$). However, this event rate difference did not reach statistical significance, which required a p-value of ≤ 0.0085, due to numerous interim analyses and other protocol modifications. Further, at 12 months, the modest effectiveness benefit observed at 6 months for the Lutonix 014 DCB was no longer present, and the event rate numerically favored the PTA group at time point and beyond. The absence of effectiveness benefit at 12 months and beyond raises questions on the clinical value of the Lutonix 014 DCB. Selected secondary endpoints largely followed the same relationship, showing a slight benefit at 6 months and no benefit thereafter. No specific safety issues associated with the Lutonix 014 DCB were identified based on the available trial data.

The panel will be asked to review the totality of the data and provide recommendations regarding whether a reasonable assurance of safety and effectiveness has been demonstrated for the Lutonix 014 DCB and if the benefits outweigh the risks for this device.

3 Proposed Indications for Use

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

4 Clinical Background

Peripheral arterial disease (PAD) is the narrowing of lower extremity arteries by atherosclerotic plaque, resulting in inadequate blood flow to tissues and eventual progression of symptoms ranging from leg pain when walking (minor, moderate, and severe claudication, designated by Rutherford Categories 1-3) to rest pain and to signs of CLI, which include tissue loss, non-healing wounds, gangrene, and amputation [1]. Approximately 3% of people between the ages of 40-59 years suffer from PAD, which increases to 20% for those >70 years of age [2]. One third of these patients will progress to CLI, which is typically characterized by rest pain, minor or major tissue loss, (Rutherford Categories 4 and 5, respectively) or potential limb loss caused by severely compromised lack of blood flow (designated by Rutherford Category 6) [3]. Adequate blood flow is needed for rest pain relief and ulcer and gangrene treatment, which can help prevent the need for amputation.

While various endovascular treatments have been developed for above-the-knee femoropopliteal lesions, standard PTA is still most commonly used for BTK interventions, especially in the US. However, PTA for BTK lesions is associated with high restenosis rates due to neointimal growth [4]. Drug-coated balloons (DCB), which are comprised of a standard PTA balloon coated with an antiproliferative drug, may have the potential to provide a more durable treatment than use of non-drug coated PTA balloons.

If approved, the Lutonix 014 DCB would be the first device indicated for the treatment of BTK CLI in the US, beyond PTA and atherectomy, which are available to treat patients with CLI based on their indications for use.

5 Product Description

The Lutonix 014 DCB is an over-the-wire PTA catheter with Lutonix drug coating on the balloon surface (Figure 1). As an angioplasty catheter, the primary mode of action for the Lutonix 014 DCB is achieved through the mechanical dilatation of the vessel during the balloon inflation. Drug delivery during the dilatation is designed to provide an additional benefit of preventing restenosis. The device is available in diameters of 2 to 4 mm and lengths of 40 to 150 mm (Table 1).

The Lutonix drug coating contains paclitaxel, an anti-proliferative drug, as the active pharmaceutical ingredient (API), excipients polysorbate and sorbitol, and methanol as the solvent. The balloon is coated with a constant 2µg/mm^2 of paclitaxel, and the total dosage of paclitaxel per balloon size is correlated to the balloon surface area.

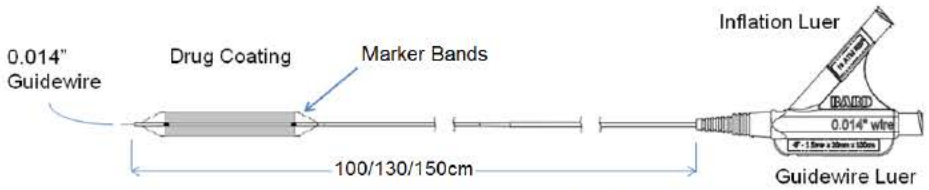


Figure 1: Lutonix 014 DCB

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
3.5 mm	X	X	X	X	X	X
4.0 mm	X	X	X	X	X	X

Table 1: Lutonix 014 DCB Product Matrix

6 Regulatory History

An Investigational Device Exemption (IDE) application for the Lutonix 014 DCB was first submitted to FDA under (b) (4) in January 2013 and disapproved on February 8, 2013. Lutonix submitted a response to the disapproval under (b) (4), and FDA conditionally approved the IDE on April 18, 2013 with full approval granted on May 30, 2013 under (b) (4).

The original IDE was approved for a total of 480 subjects (randomized 2:1 Lutonix 014 DCB:PTA). The primary safety endpoint was freedom from BTK MALE + POD at 30 days. The primary effectiveness endpoint was a composite of limb salvage and primary patency at 12 months (later changed to 6 months).

Since the original approval, the sponsor submitted 34 IDE supplements requesting modifications to the device design, manufacturing, and clinical study protocol. See Appendix A for a full listing of modifications, including protocol versions. A more in-depth discussion of notable IDE modifications, and the associated regulatory decision-making, is presented below.

6.1 Changes During the Course of the IDE Investigation

6.1.1 Background

Per Section 520(g)(4)(C) of the Food and Drug Administration Safety and Innovation Act (FDASIA), and consistent with section 520(g)(1), FDA shall not disapprove an IDE because "the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device." Per FDASIA, an IDE should only be disapproved if the investigational plan contains elements that would expose subjects to unacceptable probable risks or fails to

adequately protect study subjects from probable risks. Instead, if concerns are identified that are unrelated to subject safety, but which the Agency believes should be addressed in order for the study to support a future marketing application, then "study design considerations" can be sent in the official FDA letter to convey these concerns [5]. The sponsor has the option to make modifications in response to these concerns. Consequently, FDA approval of an IDE or IDE Supplement should not be interpreted to mean that FDA necessarily agrees that the study design is optimal or will support a marketing approval.

As noted above, the sponsor submitted 34 supplements during the course of the investigation to request various changes to the protocol, device design, or manufacturing. FDA approved changes to the clinical protocol because they did not expose study subjects to new safety risks. In many instances, however, FDA had concerns regarding the investigation plan changes, which were communicated as Study Design Considerations. The most notable changes made during the course of the IDE and the timing and content of FDA's study design considerations are discussed below.

6.1.2 Removal of Hemodynamic Inclusion Criteria

In (b) (4), approved on March 13, 2015 (approximately 2 years after the original IDE approval and after enrollment of approximately 180 patients), Lutonix eliminated the following hemodynamic inclusion criterion in order to reduce screen failures and speed up enrollment:

> "Ankle pressure ≤70 mm Hg or toe pressure ≤50 mm Hg. If ABI [Ankle Brachial Index] cannot be obtained due to calcified/non-compressible vessels (assume all ABI >1.4 are due to calcification) and TBI [Toe Brachial Index] cannot be obtained, patients will qualify for enrollment if TCPO2 ≤50 [Transcutaneous Oxygen Pressure] or non-pulsatile metatarsal/toe PVR [Pulse Volume Recording] are documented."

The sponsor noted that out of over 3,500 patients screened, 599 failed to meet the hemodynamic criteria. Given that there were no safety concerns, FDA approved this enrollment criterion change but strongly recommended the continued use of hemodynamic criteria given that this information is important to help define the patient population intended for device treatment and will better facilitate interpretation of study data. In response, while this change was implemented, the sponsor captured and reported hemodynamic data.

6.1.3 Addition of Rutherford Category 3 Patients

In (b) (4), approved on December 21, 2015 (approximately 2.5 years after the original IDE approval and after enrollment of approximately 270 patients), Lutonix proposed to enroll Rutherford Category (RC) 3 patients (in addition to the RC 4-6 patients already included) in order to improve the enrollment rate, and because they believed that RC 3 patients who have failed medical therapy may also benefit from percutaneous revascularization.

Given no safety concerns, FDA approved this change but noted that including RC 3 patients may confound the analysis of the resulting data with respect to the CLI population, especially if RC 3 subjects represent a significant percentage of study subjects. FDA recommended planned analyses to assess the impact of this protocol change, which the sponsor adhered to.

FDA Comment: A total of 9.5% subjects enrolled into the study were RC 3. Section 7.1.9.4 provides a subgroup analyses of the primary effectiveness outcome stratified by Rutherford Classification, and some outcome differences are noted. FDA is concerned that the inclusion of RC 3 patients into a CLI trial, especially after enrollment was more than halfway complete, could introduce challenges in interpreting study results. The panel will be asked to comment on the impact of this modification on study outcomes and interpretability.

6.1.4 Increased Sample Size and Added Interim Analyses

In (b) (4), approved on March 9, 2016 (approximately 3 years after the original IDE approval and after enrollment of 270 patients), Lutonix modified the trial sample size and statistical considerations related to new information on the estimated difference between treatment groups for the primary effectiveness endpoint. Based on observations from their above-the-knee device study, Lutonix determined that the expected improvement used for their initial sample size calculations for the BTK device may have been overestimated. Therefore, the sponsor changed the assumed treatment difference between groups from 20% to 12.6% and increased the sample size to 1000 patients (in order to achieve 840 evaluable patients). With this change, the sponsor also incorporated interim analyses at every 100 subjects starting at 300 subjects (which was later changed to 400 subjects). Interim analyses were intended to evaluate the predictive probability of success at the 300 (later removed upon FDA request) and 400 enrolled subjects (to determine if enrollment could be terminated early), and both predictive probability of success and futility thereafter (500, 600, and 700 subjects), using a Bayesian adaptive approach. Based on the revised study design that incorporated interim looks, the alpha was reduced from 0.025 to 0.0163. The alpha of 0.0163 provides for an overall Type I error level of 0.025 for the study.

FDA approved the increased sample size and interim analyses. See Section 7 for full details regarding the statistical methodology.

6.1.5 Shortened Primary Effectiveness Endpoint Assessment Timepoint from 12 Months to 6 Months Post-Index Procedure

In (b) (4), approved on July 19, 2016 (approximately 3 years after the original IDE approval and after enrollment of 325 patients), Lutonix shortened the primary endpoint assessment timepoint from 12 months to 6 months. The sponsor maintained that a 6-month endpoint was clinically meaningful and appropriate due to the aggressive nature of the disease.

While FDA acknowledged that an improvement at 6 months may be clinically meaningful, FDA communicated that the durability of the treatment effect was also valued by patients and physicians. *At this time, and during the course of the PMA review, FDA continued to reiterate that a durable benefit to at least 12 months would be important in demonstrating a reasonable assurance of effectiveness and a favorable benefit-risk profile for the Lutonix 014 DCB.*

Lutonix also changed the unit of analysis from "subjects" to "vessels" to provide better alignment with the primary effectiveness endpoint and allow termination of enrollment based on pathways versus subjects. Thus, based on these changes, the alpha was adjusted to 0.017.

FDA Comment: Lutonix shortened the assessment of the primary effectiveness endpoint from 12 months to 6 months. While FDA acknowledged the clinical meaningfulness of a 6-month endpoint for this patient population, FDA also communicated that a sustained benefit beyond 6 months is also important and should be demonstrated in order to support reasonable assurance of device effectiveness. The panel will be asked to comment on this change and the importance of longer-term data in the evaluation of clinically meaningful device effectiveness for this patient population.

6.1.6 Co-primary Endpoint Assessment Added for Proximal Segments

In (b) (4), approved on October 4, 2017 (approximately 4.5 years after the original IDE approval and after enrollment of 440 patients), Lutonix added a new co-primary endpoint assessment. Specifically, the primary effectiveness endpoint was revised to first include an assessment of the endpoint for "full flow pathways." If this analysis did not show superiority of the DCB vs. PTA, the sponsor proposed to repeat the analysis limited to the "proximal segment flow pathways." Due to this change, the alpha level to reach statistical significance was reduced to 0.0085 for both co-primary endpoints.

The term "flow pathway" refers to vessels corresponding to the following arteries: popliteal, tibioperoneal, anterior tibial, posterior tibial, and peroneal. 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. The term "proximal flow pathway" refers to lesions that are entirely within the proximal 2/3 segment of the target flow pathway boundary and some that are split across the 2/3 cut-off line (as long as they are within a 5 mm boundary), as depicted in Figure 2. The proximal flow pathway equals the proximal 2/3 segment and all flow pathway equals the proximal 2/3 segment plus the distal 1/3 segment. The study would be considered to have demonstrated primary effectiveness success if either of the analyses reach statistical significance.

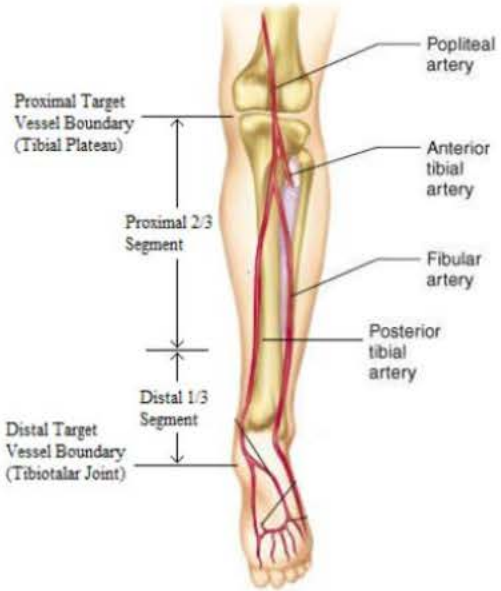


Figure 2: BTK IDE Flow Pathway Boundary

Given no safety concerns, FDA approved this change but noted that the final indications and labeling will be based on the primary endpoint that was evaluated. However, after further consideration and review of the initial dataset from this analysis, FDA noted concerns with the clinical meaningfulness of the "proximal lesion segment" analysis and the timing of the change late in the study. Lutonix agreed and chose to present the full flow pathways analysis as the primary dataset and the proximal segment flow pathway assessment would be considered a supportive analysis (though it was never formally removed as a co-primary endpoint, and the decision was made after the analysis was conducted). Please see Appendix B for details on the proximal segment analysis results.

6.1.7 Exclusion of Early Mechanical Recoil

In (b) (4), approved on October 4, 2017 (approximately 4.5 years after the original IDE approval and after enrollment of approximately 440 patients), Lutonix modified the clinical study protocol to include a hypothesis-tested secondary endpoint of primary patency excluding early mechanical recoil (as defined by any clinically-driven TLR event prior to 30 days). The sponsor's rationale for this change was that events within 30 days are a mechanical vascular response and are unlikely to be related to the "drug effect" from the Lutonix DCB (which they note is expected to occur starting at around 3 months or longer).

However, FDA noted concerns with the scientific validity of this assessment, as one cannot assume that clinically-driven TLR events prior to 30 days are solely due to early recoil or are independent of drug effects.

Lutonix maintained this evaluation as a secondary endpoint. This evaluation, however, did not yield significantly different findings and, thus, was not a focus of the sponsor's main dataset. Please see Appendix C for details regarding the secondary assessment for patency when excluding early mechanical recoil.

FDA Comment: The sponsor added further analyses, including effectiveness assessments of the proximal segment flow pathway and excluding cases of "early mechanical recoil," to explore the likelihood of showing that the Lutonix 014 DCB might provide some benefit. However, these evaluations are of questionable scientific validity and yielded no significantly different findings. The panel will be asked to comment on these modifications and evaluations and, after full review of the data, if there are specific patient populations or vessel characteristics that benefit from device treatment.

6.2 Trial Enrollment Termination

In (b) (4), approved on January 18, 2018, Lutonix proposed early termination of study enrollment. They provided the following rationale:

"The BTK IDE trial was initiated in 2013 and enrolled the first patient in June 2013. Enrollment has been increasingly a challenge in this study, and after 4 ½ years, we've enrolled 462 subjects (442 – randomized, 10 – roll-in and 10 – standard practice) in the US, EU and Japan. We have also recently completed our 2nd interim analysis at 500 vessels with neither predictive success nor futility. While this outcome would allow continued enrollment of another 340 vessels in the study, given the low enrollment rate, we anticipate that it may take another 3+ years to complete

the full enrollment of 840 vessels (~700 subjects given 20% with multiple vessels). Therefore, Lutonix has decided to end enrollment in this study. Please note that we are ending enrollment for business reasons and is not for any safety concerns. The Data Monitoring Committee (DMC) has met 14 times to date and unanimously recommended continuation of the study every time with no modifications."

6.3 IDE Timeline Summary

Figure 3 shows the timeline for major revisions to the pivotal IDE study.

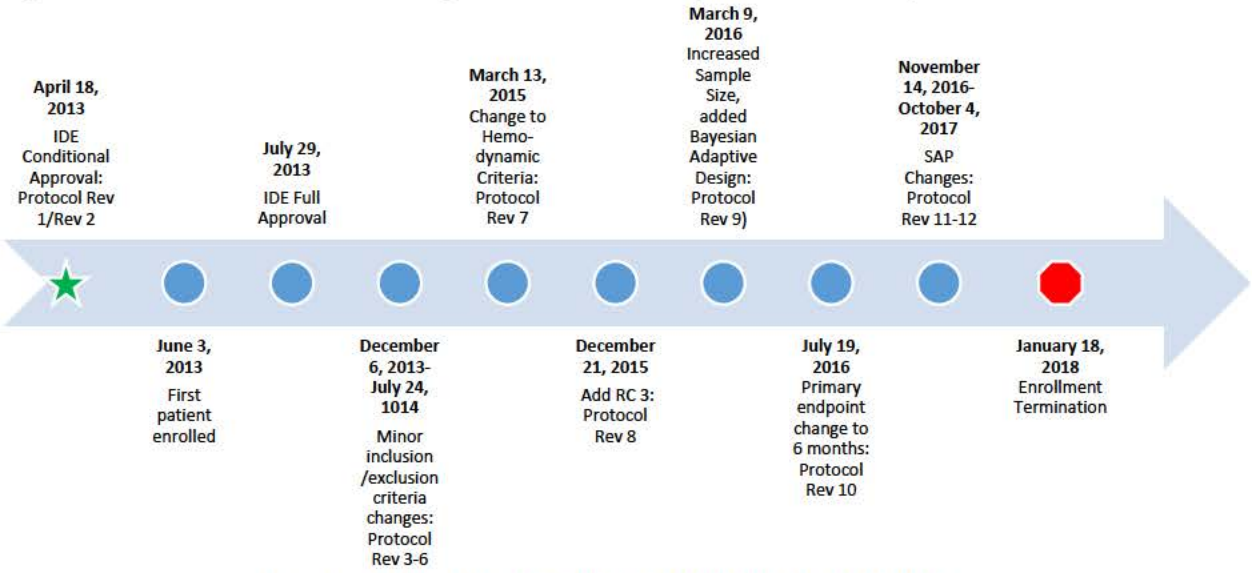


Figure 3: Timeline for Major IDE Protocol Revisions

FDA Comment: During the course of the trial, the sponsor made a number of protocol changes. These include reducing the time to primary endpoint assessment from 12 months to 6 months and decreasing the expected difference in effectiveness. As a result, the sponsor increased the sample size and incorporated a Bayesian adaptive design, which allowed for multiple interim analyses. These modifications, plus the addition of a co-primary effectiveness endpoint for the proximal segment flow pathway, resulted in an alpha level of 0.0085 required to for statistical significance, while controlling the overall type I error rate at 0.025.

The sponsor notified FDA of early termination of their IDE study, although only approximately half of the planned "vessels" were enrolled, and their interim analysis did not result in predictive success. In view of multiple study changes during trial execution and failed primary endpoint analysis, the panel will be asked to discuss how to appropriately evaluate the short-term (i.e., 6 month) and longer-term (i.e., 12 months and beyond) effectiveness outcomes for clinical-meaningfulness and whether the totality of data demonstrates a reasonable assurance of device effectiveness.

6.4 PMA Timeline

The PMA was submitted on October 9, 2018. A summary of the major decisions associated with this file is provided below. Please note that during the course of FDA's review, various pre-specified and post hoc analysis of the pivotal dataset and additional datasets were conducted. Section 7 shows the important primary and secondary analyses submitted.

6.4.1 Major Deficiency Letter

After the initial substantive review of the clinical data provided in the original PMA, a major deficiency letter was sent to the sponsor on January 4, 2019, which requested insights into the missed primary effectiveness endpoint as well as additional information and evaluation of key secondary outcomes, such as wound healing and longer-term data. At this point in the review, FDA decided to seek external expertise regarding the open clinical questions. Thus, the review team formulated questions for an agency direct assignment (ADA) (i.e., a panel homework assignment). FDA's review of the major deficiency letter response, as well as the responses to the ADA questions, was conducted concurrently during the next round of review.

6.4.2 Agency Directed Assignment (ADA) Review

Two panelists provided input on outstanding questions regarding study execution as well as the results of the primary and secondary analyses based on the "90-day update" PMA dataset (defined in Section 6.4.4). The questions focused on the primary and secondary endpoint results and the 6-month effectiveness treatment difference that favored the Lutonix 014 DCB group that was not observed at later timepoints. The two ADA panelists concluded that the benefit at 6 months without a durable effect at 12 months and beyond did not demonstrate a reasonable assurance of effectiveness for the Lutonix 014 DCB.

Please note that the ADA panelists reviewed a dataset, which is slightly different than those presented in Section 7. The main differences are discussed in Section 6.4.3. However, the primary safety and effectiveness endpoint results and study conclusions were similar.

6.4.3 Two Not Approvable (NOAP) Decisions

After review of the major deficiency letter response and the responses from the ADA, FDA issued a Not Approvable (NOAP) letter on June 24, 2019 indicating that the information submitted did not support a reasonable assurance of device effectiveness. The NOAP letter noted the limitations of the analyses including the clinical meaningfulness of the proximal segment analysis, the lack of a robust treatment effect beyond 6 months, and the ambiguity of the wound healing data.

The sponsor submitted a response to this NOAP letter on April 29, 2020, which included additional data sources, including real world evidence, and further analyses of their pivotal dataset. After reviewing this information, FDA again concluded that reasonable assurance of effectiveness was not established because of the limitations of the additional analyses and the continued absence of a beneficial treatment effect at 12 months. FDA issued a second NOAP decision letter on August 19, 2020.

6.4.4 Datasets

Three separate versions of the clinical study report (CSR) for the pivotal IDE trial were provided to FDA during the course of our review:

1) The first CSR was provided in the original PMA submission and had a datalock of August 7, 2018.
2) The sponsor then provided a "90-day update" in an amendment to the PMA (b) (4) in an updated CSR, which had a datalock of January 22, 2019.
3) The final CSR was provided in (b) (4), which was the sponsor's response to FDA's first NOAP letter, with a datalock of October 17, 2019.

The main difference in the (b) (4) report compared to the previous report from the original PMA was a change in outcomes for 3 DCB patients. These three patients initially had either a failed primary endpoint or missing primary endpoint data at the 6-month visit but later demonstrated a patent flow pathway (without any intervention). They were thus were changed to a success in the previous time point.

These three changes resulted in an increase of three in the numerator for the primary effectiveness outcome. Three other changes were noted due to missing data. One patient was initially classified as a success but later changed to missing. Two other patients were initially classified as missing but changed to a success. These changes resulted in a net increase of one in the denominator for the DCB primary effectiveness outcome assessment.

Please note that the change in outcomes for these 3 patients initially resulted in a success for the primary effectiveness endpoint for the proximal flow pathways (though not the overall flow pathways). However, the proximal segment flow pathway analysis was later abandoned as an integral part of the primary effectiveness evaluation, as conveyed by FDA after the initial review and later agreed to by Lutonix, due to a lack of clinical meaningfulness and the inability to appropriately clinically-define the proximal segment flow pathway. The proximal segment analysis was later included as a supplementary analysis in the updated CSR in response to our NOAP letter (in (b) (4)). This analysis once again failed to show statistical significance with the updated dataset.

The main difference in the (b) (4) report as compared to the previous report was the inclusion of longer-term results and additional post hoc analyses. However, (b) (4) also reported changes in the primary effectiveness outcomes for three additional flow pathways: 2 additional flow pathways in the DCB arm, which were initially missing but then both reported as successes and one in the PTA arm that was changed to success from failure.

Given that the changes in outcomes among the datasets resulted in minimal data differences and no difference in study conclusions, the final datasets and evaluations that FDA considered are those presented in (b) (4), as they were considered the most complete. These are the data that are discussed in Section 7.

FDA Comment: After submitting the PMA and conducting the initial data analysis, the sponsor has made two additional looks at the final primary dataset, and some outcome changes were noted due to some missing data becoming available and some changed patient outcomes.

Although, these modifications did not result in any notable change to the study outcomes, it is not clear to FDA if and how these changes in outcome data might bias the treatment effect estimate.

6.4.5 Determination for an Advisory Committee Request

While FDA reserves the right to refer a PMA application to panel on its own initiative, the regulations [6] also afford the applicant the right to request a panel meeting to review and help make recommendations regarding PMA applications. In this case, after receiving a second NOAP letter, the sponsor indicated that they believe that the data supports reasonable assurance of safety and effectiveness of the Lutonix 014 DCB, and they requested that an FDA Advisory Panel be convened to provide input on this matter.

7 Clinical Investigations

This section summarizes the clinical data included in the original PMA submission and subsequent amendments for the Lutonix 014 DCB. The pivotal randomized controlled trial (RCT) and Global BTK Registry were prospectively designed studies. Another supplementary prospective trial included the Japan HD, which examined smaller numbers of patients to evaluate the device for a specific patient population. The other datasets provided included a pooled propensity matched analysis of the IDE pivotal study with the Global registry and a Vascular Quality Initiative (VQI) registry analysis of off-label use of the approved 4 mm device compared to PTA patients. Finally, the sponsor submitted relevant literature reports from single-center studies.

The main focus of Section 7 is on the pivotal clinical trial, as it provides the most meaningful data to evaluate the Lutonix 014 DCB. FDA presents what we believe are the most informative analyses to assess the safety and effectiveness of the device. Summaries of additional data are included following the main dataset.

7.1 Lutonix BTK IDE Pivotal Study

The Lutonix BTK IDE Pivotal Study was a prospective, multicenter, single-blind, 2:1 randomized, controlled trial comparing the Lutonix 014 DCB (test group) vs. standard PTA (control group) for treatment of BTK arteries.

A total of 442 randomized subjects, 287 in the test arm and 155 in the control arm, were enrolled at sites in the US, Europe, Japan, and Canada. The primary study objective was to demonstrate non-inferior safety and superior effectiveness of the Lutonix DCB compared to standard PTA catheters for treating stenosis or occlusion of BTK arteries. The following sections present details regarding the study design (after all protocol changes described above were made), subject demographics and baseline characteristics, and study results.

7.1.1 Study Population

The Lutonix BTK IDE Pivotal Study population included subjects with BTK arterial disease.

7.1.2 Eligibility Criteria

7.1.2.1 Select Inclusion Criteria

Subjects could be included in the study only if they met all of the following inclusion criteria.

Clinical Criteria
1. Male or non-pregnant female ≥18 years of age
2. Rutherford Clinical Category 3-5

Angiographic Criteria
1. 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);
2. Cumulative length of target lesion(s) ≤320 mm;
3. Successful antegrade pre-dilatation of the target lesion with standard PTA catheter appropriate size for the reference vessel diameter;
4. A patent inflow artery free from significant lesions (≥50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment (<30% residual stenosis) of inflow artery lesions); and
5. Target vessel(s) diameter between 2 and 4 mm and able to be treated with available device size matrix.

7.1.2.2 Select Exclusion Criteria

Subjects were excluded from the study for any of the following reasons:

1. Gangrene extending proximal to the digit-metatarsal skin crease (index limb);
   (NOTE: Gangrene must be confined to the toe or toes)
2. Ischemic ulceration that extends more than 4 cm proximal to digit metatarsal skin crease (index limb);
   (NOTE: If ulcers are confined to toe, involvement of tendon or bone is acceptable. Ulcers proximal to digit-metatarsal skin crease must be superficial (not involving tendon or bone).
3. Neurotropic ulcer or heel pressure ulcer or ulcer potentially involving calcaneus (index limb)

7.1.3 Study Design

Subjects were randomized 2:1 to Lutonix DCB or standard PTA catheter. The study flowchart is provided in Figure 4.

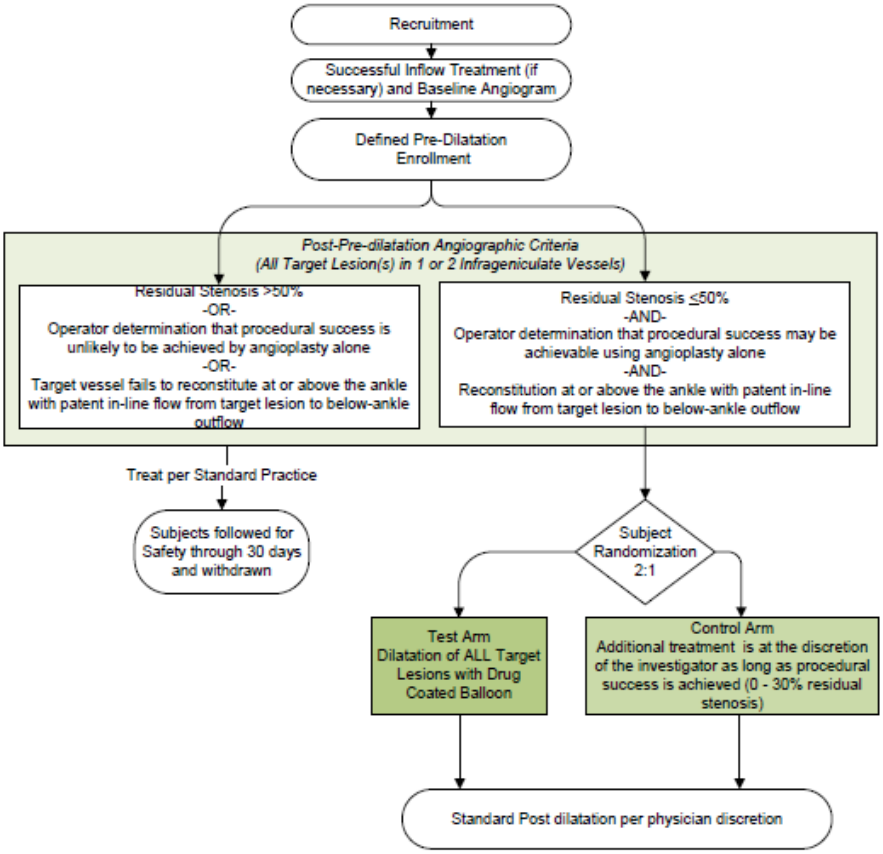


Figure 4: **Lutonix BTK IDE Pivotal Study Flowchart**

7.1.4 Blinding

Patients were blinded until the primary endpoint timepoint of 6 months. The operator/investigator and physicians and research staff performing follow-up assessments were not blinded. The clinical events committee (CEC) was blinded to the treatment group and the sponsor was also blinded.

7.1.5 Primary and Secondary Analyses

7.1.5.1 Primary Safety Endpoint

Primary safety endpoint: Freedom from BTK MALE (major adverse limb event) + POD (peri-operative death) at 30 days.

> The primary safety endpoint 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 below-the-knee artery.

7.1.5.2 Co-Primary Effectiveness Endpoints

Co-primary effectiveness endpoints for: (1) the full flow pathway; and (2) the proximal segment flow pathway:

> The composite of limb salvage and primary patency at 6 months, which includes freedom from the composite of above-ankle amputation, target lesion occlusion, and clinically-driven target lesion revascularization. All amputations included in endpoints refer to amputations in the index limb.

(Note: This endpoint timepoint was shortened from 12 months to 6 months during the course of the IDE).

7.1.5.3 Secondary Endpoints

7.1.5.3.1 Hypothesis Tested Secondary Endpoints

- 6-month primary patency with exclusion of early mechanical recoil.
- 6-month primary patency.
- 6-month freedom from clinically-driven TLR.
- 6-month composite of freedom from above ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically driven target vessel revascularization (TVR).

7.1.5.3.2 Additional Secondary Endpoints

- 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 (wound characterized as healed when completely epithelialized)
  - Change in Rutherford Class 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 (absence of total occlusion/100% diameter stenosis of the target lesion without prior target lesion revascularization)
  - Primary patency with exclusion of early mechanical recoil
  - Secondary patency (absence of total occlusion independent of whether or not patency is re-established via an endovascular procedure)
  - Clinically-driven TLR (clinically driven revascularization defined as worsening of Rutherford Class of the index limb, stagnant or worsening wound healing, or a new or recurrent wound in the index limb)
  - Clinically-driven TVR
  - Hemodynamic outcomes (ABI, TBI)
  - Change in Walking Impairment Questionnaire from baseline

- Amputation (major): Above ankle amputation of the index limb
- Unplanned minor (below the ankle) amputations
- Death, any cause

7.1.6 Statistical Methodology

7.1.6.1 Background

The original approved protocol was based on a fixed sample size estimate of 320 randomized subjects to be evaluated for primary effectiveness at 12 months. In addition to moving to a 6-month primary effectiveness endpoint, the study was amended to include an adaptive design allowing sample sizes of 400 to 840 flow pathways randomized 2:1 (DCB:PTA). The primary effectiveness endpoint was further updated to include two possible analyses:

1. The first analysis is based on the full flow pathway analysis
2. If the full flow pathway analysis did not reach the adjusted p-value threshold for success, then the analysis would be completed for the proximal segment flow pathway

   Note: While this endpoint was later considered "supplementary" and not focused on for the primary evaluation, this evaluation was never formally removed from the protocol or SAP and was analyzed before being abandoned.

The study sample size was to be based on a Bayesian adaptive design. The study enrollment could be 400, 500, 600, 700, or 840 randomized flow pathways depending upon the predicted probabilities obtained by evaluating the observed treatment results at interim assessments. Due to the use of the adaptive design for the sample size, the significance level of the primary effectiveness analysis was adjusted. Both co-primary effectiveness endpoints were included in the interim analyses.

7.1.6.2 Primary Effectiveness Endpoint Analysis

The primary effectiveness hypothesis was as follows:

$$H_0: p_{DCB} \leq p_{Control} \text{ and } H_1: p_{DCB} > p_{Control}$$

where p is the success rate in each arm.

The first primary effectiveness analysis of this endpoint was based on the total number of randomized flow pathways. The analysis of the proximal segment flow pathway co-primary endpoint 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 the flow pathway.

The treatment effect was estimated via a logistic regression model with generalized estimating equations (GEE) to account for correlation within subjects. The experimental treatment would be determined superior to control if the one-sided p-value of the above hypothesis is ≤ 0.0085. If this analysis failed for the full flow pathway analysis, the same analysis method was to be used to analyze the proximal segment flow pathway. A p-value of 0.0085 was needed to control overall Type I error of the adaptive design, as well as the co-primary effectiveness hypothesis proposed

for the proximal segment, to a level of 0.025 under the trial's design assumptions as well as planned sensitivities to those assumptions.

7.1.6.3 Primary Safety Endpoint Analysis

The primary safety hypothesis was as follows:

$$H_0: p_{Control} - p_{DCB} \geq \delta \text{ and } H_1: p_{Control} - p_{DCB} < \delta$$

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

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 <0.025.

7.1.6.4 Hypothesis-Tested Secondary Endpoints Analysis

If the study reached overall success, for both primary effectiveness and safety, the four pre-specified hypotheses presented below were to be considered for potential labeling. These would be tested sequentially at the 0.025 one-sided alpha level if all previous tests reach statistical significance.

- 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 TVR.

Note: Since the primary effectiveness endpoint was not met, no hypothesis testing of the prespecified secondary endpoints was performed, and only descriptive statistics of the results are provided.

7.1.6.5 Decision Making for Interim Analyses

Interim looks were to be made at sample sizes of 400, 500, 600, and 700 randomized vessels assuming these sample sizes were reached. A Bayesian decision process was to be used to adjust the final sample size for the study. At each interim analysis, the study would either continue to enroll subjects or enrollment will be considered complete. If the study was not complete at the 700-vessel interim analysis, the study was to enroll the full 840 vessels. Interim analyses would evaluate predictive probability for success (based on current enrollment) and futility (based on full sample size enrollment of 840) for superiority for effectiveness in the: 1) full flow pathway population or 2) proximal segment flow pathway population. Interim decision rules based on these analyses are as follows:

1. If predictive probability for success was shown to be >0.9 for either the full flow pathway population or the proximal segment flow pathway, the accrual would be stopped and full follow-up observed, and final analysis for success will take place (full flow pathway

analysis, followed by proximal segment flow pathway analysis if full flow pathway analysis did not meet success criteria).

2. If futility (predictive probability <0.01) was shown for both the full flow pathway population and the proximal segment flow pathway population, then accrual would be stopped for futility.
3. If futility was shown for the full flow pathway population but not for the proximal segment flow pathway population, enrollment would continue for the proximal segment flow pathway population only for any future next interim analysis. All subsequent interim and final analyses would only evaluate hypotheses corresponding to the proximal segment flow pathway population.
4. If none of the above criteria were met, the trial would continue enrolling to the next interim analysis or the maximum sample size of 840. If the maximum sample size of 840 vessels were enrolled, then the defined primary analysis (full flow pathway analysis, followed by proximal segment flow pathway analysis if the full flow pathway analysis did not meet success criteria) occurs 6 months after the 840th vessel was enrolled.

7.1.7 Follow Up Schedule

Subjects in the Lutonix BTK IDE Pivotal Study were consented to participate and be followed for 36 months post-procedure. Follow-up to 60 months for vital status was added later, upon request from FDA. Details of the follow-up procedures can be found in Table 2.

Event	Screening[3] / (pre-consent)	Pre- Procedure	Procedure	Post- Procedure	30 days	6 Month	12 Month	24 Month	36 Month
Visit Window	30-days	30-days			±2 weeks	±1 month	±1 month	±2 month	±2 month
Inclusion/Exclusion Criteria	√	√	√						
Informed Consent		√							
Medical History	√								
Physical Exam		√		√	√	√	√	√	√
ABI-TBI[1]		√			√	√	√	√	√
Rutherford Classification		√			√	√	√	√	√
Pregnancy Test (blood or urine)[2]		√							
WIQ and EQ-5D Questionnaires		√			√[5]	√	√	√	√
Angiogram			√						
Adverse Event Monitoring			√	√	√	√	√	√	√

Event	Screening[3] / (pre-consent)	Pre- Procedure	Procedure	Post- Procedure	30 days	6 Month	12 Month	24 Month	36 Month
Visit Window	30-days	30-days			±2 weeks	±1 month	±1 month	±2 month	±2 month
Duplex Ultrasound (after clinical assessment)					√	√	√	√	√
Wound Healing Assessment[4]		√			√	√	√	√	√

[1] TBI in cohort where data is available. Resting ABI is required within 90 days of the index procedure
[2] Pre-procedure and females of childbearing potential only
[3] Screening (pre-consent, to determine which patients to consent) must be based only on information available from the patient's medical record or collected as part of standard hospital practice; any additional protocol-required assessments must be performed after signing informed consent form.
[4] Wound imaging (including collection of images, if applicable)
[5] Only the WIQ is required at the 30-day time point

Table 2: Follow-up Schedule

7.1.8 Subject Characteristics

7.1.8.1 Subject Disposition Accountability

There were 462 subjects enrolled in the Lutonix BTK IDE Trial from June 3, 2013 to December 12, 2017 across 51 investigational centers. A total of 442 randomized subjects, 10 roll-in subjects, and 10 standard practice subjects (did not meet post pre-dilatation entry criteria) were enrolled in 4 geographies - U.S, Canada, Europe, and Japan. See Table 3 for subject disposition.

	DCB Subjects	PTA Subjects	Total Subjects
Enrolled, n	297	165	462
Non-Randomized, n			
n	10	10	20
Roll-in	10	0	10
Standard Practice	0	10	10
Randomized (ITT), n	**287**	**155**	**442**

Table 3: Subject Disposition

Subject accountability (specifically rates of death, withdrawal, and lost-to-follow-up) are shown in Figure 5. Accountability by flow pathway is presented in Figure 6. Accountability tables with further details regarding percentages of missing data can be found in Appendix D.

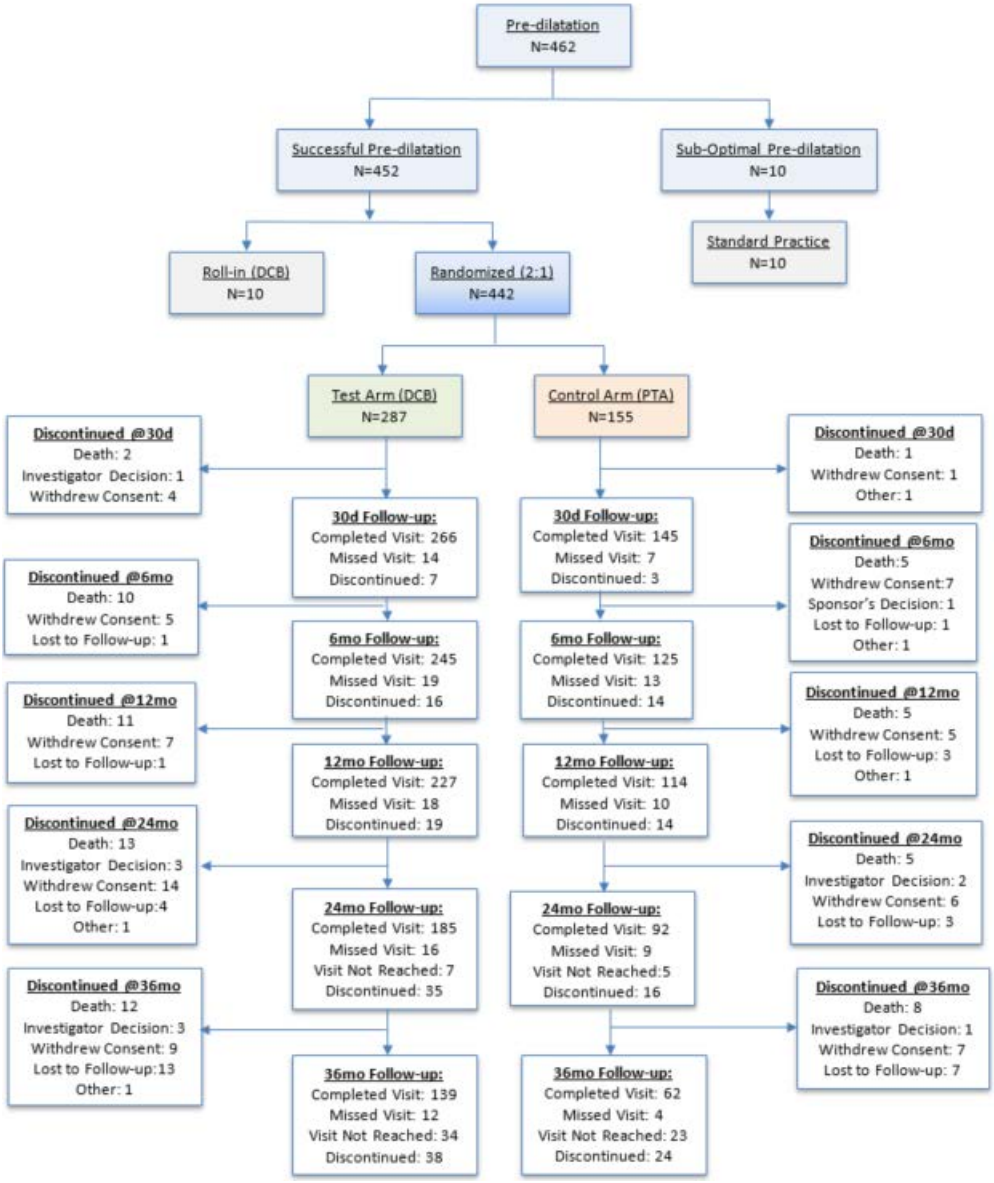


Figure 5: Subject Accountability

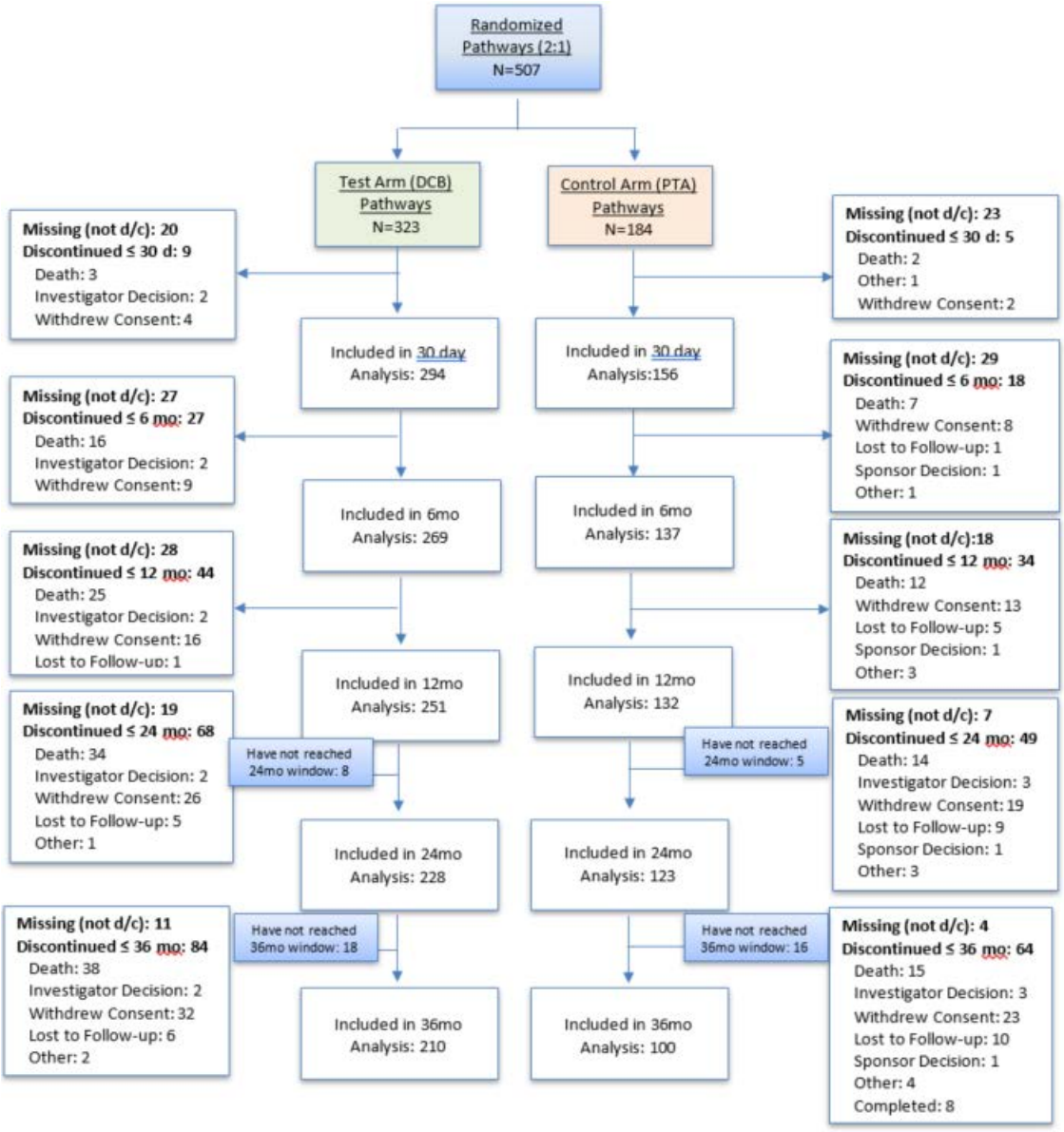
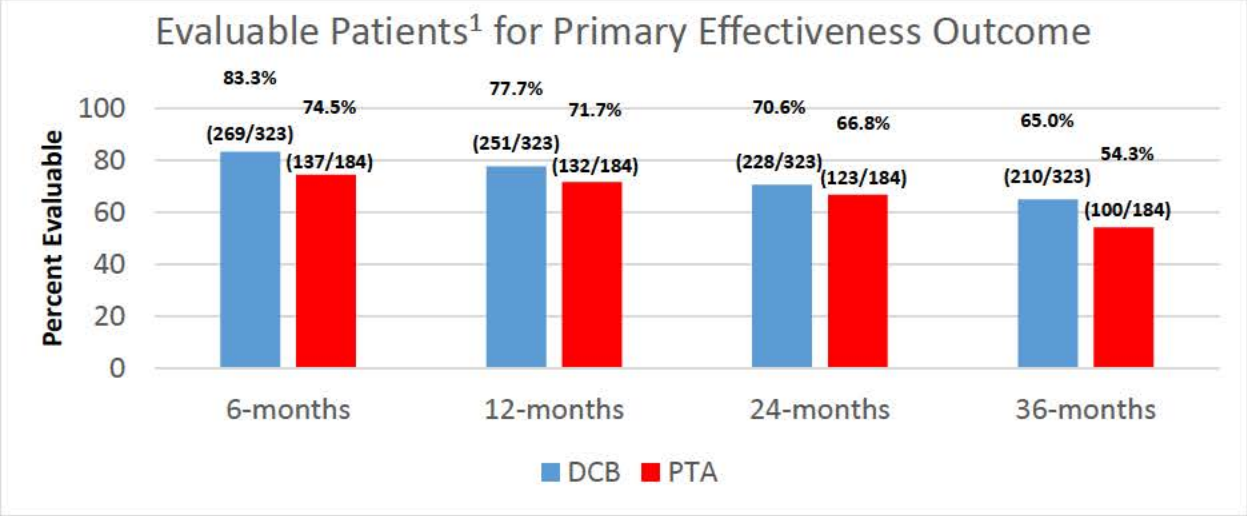


Figure 6: Accountability by Flow Pathway

It is important to consider the amount of discontinued subjects and missing data for the flow pathway analysis. Data were not available due to deaths (without previous vessel failure), withdrawal of consent, and lost-to-follow-up (LTFU). At 6 months follow-up, only 83.3% (269/323) of DCB flow pathways and 74.5% (137/184) of PTA flow pathways had evaluable effectiveness data. At 12 months, evaluable data declined to 77.7% (251/323) for the DCB arm and 71.7% (132/184) for PTA arm. At 24 months, the evaluable data rate was 70.6% (228/323) for the DCB arm and 66.8% (123/184) for the PTA arm. At 36 months, the evaluable data rate was 65.0% (210/323) for the DCB arm and 54.3% (100/184) for the PTA arm. There were more discontinued subjects and missing data for the flow pathway analysis of the PTA arm vs. the DCB arm, with increased rates of approximately 9%, 6%, 4%, and 11%, respectively, at the 6-

month, 12-month, 24-month and 36-month timepoints. However, some subjects have yet to reach their visit window for the 24-month (8 for the DCB arm and 5 for the PTA arm) and 36-month (18 for the DCB arm and 16 for the PTA arm) assessments. See Figure 7 for evaluable patients at each follow-up timepoint.



[1] Percent evaluable = Randomized Flow Pathways – [(Death) + (LTFU) + Withdrew + Other)]/Randomized Flow Pathways

Figure 7: Percent of Evaluable Patients for Primary Effectiveness Outcome

FDA Comment: FDA will ask the panel to comment on the impact of missing data on the interpretation of study outcomes.

7.1.8.2 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics were collected prior to the procedure and are shown in Table 4. The average age was 72.9 years in both arms. The majority of subjects (approximately 65-70%) were male and white (approximately 80%). There were no significant differences in baseline characteristics between groups. As a reminder, Rutherford Classification 3 patients were permitted to enroll in this study and comprised approximately 10% of the patients in each arm.

	DCB Subjects (N=287)	PTA Subjects (N=155)	Total Subjects (N=442)	P-value[1]
Age (Years):				0.9586
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	
Gender, n (%)				0.5173
Male	202/287 (70.4%)	104/155 (67.1%)	306/442 (69.2%)	

	DCB Subjects (N=287)	PTA Subjects (N=155)	Total Subjects (N=442)	P-value[1]
Female	85/287 (29.6%)	51/155 (32.9%)	136/442 (30.8%)	
Race, n (%)				0.7468
American Indian or Alaska Native	1/287 (0.3%)	0/155	1/442 (0.2%)	
Asian	25/287 (8.7%)	15/155 (9.7%)	40/442 (9.0%)	
Black or African American	33/287 (11.5%)	12/155 (7.7%)	45/442 (10.2%)	
White	226/287 (78.7%)	127/155 (81.9%)	353/442 (79.9%)	
Other	2/287 (0.7%)	1/155 (0.6%)	3/442 (0.7%)	
Weight (Kg):				0.9819
N	287	155	442	
Mean (SD)	82.6 (21.15)	81.9 (20.29)	82.3 (20.83)	
Median	81.0	82.0	81.0	
Min, Max	41, 202	38, 140	38, 202	
Height (cm):				0.8842
N	287	155	442	
Mean (SD)	170 (10.07)	170 (10.65)	170 (10.26)	
Median	170.2	170.0	170.0	
Min, Max	140, 193	145, 192	140, 193	
BMI (kg/m^2):				0.6117
N	287	155	442	
Mean (SD)	28.4 (6.31)	28.0 (5.65)	28.2 (6.08)	
Median Min,	28.0	27.4	27.7	
Max	14.1, 69.9	16.7, 51.6	14.1, 69.9	
Rutherford Category, n (%)				
n	287	155	442	
3	26 (9.1%)	16 (10.3%)	42 (9.5%)	0.9181
4	100 (34.8%)	52 (33.5%)	152 (34.4%)	
5	161 (56.1%)	87 (56.1%)	248 (56.1)	

[1] P-value associated with Wilcoxon Rank sum Test comparing DCB group and PTA group for continuous data or Fisher's Exact Test for categorical data. P-values are not adjusted for multiplicity.

Table 4: Baseline Demographics

There were also no notable differences in baseline medical history and associated risk factors between groups, including diabetes, dyslipidemia, hypertension, and cigarette smoking. See Table 5.

	DCB Subjects (N=287)	PTA Subjects (N=155)	Total Subjects (N=442)	P-value[1]
History of Risk Factors, n (%)	285 / 287 (99.3%)	155 / 155 (100.0%)	440 / 442 (99.5%)	0.5436
Diabetes	204 / 287 (71.1%)	106 / 155 (68.4%)	310 / 442 (70.1%)	
Dyslipidemia	225 / 287 (78.4%)	116 / 155 (74.8%)	341 / 442 (77.1%)	
Hypertension	264 / 287 (92.0%)	148 / 155 (95.5%)	412 / 442 (93.2%)	
Cigarette Smoking	170 / 287 (59.2%)	89 / 155 (57.4%)	259 / 442 (58.6%)	
Current	43 / 287 (15.0%)	19 / 155 (12.3%)	62 / 442 (14.0%)	
Former	127 / 287 (44.3%)	70 / 155 (45.2%)	197 / 442 (44.6%)	

	DCB Subjects (N=287)	PTA Subjects (N=155)	Total Subjects (N=442)	P-value[1]

[1] P-value associated with Fisher's Exact Test comparing DCB group and PTA group. P-values are not adjusted for multiplicity.

Table 5: Medical History

7.1.8.3 Target Lesion Characteristics

Table 6 shows baseline target lesions characteristics reported per lesion. There were no significant differences in baseline target lesion characteristics between treatment groups except for lesion length, which was slightly greater in the DCB group.

	Treated Lesions		
	DCB (N=352)	PTA (N=213)	P-value[2]
Lesion Type, n/N (%), n	352	212	0.694
Distal 1/3	17 (4.8%)	14 (6.6%)	
Proximal 2/3	194 (55.1%)	121 (57.1%)	
Split across 2/3 reference line	126 (35.8%)	70 (33.0%)	
Unknown/NA	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	
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	128 (45.1%)	88 (48.6%)	0.339
Posterior Tibial	102 (35.9%)	73 (40.3%)	0.988
Peroneal	212 (74.6%)	135 (74.6%)	
Pedal Arch, n/N (%), n	305	185	0.882
Complete	115 (37.7%)	71 (38.4%)	
Incomplete	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/N (%), n	351	209	0.072
A	182 (51.9%)	131 (62.7%)	

	Treated Lesions		
	DCB (N=352)	PTA (N=213)	P-value[2]
B	61 (17.4%)	32 (15.3%)	
C	62 (17.7%)	28 (13.4%)	
D	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] Subjects may have more than one location indicated.
[2] Wilcoxon Rank-Sum test and Likelihood Ratio Chi-Square test. P-values are not adjusted for multiplicity.

Table 6: Target Lesions Characteristics (Per Lesion)

7.1.8.4 Pre and Post-Procedure Medications

The suggested medication schedule post-procedure is shown in Table 7.

Drug	Pre-Procedure	Procedure	Post-Procedure*
Aspirin	75-325 mg/day	NA	75-100 mg/day indefinitely
Clopidogrel OR	75 mg or 300 mg loading dose	NA	75 mg daily for at least 1 month
Ticagrelor OR	180 mg loading dose	NA	90 mg BID
Prasugrel	10 mg/day or loading dose of 60 mg	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

Table 7: Suggested Medication Schedule

A summary of the relevant medications taken during the trial are shown in Table 8.

	DCB Subjects (N=287)	PTA Subjects (N=155)
Loading Dose (Anti-Platelet) in Total, n (%)[1]		
Aspirin	54 (18.8%)	25 (16.1%)
Clopidogrel	105 (36.6%)	54 (34.8%)
Heparin	5 (1.7%)	5 (3.2%)
Other Antiplatelet	2 (0.7%)	0
Ticagrelor	1 (0.3%)	0
Ticlopidine	1 (0.3%)	0

	DCB Subjects (N=287)	PTA Subjects (N=155)
Pre-Procedure (Excluding Loading Dose), n (%)[1]		
Ace Inhibitor	97 (33.8%)	51 (32.9%)
Angiotensin II Receptor Blockers	51 (17.8%)	34 (21.9%)
Aspirin	202 (70.4%)	106 (68.4%)
Beta Blockers	128 (44.6%)	67 (43.2%)
Cilostazol (Pletal)	18 (6.3%)	9 (5.8%)
Clopidogrel	129 (44.9%)	75 (48.4%)
Heparin	20 (7.0%)	9 (5.8%)
Non-Statin Lipid Lowering Agents	19 (6.6%)	9 (5.8%)
Other Antiplatelet	20 (7.0%)	13 (8.4%)
Prasugrel	1 (0.3%)	0
Statins	168 (58.5%)	79 (51.0%)
Ticagrelor	5 (1.7%)	0
Ticlopidine	1 (0.3%)	0
Post-Procedure to 30-Day Visit, n (%)[1]		
Ace Inhibitor	105 (36.6%)	58 (37.4%)
Angiotensin II Receptor Blockers	51 (17.8%)	35 (22.6%)
Aspirin	250 (87.1%)	129 (83.2%)
Beta Blockers	135 (47.0%)	71 (45.8%)
Cilostazol (Pletal)	19 (6.6%)	12 (7.7%)
Clopidogrel	224 (78.0%)	124 (80.0%)
Heparin	20 (7.0%)	9 (5.8%)
Non-Statin Lipid Lowering Agents	19 (6.6%)	9 (5.8%)
Other Antiplatelet	23 (8.0%)	14 (9.0%)
Prasugrel	1 (0.3%)	0
Statins	187 (65.2%)	91 (58.7%)
Ticagrelor	7 (2.4%)	2 (1.3%)
Ticlopidine	2 (0.7%)	0
Post 30-Day Visit to 6-Month Visit, n (%)[1]		
Ace Inhibitor	91 (31.7%)	52 (33.5%)
Angiotensin II Receptor Blockers	51 (17.8%)	33 (21.3%)
Aspirin	220 (76.7%)	109 (70.3%)
Beta Blockers	121 (42.2%)	64 (41.3%)
Cilostazol (Pletal)	15 (5.2%)	9 (5.8%)
Clopidogrel	184 (64.1%)	103 (66.5%)
Heparin	15 (5.2%)	8 (5.2%)
Non-Statin Lipid Lowering Agents	16 (5.6%)	5 (3.2%)
Other Antiplatelet	21 (7.3%)	9 (5.8%)
Statins	170 (59.2%)	83 (53.5%)
Ticagrelor	7 (2.4%)	1 (0.6%)
Post 6-Month Visit to 12-Month Visit, n (%)[1]		
Ace Inhibitor	75 (26.1%)	40 (25.8%)
Angiotensin II Receptor Blockers	44 (15.3%)	27 (17.4%)

	DCB Subjects (N=287)	PTA Subjects (N=155)
Aspirin	186 (64.8%)	82 (52.9%)
Beta Blockers	107 (37.3%)	54 (34.8%)
Cilostazol (Pletal)	13 (4.5%)	6 (3.9%)
Clopidogrel	137 (47.7%)	70 (45.2%)
Heparin	9 (3.1%)	9 (5.8%)
Non-Statin Lipid Lowering Agents	10 (3.5%)	4 (2.6%)
Other Antiplatelet	21 (7.3%)	10 (6.5%)
Statins	142 (49.5%)	68 (43.9%)
Ticagrelor	6 (2.1%)	1 (0.6%)
Post 12-Month Visit to 24-Month Visit, n (%)[1]		
Ace Inhibitor	52 (18.1%)	29 (18.7%)
Angiotensin II Receptor Blockers	42 (14.6%)	25 (16.1%)
Aspirin	138 (48.1%)	68 (43.9%)
Beta Blockers	87 (30.3%)	44 (28.4%)
Cilostazol (Pletal)	7 (2.4%)	3 (1.9%)
Clopidogrel	103 (35.9%)	52 (33.5%)
Heparin	7 (2.4%)	2 (1.3%)
Non-Statin Lipid Lowering Agents	10 (3.5%)	4 (2.6%)
Other Antiplatelet	20 (7.0%)	9 (5.8%)
Statins	108 (37.6%)	54 (34.8%)
Ticagrelor	5 (1.7%)	1 (0.6%)
Post 24-Month Visit to 36-Month Visit, n (%)[1]		
Ace Inhibitor	38 (13.2%)	22 (14.2%)
Angiotensin II Receptor Blockers	31 (10.8%)	15 (9.7%)
Aspirin	99 (34.5%)	48 (31.0%)
Beta Blockers	65 (22.6%)	24 (15.5%)
Cilostazol (Pletal)	4 (1.4%)	4 (2.6%)
Clopidogrel	66 (23.0%)	31 (20.0%)
Heparin	3 (1.0%)	4 (2.6%)
Non-Statin Lipid Lowering Agents	4 (1.4%)	2 (1.3%)
Other Antiplatelet	17 (5.9%)	7 (4.5%)
Statins	74 (25.8%)	35 (22.6%)
Ticagrelor	2 (0.7%)	0

[1] Subjects may appear in more than one category but are only counted once per category.

Table 8: Medications Taken at Through 36 Months

7.1.9 Data Sets Analyzed

The datasets analyzed were the intent-to-treat (ITT), as treated (AT), and per protocol (PP) patient populations. Safety endpoints are assessed per subject and effectiveness endpoints per flow pathway. The following definitions were used:

- *Intent-to-treat (ITT) population*: Includes all randomized subjects or flow pathways analyzed according to their randomized treatment group.

- *As Treated (AT) population:* Includes all subjects or flow pathways analyzed according to the actual treatment received. Subjects who receive DCB in at least one flow pathway were included in the AT population at the subject level and flow pathways may be DCB or PTA within the same subject. Any flow pathway that did not receive DCB was considered to be standard PTA.
- *Per Protocol (PP) population:* Includes all randomized subjects or flow pathways that were 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 were considered major were related to study eligibility criteria and were defined a priori in the analysis plan.

The ITT population was the primary analysis population for the primary safety and effectiveness outcomes. Additional analyses were conducted on the AT and PP populations, which were consistent with the ITT population results and not included in this document.

7.1.10 Lutonix BTK IDE Pivotal Study Results and Analyses

The results from the Lutonix BTK IDE Pivotal Study, including primary analyses, secondary analyses, and post hoc analyses, as presented in the PMA submission, are presented below. Additional data tables for these analyses are included in Appendices C-H. Appendix E contains the Kaplan-Meier (KM) tables for the KM curves provided in the body of this summary.

7.1.10.1 Interim Analyses

Interim analyses were performed after n=400 and n=500 vessels were enrolled. The conclusion of both interim Bayesian analyses was neither to stop accrual at the current sample size nor stop for futility. While the modified sample size could reach n=840 vessels, interim analyses planned at n=600 and n=700 vessels were never performed. After 4.5 years, the sponsor terminated enrollment for "business reasons" at n=507 vessels.

7.1.10.2 Primary Safety Results

The primary safety endpoint is 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. The Lutonix 014 DCB group had a primary safety endpoint rate of 99.3% and the control arm had a rate of 99.4% at 30 days. The non-inferiority margin was 12%, and non-inferiority was demonstrated with a p-value of <0.0001 (Table 9).

	DCB Subjects (N=287) n/N (%) (95% CI)[1]	**PTA Subjects (N=155) n/N (%) (95% CI)[1]**	**Difference in Response (95% CI)[2]**	**Farrington - Manning Test P-value[3]**
Freedom from a Primary Safety Event at 30 Days	284 / 286 (99.3%) (97.5%, 99.9%)	154 / 155 (99.4%) (96.5%, 100.0%)	-0.1% (-3.9%, 3.8%)	<.0001
Primary Safety Events Through Day 30, n[4]				

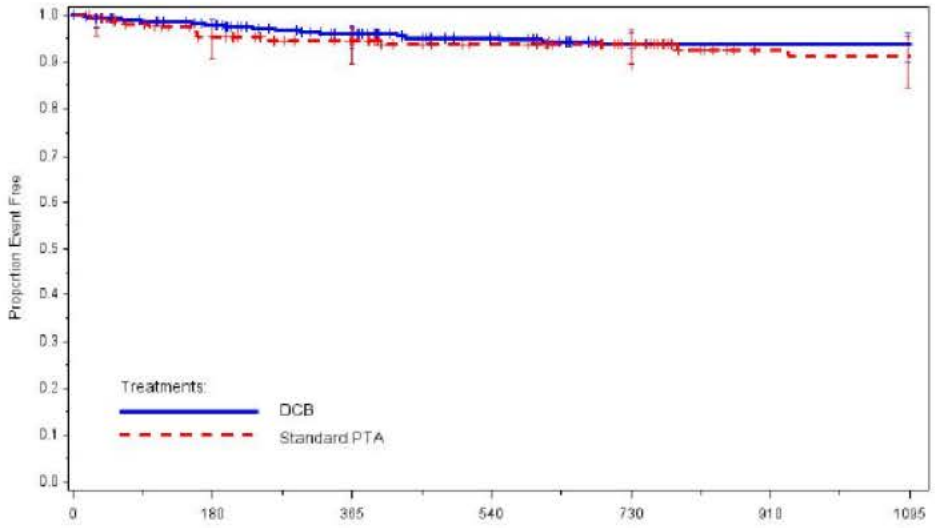
	DCB Subjects (N=287) n/N (%) (95% CI)[1]	PTA Subjects (N=155) n/N (%) (95% CI)[1]	Difference in Response (95% CI)[2]	Farrington - Manning Test P-value[3]
Death	1	1		
Above Ankle Amputation	0	0		
Major Re-intervention	1	0		

[1] 95% CI based exact binomial distribution;
[2] 95% CI is estimated by Farrington-Manning Test
[3] P-value for non-inferiority margin of 12%;
[4] Subjects may fail primary safety due to more than one cause

Table 9: Primary Safety Endpoint Results Through 30 Days

7.1.10.3 Long-Term Safety Results

The KM estimates for the primary safety endpoint through 36 months are shown in Figure 8. The safety event rate remains similar through 36 months.



	Subjects Left				
Group	Day 1	Day 180	Day 365	Day 730	Day 1095
DCB	286	264	239	187	90
PTA	155	135	121	93	44

Figure 8: Primary Safety Endpoint KM Estimates Through 36 Months

The primary safety endpoint event rates reported as binary outcomes through 36 months are presented in Table 10. The endpoint rates were generally similar between treatment groups through 36 months.

Visit	DCB Subjects (N=287)		PTA Subjects (N=155)		Difference (95% CI)[2]
	Response Rate[1]	95% CI[2]	Response Rate[1]	95% CI[2]	
30 Days	284 / 286 (99.3%)	(97.5%, 99.9%)	154 / 155 (99.4%)	(96.5%, 100.0%)	-0.1% (-1.6%, 1.5%)

Visit	DCB Subjects (N=287)		PTA Subjects (N=155)		Difference (95% CI)[2]
	Response Rate[1]	95% CI[2]	Response Rate[1]	95% CI[2]	
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%)

[1] Response Rate is freedom from BTK MALE + POD through each visit
[2] 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 10: Primary Safety Endpoint Binary Outcomes Through 36 Months

7.1.10.4 Primary Effectiveness Results

The primary effectiveness endpoint is the composite of limb salvage and primary patency at 6 months, expressed as freedom from primary effectiveness failure. The Lutonix 014 DCB had a primary effectiveness endpoint rate of 74.7%, and the control arm had a rate of 64.2% (absolute difference of 10.5%). The corresponding p-value was 0.0222. Because of planned interim analyses, a significance level of 0.0085 was required to reach statistical significance. Therefore, the event rate difference between the Lutonix 014 DCB and PTA did not reach statistical significance for superiority (see Table 11).

	DCB (N=323) n/N (%) (95% CI)[1]	PTA (N=184) n/N (%) (95% CI)[1]	Difference in Response (95% CI)[2]	P-value[3]
Freedom 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 **NS**
Composite Endpoint Failure Events Through Day 210, n (%)[4]				
Subjects with major amputation	4 (1.5%)	3 (2.2%)		
Pathways with clinically-driven TLR	28 (10.4%)	30 (21.9%)		
Pathways with primary patency failure	65 (24.2%)	46 (33.6%)		

NS = Non-significant
[1] 95% CI based exact binomial distribution
[2] Based on the model estimated response rates in both groups
[3] One-sided Wald Test based on model estimate of DCB treatment effect and subject as a random effect
[4] Subjects may fail primary effectiveness due to more than one cause and TLR failure is a component of primary patency failure
*The presented results are from the updated CSR presented in (b) (4) and are slightly different from the results presented in the original PMA

Table 11: Primary Effectiveness Endpoint Results Through 6 Months

As noted above, three datasets were provided during the course of FDA's review: in the original PMA, in (b) (4) and in (b) (4). Based on the CSRs provided in these submissions, the p-value for the primary effectiveness endpoint analysis changed from 0.0273 to 0.0179 to 0.0222. Since the p-value for each of these analyses was >0.0085 (the pre-specified alpha needed for statistical significance), the primary effectiveness endpoint was not met. Please note that in order to account for type I error, FDA considers the first analysis of the data, provided in the original PMA, as the primary determinant of study success or failure. However,

given that the (b) (4) data are the most complete, and the outcomes were not different across datasets, these are the results presented in Table 11. For completeness, the primary effectiveness endpoint results from the other datasets are shown in Table 12.

Freedom from Primary Effectiveness Failure at 6 Months	DCB	PTA	Difference	P-value
(b) (4) (data lock August 7, 2018.)	196/266 (73.7%)	87/137 63.5%	10.2%	0.0273
(b) (4) (data lock January 22, 2019)	199/267 (74.5%)	87/137 (63.5%)	11.0%	0.0179
(b) (4) (data lock October 17, 2017)	201/269 (74.7%)	88/137 (64.2%)	10.5%	0.0222

Table 12: Primary Effectiveness Endpoint Results at 6 Months (Various Data Cut Offs)

7.1.10.5 Long-Term Effectiveness Results

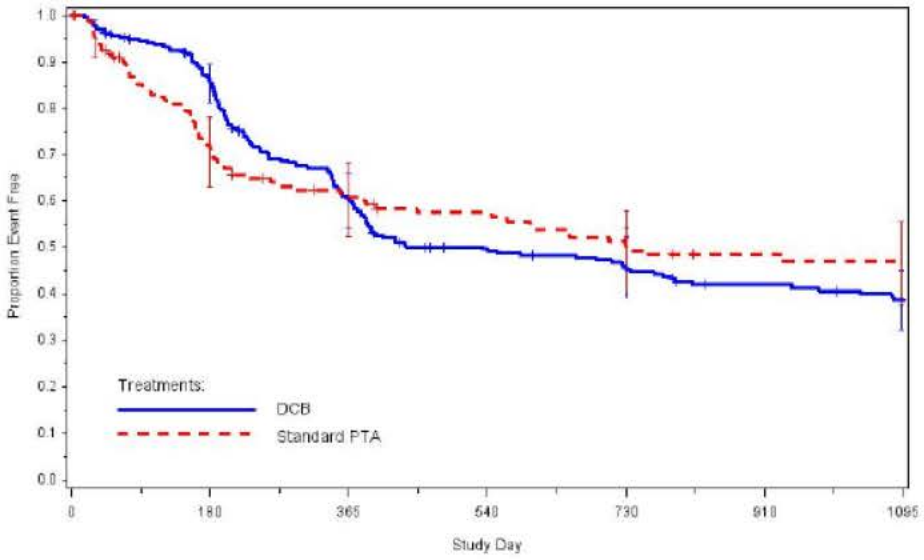
Primary effectiveness outcome of limb salvage and primary patency was evaluated through 36 months as both binary endpoints and through KM estimates. The primary effectiveness endpoint reported as a binary outcome through 36 months is presented in Table 13. As can be seen, while a 10.5% improvement for PTA was seen at 6 months, this improvement completely diminishes and the PTA arm is favored at 12 months, demonstrating a 5.8% improvement. The PTA arm continues to show improved outcomes vs. the Lutonix 014 DCB through 36 months.

Visit	DCB Pathways (N=323) Response Rate	PTA Pathways (N=184) Response Rate	Difference (95% CI)[1]
30 Days	283 / 294 (96.3%)	144 / 156 (92.3%)	4.0% (-1.0%, 7.9%)
6 Months	201 / 269 (74.7%)	88 / 137 (64.2%)	10.5% (0.3%, 18.7%)
12 Months	128 / 251 (51.0%)	75 / 132 (56.8%)	-5.8% (-17.0%, 5.2%)
24 Months	84 / 228 (36.8%)	54 / 123 (43.9%)	-7.1% (-17.5%, 4.5%)
36 Months	58 / 210 (27.6%)	29 / 100 (29.0%)	-1.4% (-11.6%, 11.3%)

[1] 95% CI based on mixed model with random subject effect. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 13: Primary Effectiveness Endpoint Binary Outcomes Through 36 Months

The Kaplan-Meier (KM) estimates for the primary effectiveness endpoint through 36 months are depicted in Figure 9. As the primary effectiveness endpoint was analyzed per flow pathway, the KM estimate assumes independence among flow pathways from the same patient, an assumption that may not hold. Thus, the KM estimate should be interpreted with caution. As can be seen, while the DCB arm initially showed a modest benefit at 6 months, the curves cross at 12 months and the PTA arm shows improved outcomes thereafter through 36 months.



	Flow Pathways Left				
Group	Day 1	Day 180	Day 365	Day 730	Day 1095
DCB	301	235	150	91	59
PTA	163	98	67	55	30

Figure 9: Primary Effectiveness Endpoint KM Estimates Through 36 Months

Results for individual components of the primary effectiveness endpoint can be found in the secondary endpoint section below.

FDA Comment: In the original version of the pivotal trial protocol, effectiveness was to be assessed at 12 months. Subsequently, Lutonix shortened the assessment time to 6 months. At 6 months, the Lutonix 014 DCB was associated with a 10.5% higher rate of a composite of limb salvage and primary patency vs. PTA. However, this difference was not statistically significant. Further, starting at 12 months, event rates numerically favored the PTA group. The panel will be asked to discuss the clinical value of the 10.5% improvement associated with the Lutonix DCB at 6 months (that did not reach statistical significance) and the absence of a durable clinical benefit starting at 12 months post-index procedure.

7.1.10.6 Subgroup Analyses of Primary Effectiveness Endpoint

Some subgroups were pre-specified, and others were included in protocol modifications, including geographic location, demographics, baseline information, lesion characteristics, and procedural characteristics. The results for select subgroup analyses, as shown in Table 14, demonstrate some differences in outcomes.

Please note that there were also some outcome differences in additional subgroups such as obesity, hypertension, and dyslipidemia, but differences were smaller in these groups or were difficult to interpret due to small sample sizes. Thus, these data were not considered to influence the overall study conclusions. For most subgroups, there was no evidence of a statistically significant interaction effect (p-value of >0.15).

		Subgroup Analysis Effectiveness Outcomes at 6 Months			
Factor	**Subgroup**	**DCB (N=269[1]) (95% CI)[2]**	**PTA (N=137[1]) (95% CI)[2]**	**Difference % CI[4]**	**Logistic Model Type[3] Test P-values**
Geographic Characteristics					
Geographic Location	US[5]	126 / 164 (76.8%) (69.6%, 83.1%)	56 / 87 (64.4%) (53.4%, 74.4%)	12.5% (0.5% - 24.4%)	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%)	7.4% (-8.4% - 23.3%)	
Site Location	Europe	53 / 78 (67.9%) (56.4%, 78.1%)	24 / 35 (68.6%) (50.7%, 83.1%)	-0.6% (-19.2% - 17.9%)	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%)	28.1% (-1.0% - 57.3%)	
	US[2]	126 / 164 (76.8%) (69.6%, 83.1%)	56 / 87 (64.4%) (53.4%, 74.4%)	12.5% (0.5% - 24.4%)	
Baseline Characteristics					
Age (Years)	<70 Years	72 / 99 (72.7%) (62.9%, 81.2%)	24 / 47 (51.1%) (36.1%, 65.9%)	21.7% (4.9% - 38.4%)	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%)	4.8% (-6.6% - 16.1%)	
Gender	Female	60 / 78 (76.9%) (66.0%, 85.7%)	29 / 42 (69.0%) (52.9%, 82.4%)	7.9% (-8.9% - 24.7%)	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%)	11.7% (0.1% - 23.3%)	
Rutherford Category	3	27 / 29 (93.1%) (77.2%, 99.2%)	12 / 12 (100.0%) (0.0%, 26.5%)	-6.9% (-16.1% - 2.3%)	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%)	12.5% (-2.5% - 27.6%)	
	5	87 / 136 (64.0%) (55.3%, 72.0%)	44 / 80 (55.0%) (43.5%, 66.2%)	9.0% (-4.6% - 22.5%)	
Target Lesion Characteristics					
Total Lesion Length (mm) [Core Lab]	≤ 50 mm	74 / 81 (91.4%) (83.0%, 96.5%)	31 / 41 (75.6%) (59.7%, 87.6%)	15.7% (1.2% - 30.2%)	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%)	6.4% (-10.9% - 23.6%)	

		Subgroup Analysis Effectiveness Outcomes at 6 Months			
Factor	**Subgroup**	**DCB (N=269[1]) (95% CI)[2]**	**PTA (N=137[1]) (95% CI)[2]**	**Difference % CI[4]**	**Logistic Model Type[3] Test P-values**
	>100 - ≤ 150 mm	21 / 36 (58.3%) (40.8%, 74.5%)	7 / 14 (50.0%) (23.0%, 77.0%)	8.3% (-22.4% - 39.1%)	
	>150 - ≤ 200 mm	15 / 27 (55.6%) (35.3%, 74.5%)	9 / 14 (64.3%) (35.1%, 87.2%)	-8.7% (-40.1% - 22.6%)	
	>200 - ≤ 250 mm	16 / 28 (57.1%) (37.2%, 75.5%)	1 / 8 (12.5%) (0.3%, 52.7%)	44.6% (15.3% - 74.0%)	
	>250 mm	26 / 37 (70.3%) (53.0%, 84.1%)	8 / 19 (42.1%) (20.3%, 66.5%)	28.2% (1.5% - 54.8%)	

[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] Subject as a random effect not included in the model
[4] 95% CI for difference based on observed data without adjustment for random effects
[5] For purposes of this report, the Canadian site will be combined with the U.S. sites in the reporting of U.S. vs. OUS results

Table 14: Primary Effectiveness Endpoint Subgroup Analyses at 6 Months

FDA Comment: The sponsor has conducted numerous supplementary analyses, including assessments of proximal segment flow pathways and excluding vessels with early recoil, as well as pre-specified subgroup analyses, to determine if a benefit was present in specific populations. Although some outcome differences were noted, FDA did not identify a subset of patients or lesions where the benefit of the Lutonix 014 DCB may be more favorable. The panel will be asked for their review of the benefit-risk profile of the device for specific subgroups.

7.1.10.7 Select Secondary Endpoint Results

7.1.10.7.1 Wound Healing

Investigational sites were required to have a wound care process/program to participate in this study and to perform follow-up wound care. Wound assessment was performed based on each site's wound care process/program. Wounds were assessed by the unblinded physicians performing treatment, and wound photographs did not undergo third-party independent review. Further, there was no uniform wound assessment or healing scale. Finally, with regard to wound photographs, no photo was required if a wound was deemed healed. The sponsor acknowledged that wound care data were inconsistently collected and reported.

A summary of the wound healing results, including presence of infection and gangrene, through 36 months is shown in Figures 10-12. The full wound care data are in Appendix F.

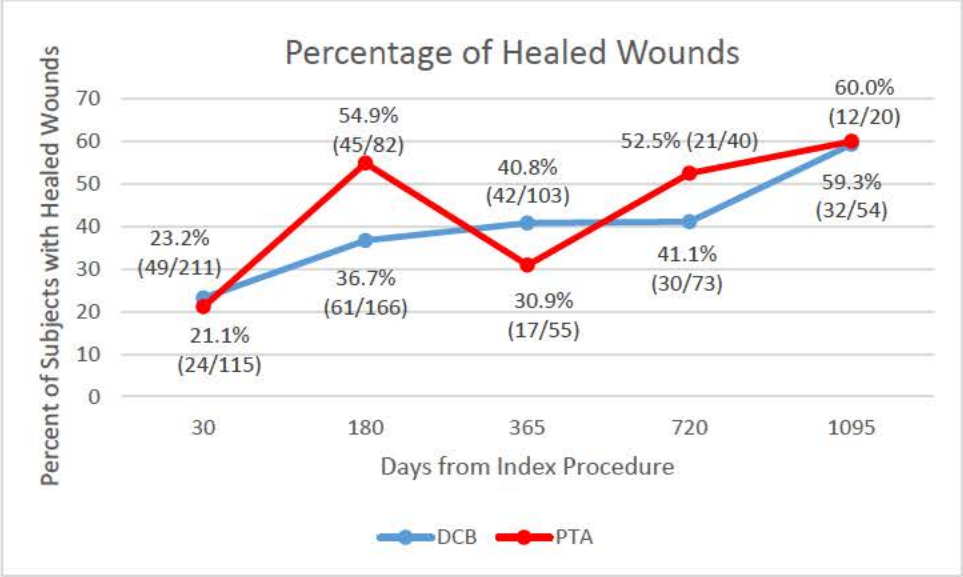


Figure 10: Percent of Subjects with Healed Wounds

FDA could not identify any consistent wound healing benefit of the Lutonix 014 DCB vs. PTA. For healed wounds from previous time points, there was a 18.2% difference in favor of PTA at 180 days followed by a 9.9% difference in favor of DCB at 365 days. Wound healing then favored PTA by a difference of 11.4% at 720 days and was essentially equal between treatment groups at 1095 days. Please note that in general, and especially at the later time points, the sample size for these evaluations were relatively low and, thus, the confidence intervals (not shown) were wide.

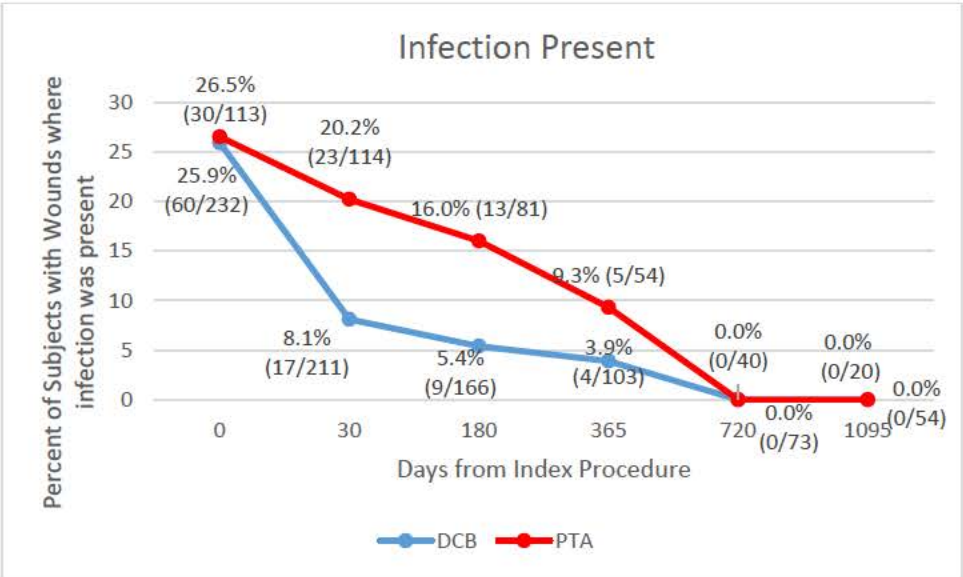


Figure 11: Percent of Subjects with Wounds where Infection was Present

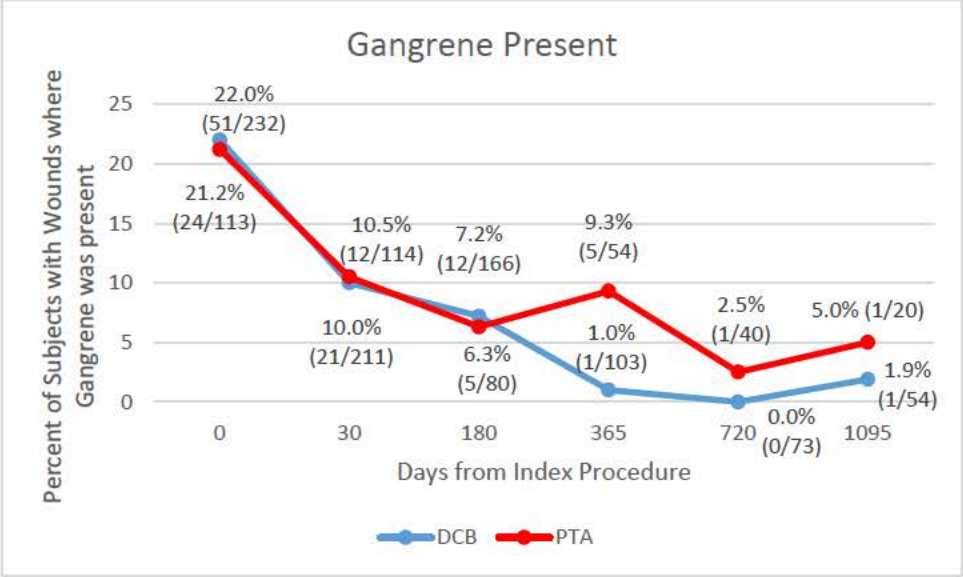


Figure 12: Percent of Subjects with Wounds where Gangrene was Present

There was generally a low incidence of infection and gangrene, so it is challenging to draw meaningful conclusions from this subset of wound data, and assessments were made by unblinded investigators. There was a numerically higher incidence of infection at 180 and 365 days, and of gangrene at 365 days in the PTA arm. Although the PTA arm demonstrated numerically higher infection and/or gangrene rates at these time points, the overall number of cases was small, improved outcomes were generally seen for both treatment groups over time, and infection and gangrene were minimal at the 36-month time point for both arms. It was initially suggested by the sponsor that this post hoc analysis of this subset correlates with clinical benefit of the DCB. However, FDA considers this post hoc analysis to be exploratory, and no statistical or clinical conclusions can be drawn from this small data subset.

FDA Comment: Wound assessments were performed based on each site's wound care program. The wounds were assessed by the unblinded physicians performing the treatment, photographs were not always taken or mandated, and these data did not undergo third-party independent review. Outcome differences between treatment groups were difficult to interpret due to missing data and low sample sizes. Due to limitations associated with the wound care analysis, FDA could not conclude that the Lutonix DCB provided a wound healing benefit vs. PTA. The panel will be asked to discuss the importance of this data and any clinically meaningful outcome differences between treatment groups.

7.1.10.7.2 Freedom from Major Amputation

The major amputation rate was low for both treatment groups through 36 months. KM estimates for the secondary endpoint of freedom from major amputation through 36 months are shown in Figure 13. The major amputation rate was similar between treatment groups.

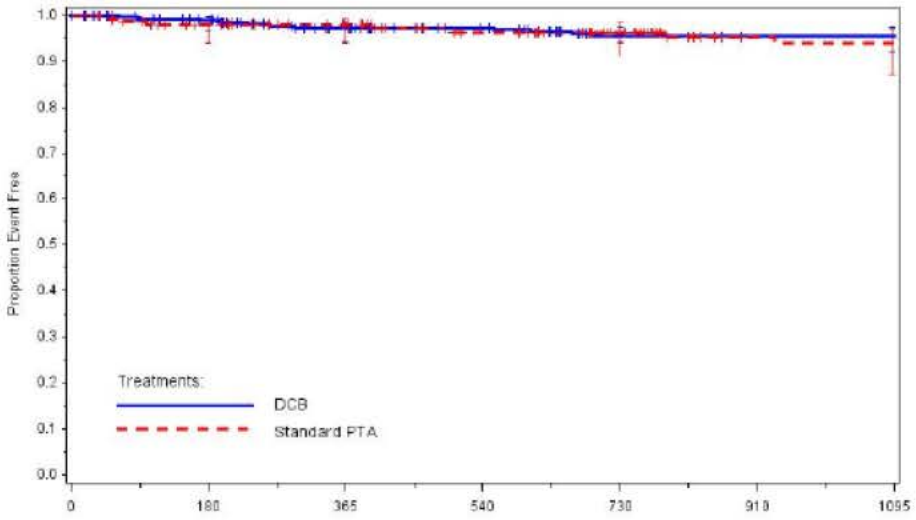


Figure 13: Freedom from Major Amputation KM Estimates Through 36 months

The freedom from major amputation reported as a binary outcome through 36 months is presented in Table 15.

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

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

[2] Exact binomial confidence interval. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 15: Freedom from Major Amputation Binary Outcomes Through 36 Months

7.1.10.7.3 Unplanned Minor Amputations

In the Lutonix BTK trial, unplanned minor amputation was defined as amputation that was below the ankle. The unplanned minor amputation rate was 14.8% for the DCB group vs 18.5% for the PTA group at 12 months and continued to favor DCB at 36 months (24.2% DCB vs. 36.1% PTA, respectively). KM estimates for unplanned minor amputations through 36 months are shown in Figure 14.

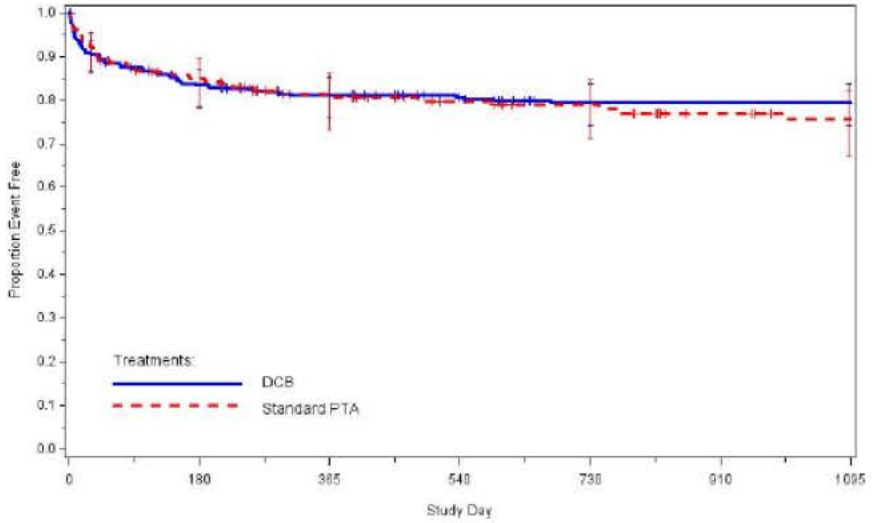


Figure 14: Freedom from Unplanned Minor Amputation KM Estimates Through 36 Months

Unplanned minor amputation rates reported as a binary outcome through 36 months is presented in Table 16.

Visit	DCB Response Rate	95% CI[1]	PTA Response Rate	95% CI[1]	Difference (95% CI)[1]
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%)

[1] 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 16: Unplanned Minor Amputation Binary Outcomes Through 36 months

FDA Comment: The panel will be asked to discuss the strengths and limitations of the observed numerically lower rates of unplanned minor amputations in the Lutonix DCB group through 36 months in view of overlap in the 95% CIs, the KM curves beginning to diverge only after 730 days, and a limited sample size at these later time points.

7.1.10.7.4 Freedom from Clinically-Driven Target Lesion Revascularization (CD-TLR) and Cumulative TLR

Analyses were conducted for freedom from CD-TLR rate as well as cumulative TLR rates. Unlike the binary and KM analyses for TLR, Lutonix has indicated that the cumulative TLR rate accounts for patients who may have had more than one intervention and may be an indication of the overall burden of interventions.

There was an 8.2% benefit for freedom from CD-TLR for the Lutonix DCB group at 6 months, which was no longer observed at 12 months, and rates were similar thereafter (Figure 15).

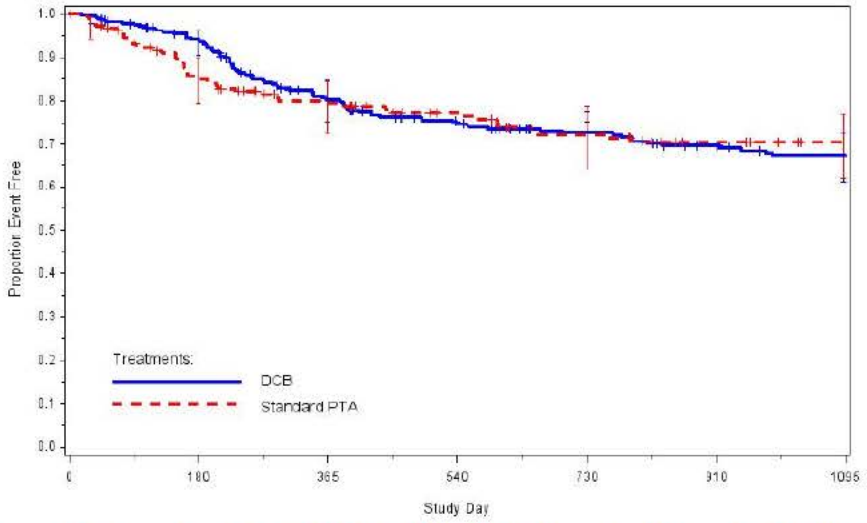


Figure 15: Freedom from CD-TLR KM Estimates Through 36 Months

Freedom from CD-TLR reported as a binary outcome through 36 months is presented in Table 17.

Visit	DCB (N=323) Response Rate	PTA (N=184) Response Rate	Difference (95% CI)[1]
30 Days	317/321 (98.8%)	179/184 (97.3%)	1.5% (-2.0%, 4.1%)
6 Months	275/303 (90.8%)	142/172 (82.6%)	8.2% (1.5%, 13.3%)
12 Months	216/281 (76.9%)	116/152 (76.3%)	0.6% (-9.8%, 8.5%)
24 Months	169/249 (67.9%)	85/130 (65.4%)	2.5% (-9.2%, 12.4%)
36 Months	115/203 (56.7%)	52/99 (52.5%)	4.1% (-9.4%, 16.8%)

[1] 95% CI based on mixed model with random subject effect. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 17: Freedom from CD-TLR Binary Outcomes Through 36 Months

The sponsor conducted a post hoc analysis of cumulative TLRs and TLR/year, which took into account patients undergoing more than one repeat revascularization. This analysis included the total number of TLRs by patient at each time point and was reported as the number of TLRs per patient per year (Table 18).

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

Table 18:Cumulative TLRs and TLR per Year

Similar to the other effectiveness analyses, although the 6-month time point analysis demonstrated a benefit in the number of TLRs per patient per year (0.24 in the DCB arm vs. 0.42 in the PTA arm), rates became essentially equivalent thereafter. Given that the 12-month TLR data available for all evaluable subjects demonstrate no added benefit for the Lutonix 014 DCB vs. PTA, the clinical valve of a lower rate of TLRs/year in the DCB group at 6-months is limited.

FDA Comment: Reduced TLR rates are clinically meaningful to patients. However, a durable benefit was not observed. The panel will be asked to discuss the clinical value of lower CD-TLR and cumulative TLR rate at 6 months without a sustained benefit vs. PTA thereafter.

7.1.10.7.5 Change in Hemodynamic Outcomes (ABI and TBI)

Figures 16 and 17 show brachial index (ABI) and toe brachial index (TBI) changes from baseline. In both groups, an improvement in ABI and TBI was present at 30 days. However, ABI improvements steadily decreased thereafter in both treatment groups through 1095 days. For TBI, the positive change decreased after 30 days and increased at 720 days in the PTA group and at 1095 days in the Lutonix DCB group. The full hemodynamic data are in Appendix G.

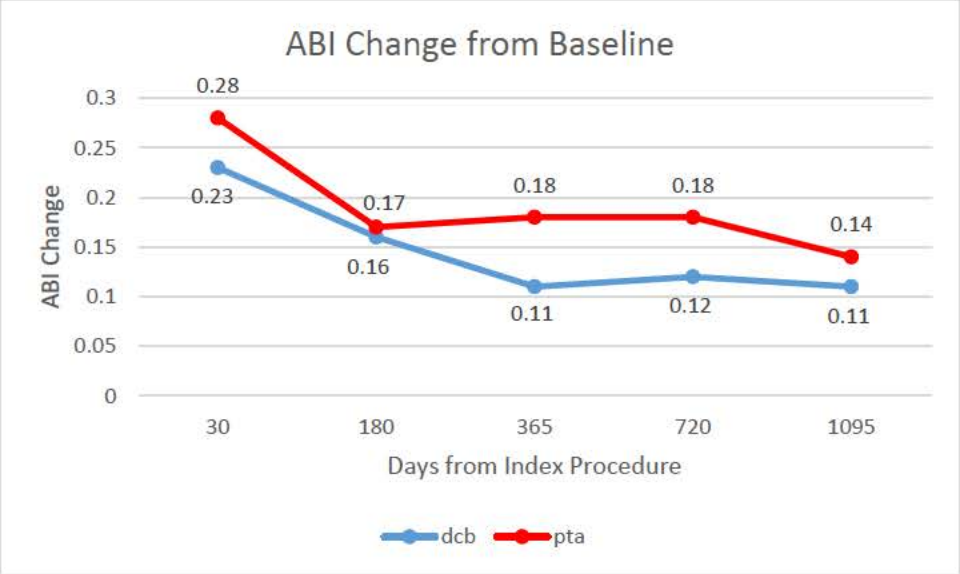


Figure 16: ABI Improvement Compared to Baseline

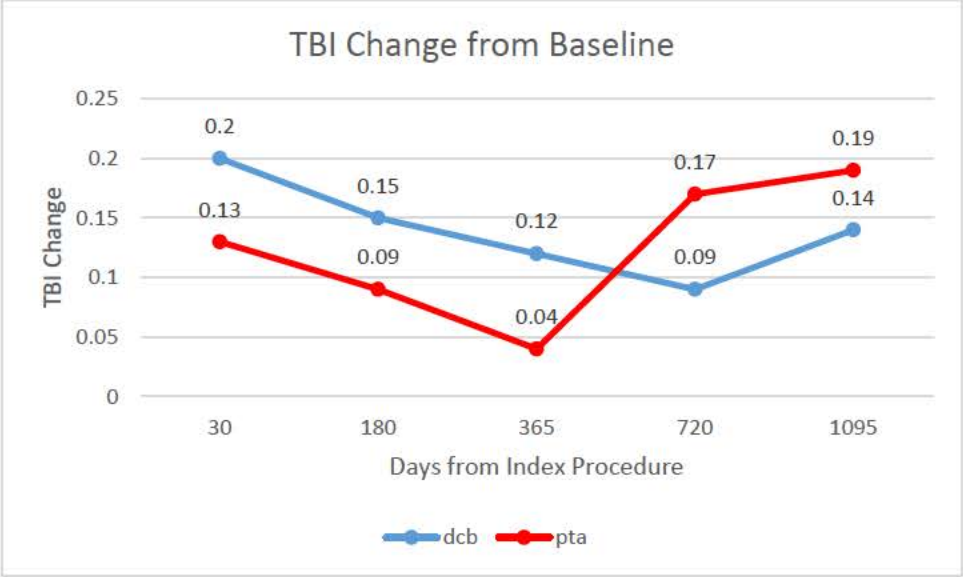


Figure 17: TBI Improvement Compared to Baseline

7.1.10.7.6 Rutherford Classification

Figure 18 shows Rutherford classification outcomes through 36 months. Both treatment groups maintained an improvement of 2 to 3 classifications through 36 months. The full Rutherford Classification data are in Appendix H.

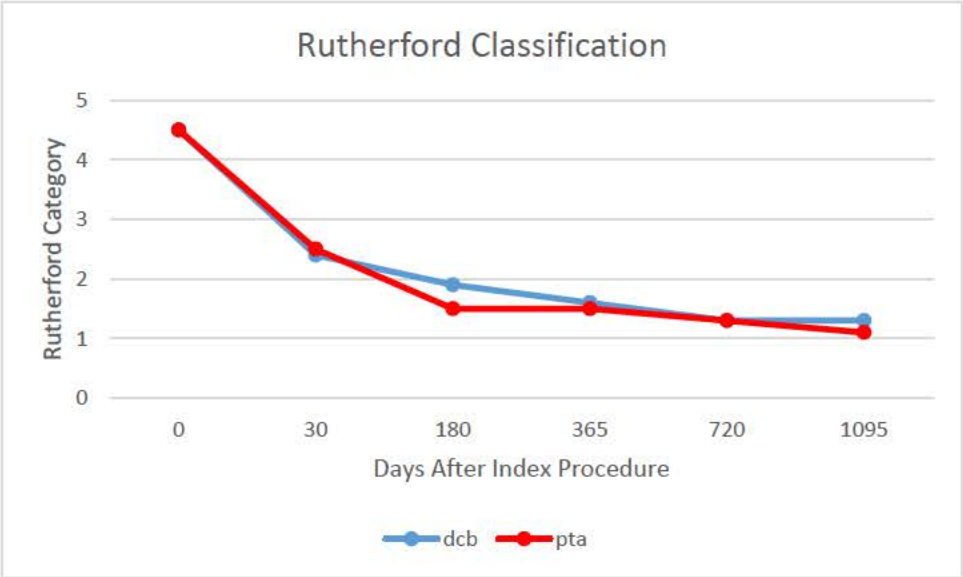


Figure 18: Rutherford Classification Through 36 Months

7.1.10.7.7 Quality of Life and Walking Impairment Questionnaires

Quality of life (QoL) measures utilizing the EQ-5D questionnaire and walking impairments questionnaire (WIQ) evaluated treatment effects on pain and mobility. The Lutonix 014 DCB was associated with no added QoL benefit vs. PTA arms (Table 19).

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

Table 19: EQ-5D and WIQ Results Through 36 Months

7.1.10.7.8 All-Cause Mortality

The KM estimates and binary outcomes for all-cause mortality through 36 months are shown in Figure 19 and Table 20. The mortality rates were similar between both groups through 36 months, although approximately 1/3 of the data are missing or are yet to be evaluated at the 36-month time point.

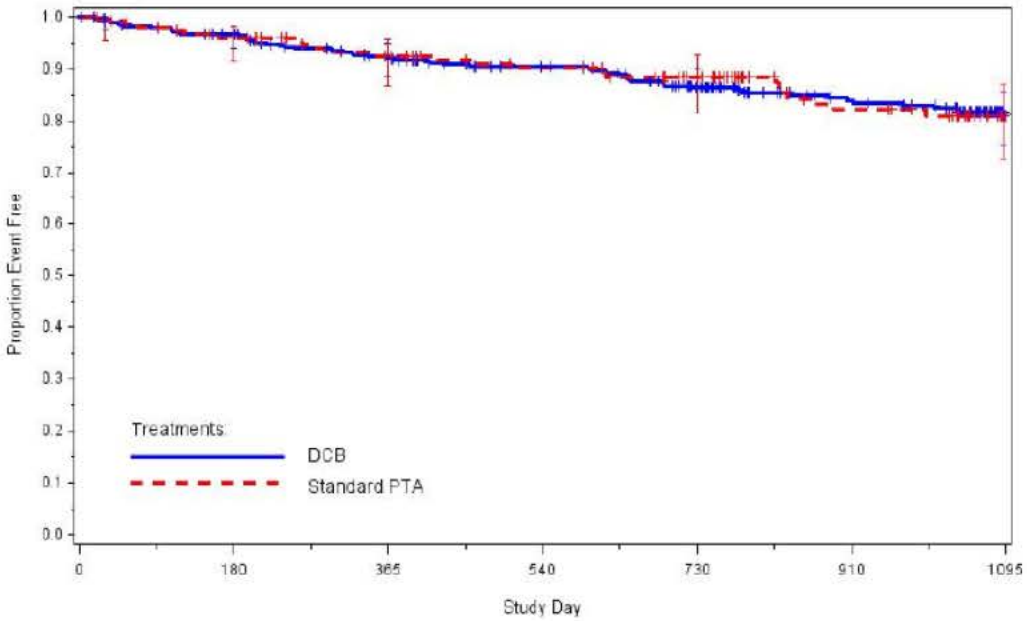


Figure 19: All-Cause Mortality KM estimates Through 3 Years

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

[1] 95% CI for individual rates based on exact binomial interval and risk difference based on asymptotic variance. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 20: All-Cause Death Binary Outcomes Through 36 Months

7.1.11 Study Strengths and Limitations

The Lutonix BTK IDE Pivotal study was a large, multi-center, prospective, randomized study.

Aside from failing to meet the primary effectiveness endpoint, FDA has identified, and the sponsor acknowledges, the following limitations of this study with regard to data collection and analysis:

- Early enrollment termination prior to enrolling the required sample size;
- Significant protocol modifications during execution of the clinical study;
- Multiple looks at the data after data unblinding and PMA submission;
- High rate of missing primary effectiveness endpoint data; and
- Lack of evaluable wound healing data.

FDA believes that these limitations introduce challenges in the interpretation of the study data.

FDA Comment: The Lutonix DCB failed to meet its primary effectiveness endpoint at 6 months (although a 10.5% improvement was noted vs. PTA). However, a longer-term benefit was not observed, and the primary effectiveness endpoint rates numerically favored the PTA group at 12 months and beyond. For secondary endpoints, a benefit of the Lutonix 014 DCB vs. PTA was not demonstrated for wound healing, major amputation, ABI, TBI or Rutherford Classification. Cumulative TLR rates to 6-months and unplanned minor amputations appeared to favor the DCB group. The panel will be asked to discuss whether the pivotal trial results support reasonable assurance of Lutonix DCB safety and effectiveness, given totality of the data and considering study limitations.

7.2 Adjunctive Data Provided in the PMA

The following data sets were provided in the original PMA or an amendment (b) (4) to the PMA in April 2020 in response to a NOAP letter:

- Global BTK Real-World Registry
- Pooled analysis of the BTK IDE Pivotal Trial and the Global BTK Real-World Registry
- Real-world data from the Society of Vascular Surgeon (SVS) Vascular Quality Initiative (VQI) Database

- Japan Hemodialysis (HD) RCT
- Optimize Study
- Literature sources from single center studies

Below is FDA's summary of the adjunctive datasets, which includes study design, results, and study strengths and limitations. Please note that the full datasets, including statistical code and associated files, were not provided to FDA for these analyses other than the Global Registry. These analyses were provided to FDA in summary form. Given the many study limitations, FDA did request or review the patient-level data and statistical codes. Thus, these results have not been fully confirmed.

7.2.1 Global BTK Real-World Registry

7.2.1.1 Study Design

This is a multicenter, single arm real-world registry to evaluate the safety and assess the clinical use outcomes of the Lutonix DCB for treatment of BTK arteries in a heterogeneous patient population in real-world clinical practice. A total of 371 subjects were enrolled at 26 sites across 11 countries. The primary safety endpoint was a composite all-cause death, above-ankle amputation, or major re-intervention at 30 days. The primary effectiveness endpoint was freedom from TLR.

7.2.1.2 Study Results

As shown in Table 21, the composite all-cause death, above-ankle amputation, or major re-intervention at 30 days was 98.3% (similar to the outcomes of the pivotal trial).

Measure	BTK Registry (N=371)	
	Freedom from primary safety events % (n/N)	95% CI[1]
Primary Safety Endpoint	98.3% (354/360)	96.4%, 99.4%

[1] Exact binomial confidence interval

Table 21: Primary Safety Endpoint Results (Freedom from BTK MALE + POD at 30 days)

The freedom from TLR rate is shown in Table 22 (primary timepoint) and Table 23 (longer-term timepoints). Results were generally similar to those observed in the pivotal clinical trial.

Measure	BTK Registry (N=371)	
	TLR-Free % (n/N)	95% CI[1]
6-Month Primary Endpoint	90.0% (289/321)	86.2%, 93.1%

[1] Exact binomial confidence interval

Table 22: Primary Effectiveness Endpoint Results (Freedom from TLR at 6 months)

Measure	(b) (6) BTK Registry (N=371)	
	Success % (n/N)	95% CI[1]
TLR-Free at 12 Months	79.9% (239/299)	74.9%, 84.3%
TLR-Free at 24 Months	74.2% (187/252)	68.3%, 79.5%

[1] Exact binomial confidence interval. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table 23: Secondary Effectiveness Endpoint (Freedom from TLR through 24 months)

7.2.1.3 Study Strengths and Limitations

This study enrolled a relatively large sample size of real-world subjects. However, the study did not include an active control, included limited objective evaluations, and follow-up was only evaluated to 24 months. FDA did not find that the data provided any additional evidence beyond what was included in the pivotal dataset.

7.2.2 Pooled analysis of the BTK IDE Pivotal Trial and Global BTK Real-World Registry

7.2.2.1 Study Design

The sponsor used a propensity score matching method to compare the DCB data pooled from the BTK IDE Trial and BTK Global Registry to the PTA data from the BTK IDE Trial at 6-, 12-, and 24-months. The primary safety endpoint was a composite of all-cause death, above-ankle amputation, or major re-intervention at 30 days. The primary effectiveness endpoint was freedom from TLR at 6 months.

7.2.2.2 Study Results

When using a propensity score-matched control group from the pivotal trial, the effectiveness results of the pooled DCB arm demonstrate a 17.7% benefit in freedom from TLR at 6 months and 5.8% improvement at 12 months, although there was a 3% improvement for the control arm at 24 months. See Table 24 and Figure 20 for the binary and KM estimates.

	LS Means Estimates	
Time Point	DCB (95% CI)	PTA (95% CI)
30 Days	95.7% (93.7%, 97.0%)	86.3% (79.8%, 91.0%)
6 Months	76.6% (72.9%, 79.9%)	58.9% (50.5%, 66.9%)
12 Months	58.1% (53.8%, 62.2%)	52.3% (43.8%, 60.7%)
24 Months	36.8% (32.1%, 41.7%)	39.8% (31.7%, 48.6%)

Table 24: Primary Effectiveness Success Binary Outcomes with Overall IPW

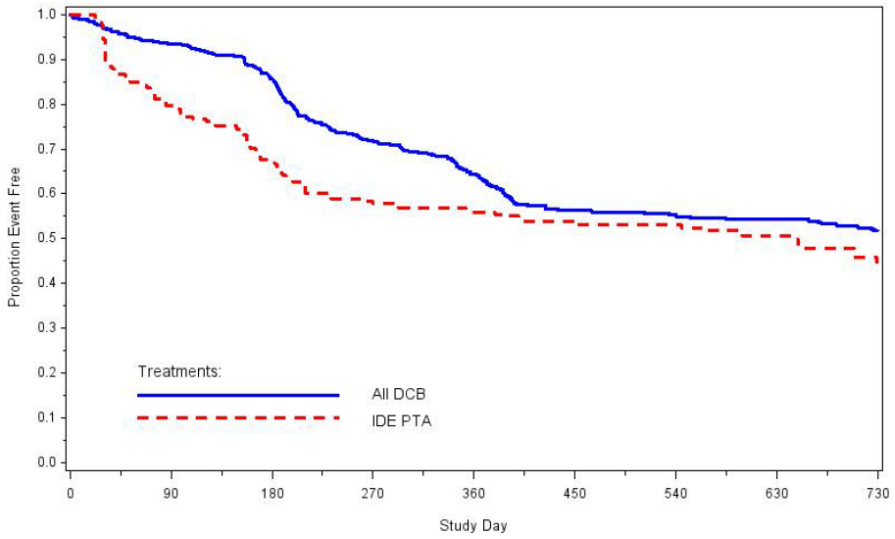


Figure 20: Freedom from TLR KM Estimate Through 2 Years

7.2.2.3 Study Strengths and Limitations

This study included a relatively large sample size of real-world subjects and provided a matched comparator for the single-arm registry. However, while the sponsor indicated that the SAP was pre-specified, it was submitted later in the PMA review cycle (after the NOAP letter was issued), and FDA did not receive the actual SAP for review prior to the analysis. There were other limitations including a lack of clarity for the propensity score methodology used and unresolved issues related to the propensity score analysis results, including lack of apparent comparability between groups and the potential of overfitting and bias due to only using patients with non-missing data.

7.2.3 Real-World Data from the Society of Vascular Surgeon (SVS) Vascular Quality Initiative (VQI) Database

7.2.3.1 Study Design

A total of 167 consecutive Lutonix DCB subjects and 397 consecutive PTA propensity adjusted subjects were evaluated. This data comes from real-world and off-label use of the SFA product that is approved in the US utilizing the VQI Peripheral Vascular Reintervention database. The primary endpoint assessment was freedom from TLR at 6 months.

7.2.3.2 Study Results

The freedom from TLR by KM estimate at 6 months was 96.1% for Lutonix DCB and 95.2% for the PTA arm (p=0.332, Table 25). The survival curve for the primary performance measure is shown below in Figure 21.

Day	Lutonix DCB				Control			
	Estimate (95% CI)	Counts			Estimate (95% CI)	Counts		
		Failed	Censored	Left		Failed	Censored	Left
0	100.0% (100.0%, 100.0%)	0.0	0.0	167.0	100.0% (100.0%, 100.0%)	0.0	0.0	397.0
30	98.9% (94.7%, 99.8%)	1.9	1.4	163.8	97.2% (94.9%, 98.5%)	11.0	13.5	372.5
180	96.1% (91.0%, 98.4%)	6.2	14.1	146.7	95.2% (92.5%, 97.0%)	18.2	41.1	337.6
365	91.8% (85.1%, 95.6%)	11.9	70.7	84.4	88.6% (84.3%, 91.7%)	38.3	171.4	187.4

Table 25: TLR Free Survival KM Estimate Through 365 Days

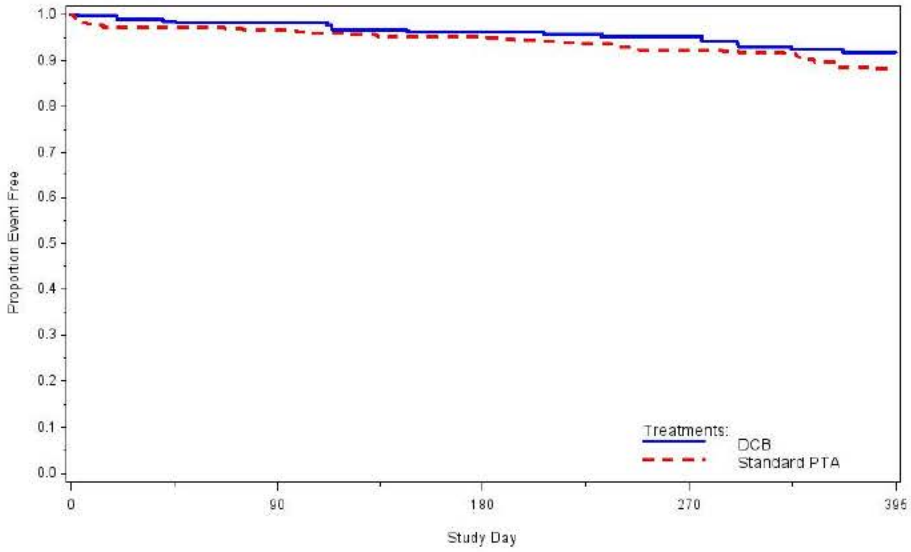


Figure 21: TLR Free Survival KM Estimate Through 365 days

7.2.3.3 Study Strengths and Limitations

This study included a relatively large sample size of real-world subjects. The SAP was submitted after the NOAP letter was issued, and the data were not known to the sponsor. The sponsor included a propensity-matched comparator. However, these data are limited to off-label use of the 4 mm size only, and outcomes may not be similar for the smaller sized vessels. Further, although the analysis had a predetermined SAP, there was a post hoc change in the primary analysis method from a propensity-matched stratification to inverse probability weighting (IPW) event-free survival estimates. Other limitations included questions and ambiguity for how the control patients were selected, the design process might not have been entirely outcome-free, concerns regarding missing data and the imputation method, and an unbalanced distribution of subjects within the propensity score strata. Finally, a clinically meaningful effect size was not observed.

7.2.4 Japan HD RCT

7.2.4.1 Study Design

This was a randomized, prospective study evaluating hemodialysis (HD) patients BTK and included 19 DCB subjects and 17 PTA subjects. The study inclusion/exclusion criteria were the same as the Lutonix BTK IDE Pivotal trial, except for enrollment limited to HD subjects, which were excluded from the IDE trial. The primary safety endpoint was freedom from the composite of all-cause death, above-ankle amputation, or major reinterventions of the index limb at 30 days. The primary effectiveness endpoint was composite of limb salvage and primary patency at 6 months.

7.2.4.2 Study Results

The primary safety and effectiveness results for this study are shown in Table 26 and Table 27. A 31.1% difference in favor of the DCB was observed for the primary effectiveness outcome, although the very small sample sizes limits the interpretability of these results.

	DCB (N=19) n/N (%) (95% CI)	**PTA (N=17) n/N (%) (95% CI)**	**Difference % (95% CI)**
Free from Key Safety Events	19/19 (100.0%) (82.4%, 100.0%)	16/17 (94.1%) (71.3%, 99.9%)	5.9% (-13.5%, 29.5%)
Key Safety Events			
Death ≤ Day 30	0	1	
Above Ankle Amputation ≤ Day 30	0	0	
Major Re-Intervention ≤ Day 30	0	0	

Table 26: Key Safety Endpoint Results (Composite of Freedom from BTK MALE + POD through 30 Days)

	DCB (N=23) n/N (%) (95% CI)	**PTA (N=21) n/N (%) (95% CI)**	**Difference % (95% CI)**
Free from Composite Efficacy Events at 6 Months	14/20 (70.0%) (45.7%, 88.1%)	7/18 (38.9%) (17.3%, 64.3%)	31.1% (-3.1%, 59.4%)
Key Efficacy Events			
Major Amputation ≤ Day 210	0	0	
Clinically Driven TLR ≤ Day 210	2	5	
Primary Patency Failure ≤ Day 210	6	11	

CI = confidence interval; DCB = Lutonix drug coated balloon (test); PTA = percutaneous transluminal angioplasty (control); TLR = target lesion revascularization

Note 1: Composite key efficacy events include limb salvage, clinically driven target lesion re-intervention or target Lesion occlusion on or before 6-month visit or Day 210

Note 2: Primary patency failure include clinically-driven TLR and target lesion occlusion.

Note 3: Denominator is the number of evaluable flow pathways.

Note 4: 95% CI is estimated by the exact binomial method.

Note 5: One composite efficacy event may be failed in multiple categories Source: Table 14.2.3.1.1

Table 27: Key Effectiveness Endpoint (Composite of Limb Salvage and Primary Patency through 6 Months)

7.2.4.3 Study Strengths and Limitations

As hemodialysis patients were excluded from the IDE due to shorter life expectancy, this RCT provides device usage data in a high-risk patient group. Additionally, this study otherwise used the same inclusion and exclusion criteria as pivotal study and was prospective and randomized. However, this dataset is limited by its small sample size of 36 patients (19 DCB and 17 PTA subjects). Thus, it is unclear if any meaningful conclusions can be drawn from this study.

7.2.5 Literature Sources

Three single center, retrospective studies were summarized. The peer-reviewed publications provide additional safety and performance information on 284 patients treated with the LTX DCB. A summary of these literature sources is provided in Table 28.

	Number of Patients	Patient Demographic	Follow-Up	Safety	Freedom from TLR	Other
Micari et al. Ital J Vasc Endovasc. 2016;23:1-4	55 – Retrospective; Approximately 127 devices	Rutherford class > 3; 70% total occlusions	Median follow- up: 182 days	96.4% freedom from amputation; No deaths were reported	TVR 78.2% 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.	208 – Retrospective: 510 devices	61.4% CLI patients, 63.6% total occlusion lesions	9-month median follow- up	Freedom from death or major amputation 93.4% 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 category by 12 months
Palena LM, et al. Cardiovasc Revasc Med. 2018, 19:83-87.	21 – Retrospective: Approximately 46 devices	95.2% Rutherford class 5-6; 100% Diabetic	Mean follow up of 356.5 days (approximatel y 12-months)	MALE 0%, no major amputations, Limb Salvage 100%, 2 deaths	CD-TLR 83.8% 390 days	Ulcer size/depth reduction 19/21 (90.4%); 87.5% demonstrated a 1 category shift in Rutherford scores at 12 months

Table 28: Literature Citations from Single Center Studies for Use of the Lutonix DCB

7.2.5.1 Summary

Micari et al. [7] reviewed the results of 55 patients treated with the Lutonix 0.014 DCB for obstructive below-knee arterial lesions and symptoms of critical limb ischemia (Rutherford 4-6). They collected retrospective, observational data on death, amputation, reintervention, and overall clinical outcomes. The median follow-up was 182 days (range: 55-398 days) with 72% of patients having greater than 6- month follow up. Twelve patients (21.8%) underwent target vessel reintervention (TVR), resulting in a freedom from TVR of 78.2%. There were two

amputations (3.6%), both in Rutherford 6 patients. Wound healing information was available on 54 of the 55 patients (98.2%). The authors noted a "marked reduction" in the size and wound depth, or complete wound healing, in 89.1% of patients.

Steiner et al. [8] retrospectively reviewed 208 patients treated with the Lutonix 0.014 DCB for symptomatic (Rutherford ≥ 3), below-knee peripheral arterial disease. One hundred thirty-five patients (61.4%) had symptoms of CLI. Follow-up outcomes included death, amputation, change in Rutherford category, number of reinterventions, and wound healing. Overall, 220 limbs were treated in the 208 patients using 510 Lutonix DCBs. The median follow-up was 9 months (range: 1-19 months). The TLR rate was 15.9% (17.8% for patients with CLI, and 12.9% for claudicants); the mean time to first TLR was 8.1 ± 4.7 months. Nine major, above-ankle amputations (4.1%) were performed, six in Rutherford category 5 patients and three in category 6 patients); the major amputation rate in CLI patients was 6.7%.

Palena et al. [9] reported retrospective, chart-review outcomes after using the Lutonix 0.014 DCB in 21 diabetic patients with CLI who underwent TLR of previously treated infrapopliteal and inframalleolar artery obstructive lesions. Outcome measures at follow-up included CD-TLR, MALE, MACE, major amputation, and amputation-free survival. The mean study follow-up was 356.5 ± 159.2 days (range: 87–639 days) with 90.4% of patients having reached 12-month follow up. The estimated freedom from CD-TLR (Kaplan-Meier analysis) was 83.8% at 390 days. At 12-months, complete wound healing or a reduction in ulcer size and depth, was reported in 19 patients (90.4%). Of those patients, 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. The estimated rates of MALE, MACE, and major amputation (Kaplan-Meier analysis) were 0%, 10%, and 0% at the mean long-term follow up of approximately 12 months. In addition, amputation-free survival was 90%, limb salvage was 100%, and overall survival was 90%.

7.2.5.2 Strengths and Limitations

While these studies are informative, they were all single-center, small, retrospective analyses with shorter-term follow-up.

FDA Comment: While some of the data sources were prospectively designed, others were retrospective. FDA notes numerous limitations to these studies, as described above. Taken together, with the results of the pivotal IDE study and adjunctive datasets, the panel will be asked to comment on whether the totality of the data demonstrate a reasonable assurance of safety and effectiveness for treating below-the-knee vascular disease with the Lutonix 014 DCB.

7.3 Potential for Post Approval Study (PAS) Collection

Lutonix has proposed a PAS utilizing continued follow up of their IDE and Global Registry cohorts. A summary of the proposal is described below:

"Given the extensive clinical history of the Lutonix DCBs across the various vascular anatomy ... we believe that continued follow-up of the currently enrolled BTK subjects in the Lutonix BTK IDE Trial (n=287 DCB patients, pivotal IDE study) and the Lutonix Global BTK Real-World registry (n=371 DCB patients, Global Registry) present significant number (n=658) of clinical results specific to the BTK anatomy and represents the least burdensome method to assess post-market performance and experience with the LUTONIX 014 DCB catheter."

FDA agrees that continued follow-up of these subjects is appropriate. If the PMA is approved, FDA could also require a PAS that enrolls new subjects, and study design options include a randomized trial or a single arm study.

Though not formally proposed to FDA, in a pre-submission discussion, the sponsor has noted that:

To further support the safety profile of the LTX 014, BD will extend follow-up of the IDE patients for 5 years for vital status and report to FDA through the IDE annual reports. In addition, BD is committed to the evaluation of this product in an effort to provide the healthcare community with a product to treat the challenging CLI patient with robust clinical data and therefore proposes a post approval study using VQI to prospectively collect clinical data on the effectiveness of the LTX 014 through 1 year and vital status through 5 years.

It appears that Lutonix is proposing a single-arm study with a 12-month primary endpoint of TLR to further evaluate the effectiveness of their device. If questions remain regarding improved outcomes to PTA, which is the primary question FDA has for the panel, it is unclear if a single arm study would be able to answer this question. However, it may be difficult to complete a new enrollment RCT PAS, as enrollment was challenging in the pivotal IDE cohort. Further, this sponsor has cited multiple challenges (i.e., IRB hesitant to approve randomization to POBA, patients' reluctance to consent to randomization due to the availability of DCB option) in completing a new enrollment RCT PAS in this device space in the past [10-11]. FDA believes the same issues and reasoning would apply for the proposed device/indication, if approved. Thus, a shift from pre-market to post-market data collection may not be reasonable for this device.

FDA Comment: The panel will be asked to comment on the remaining clinical questions for this device given the currently available data. If additional data are needed to address outstanding questions regarding the Lutonix DCB, the panel will be asked to comment on the design and feasibility of a new enrollment PAS. Please note that PAS studies are not intended to provide initial support for reasonable assurance of safety and effectiveness, as that determination must be established prior to device approval.

8 Benefit-Risk Discussion

To date, FDA has not noted any safety concerns associated with the use of the Lutonix 014 DCB that would be expected to exceed those of current standard of care with non-drug containing devices. While a safety signal for increased mortality was noted for use of paclitaxel-coated devices in the superficial femoral artery [12-14], this trend was not evident in the current study in the BTK anatomy. However, long-term data are limited. Nevertheless, uncertainty remains, and

outstanding concerns associated with paclitaxel-coated devices should be considered, especially if no compelling benefit is identified.

A modest benefit in regard to the primary effectiveness endpoint compared to PTA can be seen at 6 months but a reversed outcome was noted at 12 months and beyond. Both pre-specified and post hoc secondary endpoint effectiveness evaluations did not demonstrate a clear benefit of the Lutonix 014 DCB vs. PTA.

Overall, the study was terminated early and did not meet the pre-specified hypothesis test success criteria. It remains unclear whether the effectiveness differences at 6 months are clinically meaningful, and that the benefits of the paclitaxel-coated Lutonix 014 DCB outweigh the risks compared to treatment with an uncoated balloon for treatment of atherosclerotic lesions below the knee.

9 Conclusions

The Lutonix BTK IDE Pivotal Study was a prospective, multicenter, 2:1 randomized, controlled trial comparing the Lutonix 014 DCB (test group) vs. PTA (control group) for treatment of BTK arteries. The study was terminated after enrolling 507 of the pre-specified 840 vessels.

The Lutonix 014 DCB met the non-inferiority primary safety endpoint at 30 days. The primary effectiveness endpoint results did not reach statistical significance, although a 10.5% improvement was noted at 6 months. However, a durable benefit was not seen at later timepoints, with the KM curves converging at 12 months and primary effectiveness event rates favoring the PTA group thereafter. For secondary endpoints, a benefit of the Lutonix 014 DCB vs. PTA was not demonstrated for wound healing, major amputation, ABI, TBI or Rutherford Classification. Cumulative TLR rates at 6 months and unplanned minor amputations at later time points appeared to favor the DCB group.

Additional data were provided from registries and real-world data sources. However, there were numerous limitations to these studies.

Overall, the limitations associated with the primary and supplementary data make it challenging to draw conclusions regarding the safety and effectiveness of this device.

10 References

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11 Appendices

A. IDE Modifications Summary
B. Subject and Flow Pathway Accountability Tables
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D. Primary Patency with Exclusion of Early Mechanical Recoil Data
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A. IDE Modifications Summary

IDE Submission	Description	Status
(b) (4)	Original IDE and Amendment	Conditional Approval: 04/18/13
	Response to COAs – Set 1	Approved: 05/30/13
	Change in correspondence	Accepted: 05/09/13
	Minor change in EtO residual testing	Accepted: 06/07/13
	Response to COAs – Set 2	Approved: 05/30/13
	Response to COAs – Set 3	Approved: 06/10/13
	Response to FDA questions	Approved: 07/02/13
	Extension request	Granted: 07/02/13
	Response to FDA questions	Approved: 07/29/13
	Response to COAs – Set 4	Approved: 08/08/13
	Request for 9-month shelf-life	Approved: 09/18/13
	Protocol change (Rev 3) – Eligibility criteria changes	Approved: 12/06/13
	Request for 12-month shelf-life	Approved: 12/13/13
	Protocol change (Rev 4) – Eligibility criteria changes	Approved: 02/06/14
	Protocol change (Rev 5) - Eligibility criteria changes	Approved: 06/11/14
	Protocol change (Rev 6) – Ischemic Ulcerations	Accepted: 07/24/14
	Change in correspondence	Accepted: 10/20/14
	Request for 24-month shelf-life	Disapproved: 12/05/14
	Request for 18- month shelf-life	Accepted: 01/12/15
	Protocol change (Rev 7) – Hemodynamic criteria	Approved: 03/13/15
	Request for 24-month shelf-life	Approved: 04/09/15
	Addition of 150 mm balloon length	Approved: 12/08/15
	Change in correspondence	Accepted: 09/22/15
	Protocol change (Rev 8) – Enhance enrollment	Approved: 12/21/15
	Protocol change (Rev 9) – Bayesian SAP	Approved: 03/09/16
	3-year shelf-life extension	Approved: 04/29/16
	Protocol change (Rev 10) – 6m endpoint	Approved: 07/19/16
	Protocol change (Rev 11) – update of SAP	Approved: 09/21/16
	Statistical Analysis Plan (Rev 01)	Approved: 11/14/16
	Protocol change (Rev 12) – secondary endpoint	Approved: 10/04/17
	Compassionate Use – Dr. Stout	Approved: 11/14/17
	Compassionate Use – Dr. Mueller	Approved: 12/28/17
	End of Enrollment	Approved: 01/18/18
	Protocol & SAP Update	Approved: 05/07/18
	Protocol Update – Informed Consent/5-year follow up	Approved: 12/20/19

Table A.1: IDE Changes During the Course of the Investigation

B. Subject and Flow Pathway Accountability Tables

Subject accountability at each timepoint, plus the visit window, is summarized below.

	DCB Subjects (N=287)	PTA Subjects (N=155)
Overall Subject Disposition, n (%)		
Completed the study	137 (47.7%)	59 (38.1%)
Ongoing in study	35 (12.2%)	25 (16.1%)
Died	48 (16.7%)	24 (15.5%)
Stopped for other reason	67 (23.3%)	47 (30.3%)
Lost to follow-up	19 (6.6%)	14 (9.0%)
Withdrew from study	39 (13.6%)	26 (16.8%)
Other	9 (3.1%)	7 (4.5%)
Subjects Status from Treatment to Day 44, n (%)		
Evaluable Subjects	286 (99.7%)	155 (100.0%)
Died	3 (1.0%)	1 (0.6%)
Alive	283 (98.6%)	154 (99.4%)
Not Evaluable	1 (0.3%)	0 (0.0%)
Ongoing, did not reach Day 16	0 (0.0%)	0 (0.0%)
Discontinued by Day 16	1 (0.3%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)
Withdrew from study	0 (0.0%)	0 (0.0%)
Other	1 (0.3%)	0 (0.0%)
Subjects Status from Treatment to Day 210, n (%)		
Evaluable Subjects	280 (97.6%)	150 (96.8%)
Died	14 (4.9%)	6 (3.9%)
Alive	266 (92.7%)	144 (92.9%)
Not Evaluable	7 (2.4%)	5 (3.2%)
Ongoing, did not reach Day 150	0 (0.0%)	0 (0.0%)
Discontinued by Day 150	7 (2.4%)	5 (3.2%)
Lost to follow-up	0 (0.0%)	0 (0.0%)
Withdrew from study	6 (2.1%)	3 (1.9%)
Other	1 (0.3%)	2 (1.3%)
Subjects Status from Treatment to Day 395, n (%)		
Evaluable Subjects	270 (94.1%)	139 (89.7%)
Died	23 (8.0%)	11 (7.1%)
Alive	247 (86.1%)	128 (82.6%)
Not Evaluable	17 (5.9%)	16 (10.3%)
Ongoing, did not reach Day 335	0 (0.0%)	0 (0.0%)
Discontinued by Day 335	17 (5.9%)	16 (10.3%)
Lost to follow-up	2 (0.7%)	2 (1.3%)
Withdrew from study	14 (4.9%)	11 (7.1%)
Other	1 (0.3%)	3 (1.9%)
Subjects Status from Treatment to Day 790, n (%)		
Evaluable Subjects	247 (86.1%)	124 (80.0%)

	DCB Subjects (N=287)	PTA Subjects (N=155)
Died	38 (13.2%)	16 (10.3%)
Alive	209 (72.8%)	108 (69.7%)
Not Evaluable	40 (13.9%)	31 (20.0%)
Ongoing, did not reach Day 670	7 (2.4%)	5 (3.2%)
Discontinued by Day 670	33 (11.5%)	26 (16.8%)
Lost to follow-up	4 (1.4%)	6 (3.9%)
Withdrew from study	27 (9.4%)	15 (9.7%)
Other	2 (0.7%)	5 (3.2%)
Subjects Status from Treatment to Day 1155, n (%)		
Evaluable Subjects	200 (69.7%)	94 (60.6%)
Died	47 (16.4%)	23 (14.8%)
Alive	153 (53.3%)	71 (45.8%)
Not Evaluable	87 (30.3%)	61 (39.4%)
Ongoing, did not reach Day 1035	34 (11.8%)	23 (14.8%)
Discontinued by Day 1035	53 (18.5%)	38 (24.5%)
Lost to follow-up	6 (2.1%)	8 (5.2%)
Withdrew from study	38 (13.2%)	23 (14.8%)
Other	9 (3.1%)	7 (4.5%)

Table B.1: Accountability by Subject

Flow pathway accountability at each timepoint is summarized below.

	DCB (N=323)	PTA (N=184)
Primary Effectiveness at 30 Days, n (%)		
Subject had primary effectiveness outcome	294/323 (91.0%)	156/184 (84.8%)
Subject without outcome discontinued by end of visit window	9/323 (2.8%)	5/184 (2.7%)
Subject without outcome, available in window	20/323 (6.2%)	23/184 (12.5%)
Reasons for Discontinuation to 30 Days, n (%)		
n	9	5
Death	3/9 (33.3%)	2/5 (40.0%)
Investigator's Decision	2/9 (22.2%)	0/5 (0.0%)
Other	0/9 (0.0%)	1/5 (20.0%)
Withdrawal of Consent	4/9 (44.4%)	2/5 (40.0%)
Primary Effectiveness at 6 Months, n (%)		
Subject had primary effectiveness outcome	269/323 (83.3%)	137/184 (74.5%)
Subject without outcome discontinued by end of visit window	27/323 (8.4%)	18/184 (9.8%)
Subject without outcome, available in window	27/323 (8.4%)	29/184 (15.8%)

	DCB (N=323)	PTA (N=184)
Reasons for Discontinuation to 6 Months, n (%)		
n	27	18
Death	16/27 (59.3%)	7/18 (38.9%)
Investigator's Decision	2/27 (7.4%)	0/18 (0.0%)
Lost to Follow-up	0/27 (0.0%)	1/18 (5.6%)
Other	0/27 (0.0%)	1/18 (5.6%)
Sponsor's Decision	0/27 (0.0%)	1/18 (5.6%)
Withdrawal of Consent	9/27 (33.3%)	8/18 (44.4%)
Primary Effectiveness at 12 Months, n (%)		
Subject had primary effectiveness outcome	251/323 (77.7%)	132/184 (71.7%)
Subject without outcome discontinued by end of visit window	44/323 (13.6%)	34/184 (18.5%)
Subject without outcome, available in window	28/323 (8.7%)	18/184 (9.8%)
Reasons for Discontinuation to 12 Months, n (%)		
n	44	34
Death	25/44 (56.8%)	12/34 (35.3%)
Investigator's Decision	2/44 (4.5%)	0/34 (0.0%)
Lost to Follow-up	1/44 (2.3%)	5/34 (14.7%)
Other	0/44 (0.0%)	3/34 (8.8%)
Sponsor's Decision	0/44 (0.0%)	1/34 (2.9%)
Withdrawal of Consent	16/44 (36.4%)	13/34 (38.2%)
Primary Effectiveness at 24 Months, n (%)		
Subject had primary effectiveness outcome	228/323 (70.6%)	123/184 (66.8%)
Subject without outcome discontinued by end of visit window	68/323 (21.1%)	49/184 (26.6%)
Subject without outcome, available in window	27/323 (8.4%)	12/184 (6.5%)
Reasons for Discontinuation to 24 Months, n (%)		
n	68	49
Death	34/68 (50.0%)	14/49 (28.6%)
Investigator's Decision	2/68 (2.9%)	3/49 (6.1%)
Lost to Follow-up	5/68 (7.4%)	9/49 (18.4%)
Other	1/68 (1.5%)	3/49 (6.1%)
Sponsor's Decision	0/68 (0.0%)	1/49 (2.0%)
Withdrawal of Consent	26/68 (38.2%)	19/49 (38.8%)

	DCB (N=323)	PTA (N=184)
Primary Effectiveness at 36 Months, n (%)		
Subject had primary effectiveness outcome	210/323 (65.0%)	100/184 (54.3%)
Subject without outcome discontinued by end of visit window	80/323 (24.8%)	56/184 (30.4%)
Subject without outcome, available in window	33/323 (10.2%)	28/184 (15.2%)
Reasons for Discontinuation to 36 Months, n (%)		
n	80	56
Death	38/80 (47.5%)	15/56 (26.8%)
Investigator's Decision	2/80 (2.5%)	3/56 (5.4%)
Lost to Follow-up	6/80 (7.5%)	10/56 (17.9%)
Other	2/80 (2.5%)	4/56 (7.1%)
Sponsor's Decision	0/80 (0.0%)	1/56 (1.8%)
Withdrawal of Consent	32/80 (40.0%)	23/56 (41.1%)

Table B.2: Accountability by Flow Pathway

C. Proximal Segment Endpoint Data

1 Background

The sponsor's approved protocol noted that if the first (i.e. all flow pathways) primary effectiveness analysis fails to reach statistical significance at the pre-specified level, the analysis is 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 a clinically-driven target lesion revascularization in the proximal segment of the flow pathway.

Please note that, as described above, this analysis was largely abandoned as the clinical relevance could not be supported.

The proximal-segment analysis is based on flow pathways that have lesion(s) that are entirely within the proximal 2/3 segment of the target flow pathway boundary or are split across the 2/3 cut-off. The proximal-segment population was analyzed using a one-sided significance level of 0.0085 for the primary effectiveness analysis. In order to evaluate the second primary effectiveness analysis, the following approach was used for each of the components (see above for origin of data, that is, site reported or CEC adjudicated):

- Above-the-ankle amputation results in a failure of all flow pathways in the target limb.
- Clinically-driven Target Lesion Revascularizations were considered failures if they were reported in a proximal lesion or the proximal portion of a split lesion. Distal lesion TLRs and distal portion of a split lesion were ignored. Patency failures were counted as failures if they occurred in a proximal lesion or the proximal portion of a split lesion. Occlusions in distal lesions or the distal portion of a split lesion were not counted as failures. In cases where a failure occurred in the distal portion of a split lesion, if patency was not demonstrated in the proximal portion of the lesion it was counted as 'not evaluable'.

The proximal segment population made up approximately 95% of the overall BTK IDE study population (95.1% DCB / 94.8% PTA).

2 Results

2.1 Safety

The primary safety endpoint of non-inferiority of 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 below-the-knee artery of the test arm compared to the control for the proximal segment of the flow pathway was met with a p-value of <0.0001. The Lutonix 014 DCB had a primary safety endpoint rate of 99.3% at 30 days and the control arm had a rate of 99.3% at 30 days. See results in Table C.1 below.

	DCB Subjects (N=273) n/N (%) (95% CI)1	PTA Subjects (N=147) n/N (%) (95% CI)1	Difference in Response (95% CI)[2]	Farrington-Manning Test P-value[3]
Free from Primary Safety Event at 30 Days	270 / 272 (99.3%) (97.4%, 99.9%)	146 / 147 (99.3%) (96.3%, 100.0%)	-0.1% (-4.0%, 3.9%)	<.0001
Primary Safety Events, n4				
Death ≤ Day 30	1	1		
Above Ankle Amputation ≤ Day 30	0	0		
Major Re-intervention ≤ Day 30	1	0		

[1] 95% CI based exact binomial distribution; [2] 95% CI is estimated by Farrington-Manning Test.;
[3] P-value for non-inferiority margin of 12%; [4] Subjects may fail primary safety due to more than one cause

Table C.1: Primary Safety Endpoint of Proximal Segment of the Flow Pathway at 30 Days

2.2 Effectiveness

The primary effectiveness endpoint of superiority of Composite of Limb Salvage and Primary Patency for the proximal flow pathway at 6 months was not met with a p-value of 0.0139. The Lutonix 014 DCB had a primary effectiveness endpoint rate in the proximal segment of the flow pathway of 76.2% at 6 months and the control arm had a rate of 64.4%, demonstrating a difference of 11.8%. See results in Table C.2 below.

	DCB Pathways (N=304) n/N (%) (95% CI)[1]	PTA Pathways (N=172) n/N (%) (95% CI)[1]	Difference in Response (95% CI)[2]	P-value[3]
Free from Primary Efficacy Failure at 6 Months	195 / 256 (76.2%) (70.5%, 81.3%)	85 / 132 (64.4%) (55.6%, 72.5%)	11.8% (1.4%, 19.8%)	0.0139 **NS**
Composite Endpoint Failure Events, n[4]				
Subjects with major amputation ≤ Day 210	4	3		
Pathways with clinically-driven TLR ≤ Day 210	25	30		
Pathways with primary patency failure ≤ Day 210	58	44		

[1] 95% CI based exact binomial distribution
[2] Based on the model estimated response rates in both groups
[3] One-sided Wald Test based on model estimate of DCB treatment effect and subject as a random effect
[4] Subjects may fail primary effectiveness due to more than one cause and TLR failure is a component of primary patency failure

Table C.2: Primary Effectiveness Endpoint of Proximal Segment of the Flow Pathway at 6 Months

The KM estimates for the primary effectiveness endpoint through 36 months for the proximal segment of the flow pathway are depicted in Figure C.1 and Table C.3 below. As can be seen, the curves cross at 12 months and the PTA arm is showing improved outcomes through 36 months.

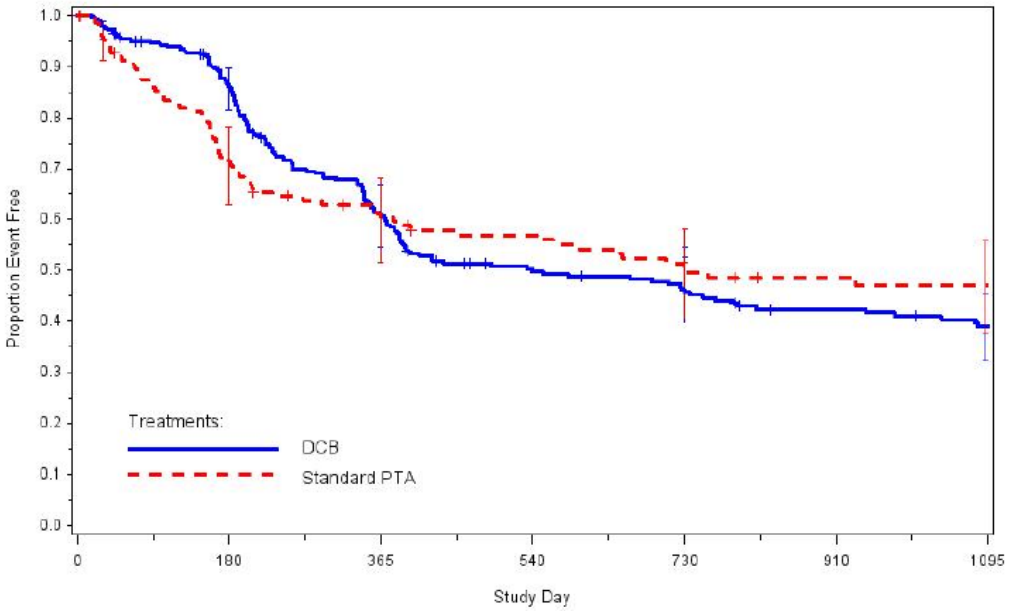

Figure C.1: Primary Effectiveness Endpoint KM Estimates for the Proximal Segment of the Flow Pathway through 36 Months

D. Primary Patency with Exclusion of Early Mechanical Recoil

As noted above, a hypothesis-tested secondary endpoint for primary patency with the exclusion of early mechanical recoil was included in the clinical protocol. However, FDA had noted concerns with this exclusion due to the inability to separate any unintended drug effect that may be occurring prior to 30 days. No differences in conclusions were reached when early mechanical recoil was excluded. Hypothesis testing was not conducted due to failure to meet the sequential primary endpoints prior to it. The results of this endpoint are depicted in Table D.1 below. The Lutonix 014 DCB had a primary patency rate of 76.4% at 6 months and the control arm had a rate of 59.4%, demonstrating a difference of 9.5%.8% when excluding what were deemed to be early recoil events. However, similar to the primary endpoint results, results of later time points through 36 months favored PTA.

	DCB Pathways (N=323)		PTA Pathways (N=184)		
Visit	**Response Rate**	**95% CI[1]**	**Response Rate**	**95% CI[1]**	**Difference (95% CI)[1]**
30 Days	283 / 288 (98.3%)	(96.0%, 99.4%)	147 / 152 (96.7%)	(92.5%, 98.9%)	1.6% (-1.7%, 4.8%)
6 Months	201 / 263 (76.4%)	(70.8%, 81.4%)	89 / 133 (66.9%)	(58.2%, 74.8%)	9.5% (0.0%, 19.0%)
12 Months	128 / 246 (52.0%)	(45.6%, 58.4%)	76 / 128 (59.4%)	(50.3%, 68.0%)	-7.3% (-17.9%, 3.2%)
24 Months	84 / 223 (37.7%)	(31.3%, 44.4%)	54 / 117 (46.2%)	(36.9%, 55.6%)	-8.5% (-19.5%, 2.6%)
36 Months	58 / 205 (28.3%)	(22.2%, 35.0%)	29 / 93 (31.2%)	(22.0%, 41.6%)	-2.9% (-14.1%, 8.4%)

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

Table D.1: Primary Patency Excluding Early Mechanical Recoil through 36 Months

E. KM Tables for Primary and Secondary Endpoints

KM tables for some of the primary and secondary endpoints, as depicted in graphical format in Section 7 of this document, are provided below.

1 KM Estimates for the Primary Safety Endpoint through 36 Months

			Count Information at Visit Day			Survival Difference
Group	Time Point	Survival %[1] (95% CI)	Cumulative Subjects with Events	Cumulative Subjects Censored	Subjects Left[2]	Difference (95% CI)[3]
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%)
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	

[1] Kaplan-Meier estimate of proportion of subjects without a key safety event at the visit day

[2] Subjects ongoing without an event at the visit day

[3] 95% CI for difference obtained from Kaplan-Meier estimates and standard error estimates from Greenwood's method. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table E.1: Primary Safety Endpoint KM estimates through 36 months

2 KM Estimates for the Primary Effectiveness Endpoint through 36 Months

			Count Information at Visit Day			Survival Difference
Group	Time Point	Survival %[1] (95% CI)	Cumulative Flow Pathways with Events	Cumulative Flow Pathways Censored	Flow Pathways Left[2]	Difference (95% CI)[3]
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, 10.1%)
	Day 395	53.1% (46.8%, 58.9%)	124	88	111	-6.2% (-16.7, 4.6%)
	Day 730	45.7% (39.3%, 51.8%)	139	93	91	-3.7% (-14.9, 7.5%)
	Day 790	43.2% (36.8%, 49.4%)	144	110	69	-5.3% (-16.5, 5.7%)
	Day 1095	38.7% (32.2%, 45.1%)	151	113	59	-8.3% (-19.7, 3.1%)
	Day 1155	38.0% (31.5%, 44.5%)	152	171	0	-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	

[1] Kaplan-Meier estimate of proportion of subjects without a composite failure event at the visit day. As the primary effectiveness endpoint was analyzed per flow pathway, the KM estimate is reported per flow pathway, and assumes independence among flow pathways from the same patient, which may not be a correct assumption

[2] Subjects ongoing without an event at the visit day

[3] 95% CI for difference obtained with bootstrap approach resampling individual flow pathways. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table E.2: Primary Effectiveness Endpoint KM estimates through 36 Months

3 KM Estimates for the Secondary Endpoint of Freedom from Major Amputation through 36 Months

			Count Information at Visit Day			Survival Difference
Group	Time Point	Survival %[1] (95% CI)	Cumulative Subjects with Events	Cumulative Subjects Censored	Subjects Left[2]	Difference (95% CI)[3]
DCB	Day 1	100.0% (NA, NA)	0	1	286	
	Day 30	100.0% (100.0%, 100.0%)	0	5	282	0.0% (0.0, 0.0%)
	Day 44	100.0% (100.0%, 100.0%)	0	8	279	0.7% (-0.6, 1.9%)
	Day 180	98.9% (96.6%, 99.6%)	3	18	266	0.9% (-1.7, 3.5%)
	Day 210	98.5% (96.1%, 99.4%)	4	25	258	0.5% (-2.1, 3.2%)
	Day 365	97.4% (94.5%, 98.7%)	7	39	241	-0.6% (-3.6, 2.3%)
	Day 395	97.4% (94.5%, 98.7%)	7	46	234	-0.6% (-3.6, 2.3%)
	Day 730	95.5% (92.0%, 97.5%)	11	87	189	-0.8% (-4.9, 3.3%)
	Day 790	95.5% (92.0%, 97.5%)	11	111	165	0.4% (-4.3, 5.0%)
	Day 1095	95.5% (92.0%, 97.5%)	11	185	91	1.7% (-3.6, 7.0%)
	Day 1155	95.5% (92.0%, 97.5%)	11	253	23	1.7% (-3.6, 7.0%)
PTA	Day 1	100.0% (NA, NA)	0	0	155	
	Day 30	100.0% (100.0%, 100.0%)	0	2	153	
	Day 44	99.3% (95.4%, 99.9%)	1	3	151	
	Day 180	98.0% (93.9%, 99.4%)	3	14	138	
	Day 210	98.0% (93.9%, 99.4%)	3	17	135	
	Day 365	98.0% (93.9%, 99.4%)	3	27	125	
	Day 395	98.0% (93.9%, 99.4%)	3	33	119	
	Day 730	96.3% (91.3%, 98.5%)	5	54	96	
	Day 790	95.1% (89.3%, 97.8%)	6	67	82	
	Day 1095	93.8% (87.2%, 97.1%)	7	103	45	
	Day 1155	93.8% (87.2%, 97.1%)	7	131	17	

[1] Kaplan-Meier estimate of proportion of subjects without a major amputation at the visit day

[2] Subjects ongoing without an event at the visit day

[3] 95% CI for difference obtained from Kaplan-Meier estimates and standard error estimates from Greenwood's method. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table E.3: Freedom from Major Amputation KM estimates through 36 Months

4 KM Estimates for the Secondary Endpoint of Freedom from Unplanned Minor Amputation through 36 Months

			Count Information at Visit Day			Survival Difference
Group	Time Point	Survival %[1] (95% CI)	Cumulative Subjects with Events	Cumulative Subjects Censored	Subjects Left2	Difference (95% CI)[3]
DCB	Day 1	100.0% (NA, NA)	0	1	286	
	Day 30	95.8% (92.7%, 97.6%)	12	1	274	0.3% (-3.7, 4.3%)
	Day 44	95.1% (91.9%, 97.1%)	14	8	265	2.8% (-2.0, 7.7%)
	Day 180	88.6% (84.2%, 91.8%)	32	13	242	0.3% (-6.0, 6.7%)
	Day 210	88.2% (83.8%, 91.5%)	33	20	234	0.7% (-5.8, 7.1%)
	Day 365	86.3% (81.6%, 89.8%)	38	30	219	3.2% (-4.1, 10.5%)
	Day 395	86.3% (81.6%, 89.8%)	38	39	210	3.2% (-4.1, 10.5%)
	Day 730	84.0% (79.0%, 87.9%)	43	61	183	2.7% (-5.1, 10.4%)
	Day 790	84.0% (79.0%, 87.9%)	43	94	150	4.5% (-3.6, 12.5%)
	Day 1095	84.0% (79.0%, 87.9%)	43	109	135	5.9% (-2.5, 14.3%)
	Day 1155	84.0% (79.0%, 87.9%)	43	226	18	5.9% (-2.5, 14.3%)
PTA	Day 1	100.0% (NA, NA)	0	0	155	
	Day 30	95.5% (90.8%, 97.8%)	7	0	148	
	Day 44	92.3% (86.8%, 95.5%)	12	3	140	
	Day 180	88.2% (81.9%, 92.4%)	18	8	129	
	Day 210	87.5% (81.1%, 91.9%)	19	13	123	
	Day 365	83.1% (76.0%, 88.3%)	25	20	110	
	Day 395	83.1% (76.0%, 88.3%)	25	28	102	
	Day 730	81.4% (73.9%, 86.9%)	27	38	90	
	Day 790	79.6% (71.8%, 85.4%)	29	59	67	
	Day 1095	78.1% (69.9%, 84.4%)	30	72	53	
	Day 1155	78.1% (69.9%, 84.4%)	30	114	11	

[1] Kaplan-Meier estimate of proportion of subjects without an unplanned amputation at the visit day

[2] Subjects ongoing in the study and alive at the visit day

[3] 95% CI for difference obtained from Kaplan-Meier estimates and standard error estimates from Greenwood's method. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table E.4: Freedom from Unplanned Minor Amputation KM estimates through 36 Months

5 KM Estimates for All-Cause Mortality through 36 Months

			Count Information at Visit Day		
Group	Time Point	Survival %[1] (95% CI)	Cumulative Subjects with Events	Cumulative Subjects Censored	Subjects Left[2]
DCB	Day 1	100.0% (NA, NA)	0	1	286
	Day 30	99.6% (97.5%,100.0%)	1	4	282
	Day 44	98.9% (96.8%, 99.7%)	3	5	279
	Day 180	96.8% (94.0%, 98.3%)	9	9	269
	Day 210	95.0% (91.7%, 97.0%)	14	12	261
	Day 365	92.4% (88.6%, 95.0%)	21	19	247
	Day 395	91.7% (87.7%, 94.4%)	23	24	240
	Day 730	86.4% (81.6%, 90.0%)	36	52	199
	Day 790	85.4% (80.5%, 89.2%)	38	74	175
	Day 1095	81.0% (75.3%, 85.5%)	46	145	96
	Day 1155	80.0% (73.9%, 84.8%)	47	214	26
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

1 Kaplan-Meier estimate of proportion of subjects without all cause death at the visit day
2 Subjects ongoing in the study and alive at the visit day

Table E.5: All-Cause Mortality KM Estimates through 36 Months

6 KM estimates for the Primary Effectiveness Endpoint of the Proximal Segment of the Flow Pathway through 36 months

			Count Information at Visit Day			Survival Difference
Group	Time Point	Survival %[1] (95% CI)	Cumulative Flow Pathways with Events	Cumulative Flow Pathways Censored	Flow Pathways Left[2]	Difference (95% CI)[3]
DCB	Day 1	100.0% (NA, NA)	0	17	287	
	Day 30	97.9% (95.4%, 99.1%)	6	17	281	1.9% (-1.5, 5.7%)
	Day 44	96.5% (93.6%, 98.1%)	10	36	258	3.8% (-1.0, 9.1%)
	Day 180	86.2% (81.5%, 89.8%)	37	42	225	14.8% (5.7, 24.0%)
	Day 210	77.0% (71.5%, 81.6%)	61	59	184	11.7% (1.8, 21.6%)
	Day 365	61.0% (54.7%, 66.8%)	99	60	145	0.6% (-10.1, 11.4%)
	Day 395	53.9% (47.4%, 59.9%)	116	79	109	-4.9% (-15.7, 6.2%)
	Day 730	46.2% (39.7%, 52.5%)	131	84	89	-3.3% (-14.6, 8.1%)
	Day 790	43.6% (37.1%, 50.0%)	136	100	68	-5.0% (-16.3, 6.7%)
	Day 1095	39.0% (32.4%, 45.6%)	143	103	58	-8.0% (-19.7, 4.0%)
	Day 1155	38.3% (31.7%, 44.9%)	144	160	0	-7.1% (-18.9, 5.1%)
PTA	Day 1	100.0% (NA, NA)	0	19	153	
	Day 30	96.0% (91.3%, 98.2%)	6	22	144	
	Day 44	92.7% (87.1%, 95.9%)	11	39	122	
	Day 180	71.4% (63.0%, 78.2%)	39	39	94	
	Day 210	65.3% (56.6%, 72.7%)	47	44	81	
	Day 365	60.4% (51.5%, 68.2%)	53	46	73	
	Day 395	58.7% (49.8%, 66.6%)	55	52	65	
	Day 730	49.6% (40.5%, 58.0%)	65	53	54	
	Day 790	48.7% (39.6%, 57.1%)	66	74	32	
	Day 1095	47.0% (37.7%, 55.8%)	67	76	29	
	Day 1155	45.4% (35.9%, 54.4%)	68	98	6	

[1] Kaplan-Meier estimate of proportion of subjects without a composite failure event at the visit day. As the primary effectiveness endpoint was analyzed per flow pathway, the KM estimate is reported per flow pathway, and assumes independence among flow pathways from the same patient, which may not be a correct assumption

[2] Subjects ongoing without an event at the visit day

[3] 95% CI for difference obtained with bootstrap approach resampling individual flow pathways. All confidence intervals are based on nominal levels and not adjusted for multiple comparisons.

Table E.6: Primary Effectiveness Endpoint KM Estimates for the Proximal Segment of the Flow Pathway through 36 Months

F. Wound Care Data

More detailed quantitative outcomes for the wound care data, including the presence of a wound, total number of wounds, wound type, and wound status, are provide in the tables below.

	DCB Subjects (N=287)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
Subject Assessed for Presence of Wound, n/N (%)	285	262	242	212	174	130
Any Wound Present, n/N (%)	161/285 (56.5%)	145/262 (55.3%)	101/242 (41.7%)	63/212 (29.7%)	41/174 (23.6%)	26/130 (20.0%)
Total Wounds (num)						
n	285	262	242	212	174	130
Mean	0.8	0.8	0.7	0.5	0.4	0.4
SD	0.91	0.91	1.08	0.95	1.34	1.55
Median	1.0	1.0	0.0	0.0	0.0	0.0
Min - Max	0 - 5	0 - 4	0 - 7	0 - 7	0 - 15	0 - 16
Total Wounds, n (%)						
n	285	262	242	212	174	130
0	124 (43.5%)	117 (44.7%)	141 (58.3%)	149 (70.3%)	133 (76.4%)	104 (80.0%)
1	108 (37.9%)	96 (36.6%)	64 (26.4%)	39 (18.4%)	30 (17.2%)	18 (13.8%)
2	40 (14.0%)	36 (13.7%)	21 (8.7%)	15 (7.1%)	4 (2.3%)	2 (1.5%)
3	9 (3.2%)	9 (3.4%)	9 (3.7%)	5 (2.4%)	4 (2.3%)	4 (3.1%)
4	3 (1.1%)	4 (1.5%)	5 (2.1%)	3 (1.4%)	2 (1.1%)	1 (0.8%)
5	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
7	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
15	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
16	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Wound by Type[1], n (%)						
n		211	166	103	73	54
Existing		203 (96.2%)	125 (75.3%)	79 (76.7%)	43 (58.9%)	35 (64.8%)
New		7 (3.3%)	35 (21.1%)	19 (18.4%)	26 (35.6%)	15 (27.8%)
Recurrent		1 (0.5%)	6 (3.6%)	5 (4.9%)	4 (5.5%)	4 (7.4%)
Wound Location[1], n (%)						
n	232	211	166	103	73	54
Above Ankle	1 (0.4%)	2 (0.9%)	3 (1.8%)	4 (3.9%)	7 (9.6%)	11 (20.4%)
Ankle	2 (0.9%)	2 (0.9%)	5 (3.0%)	4 (3.9%)	1 (1.4%)	3 (5.6%)
Digit 1	88 (37.9%)	79 (37.4%)	55 (33.1%)	21 (20.4%)	18 (24.7%)	11 (20.4%)
Digit 2	49 (21.1%)	42 (19.9%)	31 (18.7%)	19 (18.4%)	10 (13.7%)	6 (11.1%)
Digit 3	31 (13.4%)	29 (13.7%)	21 (12.7%)	15 (14.6%)	8 (11.0%)	5 (9.3%)
Digit 4	24 (10.3%)	23 (10.9%)	16 (9.6%)	5 (4.9%)	3 (4.1%)	3 (5.6%)

	DCB Subjects (N=287)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
Digit 5	23 (9.9%)	19 (9.0%)	13 (7.8%)	11 (10.7%)	9 (12.3%)	5 (9.3%)
Heel	0 (0.0%)	0 (0.0%)	1 (0.6%)	4 (3.9%)	3 (4.1%)	3 (5.6%)
Metatarsal	14 (6.0%)	15 (7.1%)	21 (12.7%)	20 (19.4%)	14 (19.2%)	7 (13.0%)
Infection Present, n/N (%)	60/232 (25.9%)	17/211 (8.1%)	9/166 (5.4%)	4/103 (3.9%)	0/73 (0.0%)	0/54 (0.0%)
Gangrene Present, n/N (%)	51/232 (22.0%)	21/211 (10.0%)	12/166 (7.2%)	1/103 (1.0%)	0/73 (0.0%)	1/54 (1.9%)
Wound Status[1], n (%)	NA					
n		211	166	103	73	54
Amputated		27 (12.8%)	20 (12.0%)	20 (19.4%)	5 (6.8%)	3 (5.6%)
Healed		49 (23.2%)	61 (36.7%)	42 (40.8%)	30 (41.1%)	32 (59.3%)
NA (New Wound)		5 (2.4%)	35 (21.1%)	13 (12.6%)	24 (32.9%)	11 (20.4%)
Not Healed		130 (61.6%)	50 (30.1%)	28 (27.2%)	14 (19.2%)	8 (14.8%)
Status of Non-Healed Wounds[1], n (%)	NA					
n		130	51	28	14	8
Improving		90 (69.2%)	26 (51.0%)	18 (64.3%)	8 (57.1%)	3 (37.5%)
Stagnant		24 (18.5%)	13 (25.5%)	9 (32.1%)	4 (28.6%)	4 (50.0%)
Worsening		16 (12.3%)	12 (23.5%)	1 (3.6%)	2 (14.3%)	1 (12.5%)
Treatments[1], n (%)						
n	232	199	156	101	71	53
Debridement	16 (6.9%)	15 (7.5%)	3 (1.9%)	3 (3.0%)	3 (4.2%)	0 (0.0%)
Medication	77 (33.2%)	50 (25.1%)	23 (14.7%)	11 (10.9%)	5 (7.0%)	1 (1.9%)
Med/Debridement	23 (9.9%)	12 (6.0%)	9 (5.8%)	3 (3.0%)	2 (2.8%)	0 (0.0%)
None	116 (50.0%)	122 (61.3%)	121 (77.6%)	84 (83.2%)	61 (85.9%)	52 (98.1%)

[1] Subjects may have more than one wound type or wounds in more than one location.

Table F.1: Wound Care Data through 36 Months for DCB Patients

	PTA Subjects (N=155)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
Subject Assessed for Presence of Wound, n/N (%)	155	143	122	108	87	59
Any Wound Present, n/N (%)	87/155| (56.1%)	80/143 (55.9%)	55/122 (45.1%)	28/108 (25.9%)	20/87 (23.0%)	12/59 (20.3%)
Total Wounds (num)						
n	155	143	122	108	87	59
Mean	0.7	0.8	0.7	0.5	0.5	0.3
SD	0.84	0.91	0.94	1.16	0.94	0.80
Median	1.0	1.0	0.0	0.0	0.0	0.0
Min - Max	0 - 5	0 - 4	0 - 5	0 - 8	0 - 4	0 - 4
Total Wounds, n (%)						
n	155	143	122	108	87	59
0	68 (43.9%)	63 (44.1%)	68 (55.7%)	80 (74.1%)	67 (77.0%)	47 (79.7%)

	PTA Subjects (N=155)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
1	70 (45.2%)	56 (39.2%)	36 (29.5%)	15 (13.9%)	6 (6.9%)	7 (11.9%)
2	11 (7.1%)	17 (11.9%)	12 (9.8%)	6 (5.6%)	9 (10.3%)	3 (5.1%)
3	4 (2.6%)	4 (2.8%)	4 (3.3%)	4 (3.7%)	4 (4.6%)	1 (1.7%)
4	1 (0.6%)	3 (2.1%)	1 (0.8%)	2 (1.9%)	1 (1.1%)	1 (1.7%)
5	1 (0.6%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
7	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
15	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
16	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wound by Type[1], n (%)						
n		114	81	55	40	20
Existing		96 (84.2%)	68 (84.0%)	36 (65.5%)	27 (67.5%)	12 (60.0%)
New		18 (15.8%)	12 (14.8%)	16 (29.1%)	12 (30.0%)	8 (40.0%)
Recurrent		0 (0.0%)	1 (1.2%)	3 (5.5%)	1 (2.5%)	0 (0.0%)
Wound Location[1], n (%)						
n	113	114	82	55	40	20
Above Ankle	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (7.3%)	3 (7.5%)	2 (10.0%)
Ankle	0 (0.0%)	1 (0.9%)	1 (1.2%)	0 (0.0%)	1 (2.5%)	4 (20.0%)
Digit 1	44 (38.9%)	38 (33.3%)	22 (26.8%)	15 (27.3%)	14 (35.0%)	6 (30.0%)
Digit 2	17 (15.0%)	17 (14.9%)	14 (17.1%)	4 (7.3%)	3 (7.5%)	2 (10.0%)
Digit 3	16 (14.2%)	14 (12.3%)	7 (8.5%)	5 (9.1%)	4 (10.0%)	0 (0.0%)
Digit 4	10 (8.8%)	10 (8.8%)	7 (8.5%)	6 (10.9%)	4 (10.0%)	0 (0.0%)
Digit 5	16 (14.2%)	19 (16.7%)	15 (18.3%)	4 (7.3%)	2 (5.0%)	0 (0.0%)
Heel	0 (0.0%)	1 (0.9%)	2 (2.4%)	7 (12.7%)	2 (5.0%)	1 (5.0%)
Metatarsal	10 (8.8%)	14 (12.3%)	14 (17.1%)	10 (18.2%)	7 (17.5%)	5 (25.0%)
Infection Present, n/N (%)	30/113 (26.5%)	23/114 (20.2%)	13/81 (16.0%)	5/54 (9.3%)	0/40 (0.0%)	0/20 (0.0%)
Gangrene Present, n/N (%)	24/113 (21.2%)	12/114 (10.5%)	5/80 (6.3%)	5/54 (9.3%)	1/40 (2.5%)	1/20 (5.0%)
Wound Status[1], n (%)	NA					
n		114	82	55	40	20
Amputated		15 (13.2%)	11 (13.4%)	8 (14.5%)	5 (12.5%)	1 (5.0%)
Healed		24 (21.1%)	45 (54.9%)	17 (30.9%)	21 (52.5%)	12 (60.0%)
NA (New Wound)		14 (12.3%)	9 (11.0%)	16 (29.1%)	10 (25.0%)	5 (25.0%)
Not Healed		61 (53.5%)	17 (20.7%)	14 (25.5%)	4 (10.0%)	2 (10.0%)
Status of Non-Healed Wounds[1], n (%)	NA					
n		61	17	14	4	2
Improving		37 (60.7%)	6 (35.3%)	8 (57.1%)	2 (50.0%)	2 (100.0%)
Stagnant		16 (26.2%)	7 (41.2%)	4 (28.6%)	1 (25.0%)	0 (0.0%)
Worsening		8 (13.1%)	4 (23.5%)	2 (14.3%)	1 (25.0%)	0 (0.0%)

	PTA Subjects (N=155)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
Treatments[1], n (%)						
n	113	113	73	54	35	19
Debridement	7 (6.2%)	6 (5.3%)	4 (5.5%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
Medication	36 (31.9%)	31 (27.4%)	8 (11.0%)	10 (18.5%)	2 (5.7%)	2 (10.5%)
Med/Debridement	14 (12.4%)	10 (8.8%)	4 (5.5%)	5 (9.3%)	0 (0.0%)	0 (0.0%)
None	56 (49.6%)	66 (58.4%)	57 (78.1%)	39 (72.2%)	33 (94.3%)	16 (84.2%)

1Subjects may have more than one would type or wounds in more than one location

Table F.2: Wound Dare Data through 36 Months for PTA Patients

G. Hemodynamic Data

More detailed outcomes for the hemodynamic data, including ABI and TBI values, as well as changes in these outcomes from the baseline, are provide in the tables below.

	DCB Subjects (N=287)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
ABI						
n	264	254	232	202	162	121
Mean	0.81	1.05	0.97	0.92	0.94	0.94
SD	0.40	0.32	0.34	0.35	0.33	0.33
Median	0.75	1.01	0.95	0.87	0.89	0.92
Min - Max	0.00 - 2.38	0.00 - 2.27	0.00 - 2.53	0.00 - 2.68	0.19 - 2.33	0.21 - 2.27
ABI Change from Baseline						
n		237	218	193	155	118
Mean		0.23	0.16	0.11	0.12	0.11
SD		0.36	0.36	0.36	0.36	0.37
Median		0.24	0.19	0.12	0.12	0.16
Min - Max		-1.48 - 1.28	-1.13 - 1.64	-1.09 - 1.25	-0.94 - 1.74	-0.96 - 1.45
TBI						
n	149	152	147	127	101	82
Mean	0.35	0.57	0.52	0.50	0.49	0.48
SD	0.24	0.23	0.26	0.22	0.24	0.20
Median	0.32	0.57	0.50	0.48	0.47	0.46
Min - Max	0.00 - 1.75	0.00 - 1.36	0.00 - 1.33	0.00 - 1.17	0.00 - 1.33	0.10 - 1.05
TBI Change from Baseline						
n		119	104	84	67	56
Mean		0.20	0.15	0.12	0.09	0.14
SD		0.25	0.24	0.23	0.27	0.28
Median		0.21	0.15	0.12	0.09	0.16
Min - Max		-0.88 - 0.88	-0.75 - 0.73	-0.79 - 0.63	-0.99 - 0.59	-1.01 - 0.70
TcPO2 (mm Hg)						
n	9	3	5	5	2	2
Mean	33.89	50.00	27.80	55.80	49.50	101.0
SD	16.12	21.66	22.44	28.31	3.54	66.47
Median	30.00	62.00	28.00	58.00	49.50	101.0
Min - Max	17.00 - 60.00	25.00 - 63.00	1.00 - 62.00	17.00 - 96.00	47.00 - 52.00	54.00 - 148.0
TcPO2 Change from Baseline						
n		3	3	3	2	2
Mean		4.00	11.33	19.67	26.00	77.50
SD		16.64	29.37	22.55	5.66	75.66
Median		11.00	-2.00	18.00	26.00	77.50
Min - Max		-15.0 - 16.00	-9.00 - 45.00	-2.00 - 43.00	22.00 - 30.00	24.00 - 131.0

Table G.1: Change in Hemodynamic Outcomes of DCB Subjects through 36 Months

	PTA Subjects (N=155)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
ABI						
n	146	132	117	107	85	53
Mean	0.83	1.11	0.99	0.96	0.99	0.95
SD	0.39	0.37	0.40	0.32	0.30	0.33
Median	0.77	1.04	0.93	0.96	0.94	0.91
Min - Max	0.00 - 2.51	0.00 - 2.51	0.00 - 2.51	0.02 - 2.02	0.30 - 2.18	0.00 - 2.18
ABI Change from Baseline						
n		128	113	104	80	50
Mean		0.28	0.17	0.18	0.18	0.14
SD		0.42	0.43	0.40	0.34	0.42
Median		0.19	0.11	0.12	0.17	0.14
Min - Max		-1.03 - 1.56	-0.92 - 1.66	-0.75 - 1.50	-0.59 - 1.65	-1.53 - 1.93
TBI						
n	79	79	74	63	61	37
Mean	0.39	0.51	0.49	0.43	0.50	0.52
SD	0.26	0.24	0.26	0.21	0.27	0.23
Median	0.33	0.48	0.50	0.45	0.48	0.53
Min - Max	0.00 - 1.08	0.00 - 1.20	0.00 - 1.48	0.00 - 0.99	0.00 - 1.52	0.01 - 1.17
TBI Change from Baseline						
n		59	56	49	44	27
Mean		0.13	0.09	0.04	0.17	0.19
SD		0.26	0.29	0.25	0.29	0.24
Median		0.10	0.06	0.02	0.15	0.14
Min - Max		-0.43 - 0.81	-0.60 - 0.95	-0.62 - 0.57	-0.40 - 1.20	-0.21 - 0.82
TcPO2 (mm Hg)						
n	3	2	1	0	0	0
Mean	34.00	54.50	63.00	NA	NA	NA
SD	9.85	36.06		NA	NA	NA
Median	31.00	54.50	63.00	NA	NA	NA
Min - Max	26.00 - 45.00	29.00 - 80.00	63.00 - 63.00	NA - NA	NA - NA	NA - NA
TcPO2 Change from Baseline						
n	0	0	0	0	0	0
Mean	NA	NA	NA	NA	NA	NA
SD	NA	NA	NA	NA	NA	NA
Median	NA	NA	NA	NA	NA	NA
Min - Max	NA - NA	NA - NA	NA - NA	NA - NA	NA - NA	NA - NA

Table G.2: Change in Hemodynamic Outcomes of PTA Subjects through 36 Months

H. Rutherford Classification Data

More detailed outcomes for the Rutherford Classification data are provide in the tables below.

	DCB Subjects (N=287)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
Score						
n	287	263	243	220	175	131
Mean	4.5	2.4	1.9	1.6	1.3	1.3
SD	0.66	2.19	2.03	1.88	1.71	1.54
Median	5.0	2.0	1.0	1.0	0.0	1.0
Min - Max	3 - 5	0 - 6	0 - 6	0 - 5	0 - 5	0 - 5
Change from Baseline						
n		263	243	220	175	131
Mean		-2.0	-2.5	-2.8	-3.1	-3.1
SD		1.91	1.95	1.89	1.76	1.64
Median		-2.0	-3.0	-3.0	-4.0	-3.0
Min - Max		-5 - 1	-5 - 2	-5 - 1	-5 - 1	-5 - 0
Rutherford Category, n (%)						
n	287	263	243	220	175	131
0	0 (0.0%)	88 (33.5%)	99 (40.7%)	105 (47.7%)	91 (52.0%)	58 (44.3%)
1	0 (0.0%)	37 (14.1%)	37 (15.2%)	31 (14.1%)	25 (14.3%)	29 (22.1%)
2	0 (0.0%)	16 (6.1%)	22 (9.1%)	16 (7.3%)	23 (13.1%)	18 (13.7%)
3	26 (9.1%)	16 (6.1%)	19 (7.8%)	22 (10.0%)	10 (5.7%)	12 (9.2%)
4	100 (34.8%)	13 (4.9%)	15 (6.2%)	14 (6.4%)	7 (4.0%)	4 (3.1%)
5	161 (56.1%)	92 (35.0%)	47 (19.3%)	32 (14.5%)	19 (10.9%)	10 (7.6%)
6	0 (0.0%)	1 (0.4%)	4 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Shift from Baseline, n (%)						
n		263	243	220	175	131
Improved		161 (61.2%)	179 (73.7%)	176 (80.0%)	152 (86.9%)	117 (89.3%)
Same		100 (38.0%)	58 (23.9%)	39 (17.7%)	19 (10.9%)	14 (10.7%)
Worsened		2 (0.8%)	6 (2.5%)	5 (2.3%)	4 (2.3%)	0 (0.0%)

Table H.1: Change in Rutherford Category of DCB Subjects through 36 Months

	PTA Subjects (N=155)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
Score						
n	155	144	120	110	88	57
Mean	4.5	2.5	1.5	1.5	1.3	1.1
SD	0.68	2.19	1.84	1.87	1.72	1.70
Median	5.0	2.0	0.5	1.0	1.0	0.0
Min - Max	3 - 5	0 - 6	0 - 5	0 - 5	0 - 5	0 - 5
Change from Baseline						
n		144	120	110	88	57
Mean		-2.0	-3.0	-2.9	-3.1	-3.3

	PTA Subjects (N=155)					
	Baseline	**30 Days**	**6 Months**	**12 Months**	**24 Months**	**36 Months**
SD		1.92	1.78	1.84	1.79	1.70
Median		-2.0	-3.0	-4.0	-4.0	-4.0
Min - Max		-5 - 1	-5 - 1	-5 - 2	-5 - 1	-5 - 1
Rutherford Category, n (%)						
n	155	144	120	110	88	57
0	0 (0.0%)	45 (31.3%)	60 (50.0%)	52 (47.3%)	43 (48.9%)	32 (56.1%)
1	0 (0.0%)	20 (13.9%)	18 (15.0%)	21 (19.1%)	16 (18.2%)	10 (17.5%)
2	0 (0.0%)	13 (9.0%)	9 (7.5%)	8 (7.3%)	13 (14.8%)	6 (10.5%)
3	16 (10.3%)	7 (4.9%)	10 (8.3%)	7 (6.4%)	2 (2.3%)	1 (1.8%)
4	52 (33.5%)	5 (3.5%)	7 (5.8%)	5 (4.5%)	3 (3.4%)	1 (1.8%)
5	87 (56.1%)	53 (36.8%)	16 (13.3%)	17 (15.5%)	11 (12.5%)	7 (12.3%)
6	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Shift from Baseline, n (%)						
n		144	120	110	88	57
Improved		83 (57.6%)	98 (81.7%)	90 (81.8%)	75 (85.2%)	49 (86.0%)
Same		59 (41.0%)	21 (17.5%)	16 (14.5%)	11 (12.5%)	7 (12.3%)
Worsened		2 (1.4%)	1 (0.8%)	4 (3.6%)	2 (2.3%)	1 (1.8%)

Table H.2: Change in Rutherford Category of PTA Subjects through 36 Months