# Premarket Approval Application (PMA) for the Lutonix 014 Drug Coated Balloon (Lutonix 014 DCB)

Cardiovascular Devices Advisory Panel Meeting
February 17, 2021

*Presentations By: Eleni Whatley, Ph.D.,*
*Rong (Rona) Tang, Ph.D., and Donna Buckley, M.D., M.S.*
*Office of Cardiovascular Devices (OCVD)/Office of Clinical Evidence and Analysis (OCEA)*
*Office of Product Evaluation and Quality (OPEQ)*
*Center for Devices and Radiological Health (CDRH)*

# Review Team

| | |
|---|---|
| Eleni Whatley, PhD | - Lead and Engineering Reviewer |
| Donna Buckley, MD, MS | - Clinical Reviewer |
| Rong (Rona) Tang, PhD | - Statistical Reviewer |
| Karen Manhart, VMD | - Animal Studies Reviewer |
| Hajira Ahmad, PhD | - Biocompatibility Reviewer |
| Michelle Johnson, PhD | - Chemistry Reviewer |
| Ron Brown, PhD | - Toxicology Reviewer |
| Parnali Chatterjee, PhD | - CDER PK reviewer |
| Monica Cooper, PhD | - CDER CMC reviewer |
| Steve Hertz, PE | - CDER cGMP reviewer |
| Kimberly Kopecki, MS, RAC | - Lead and GMP reviewer |
| Megha Reddy | - Sterility Reviewer |

# Presentation Outline

- Introduction
- Clinical Background
- Device Description and Indications for Use
- Regulatory History
- IDE Clinical Trial Design and Statistical Analysis Plan
- Clinical Data Review
- Additional Data Evaluations
- Post-Approval Study Proposal
- Benefit/Risk Summary and Conclusions

## Introduction, Clinical Background, Device Description, and Regulatory History

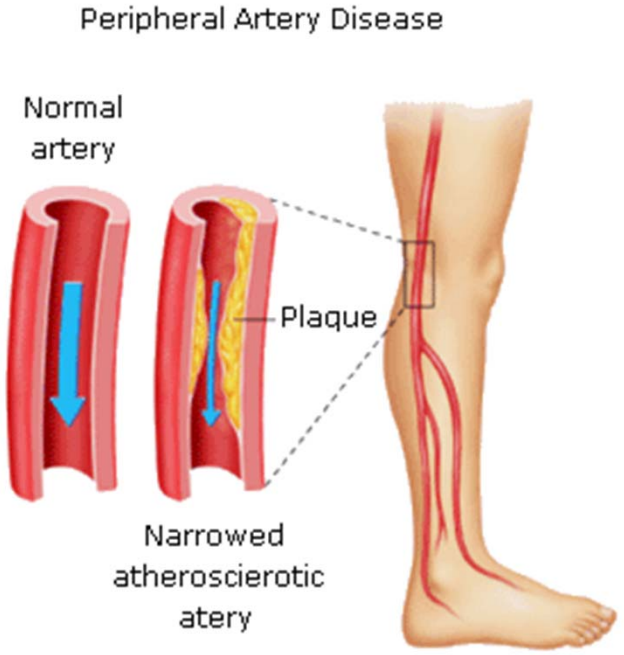
Eleni Whatley, Ph.D.
Biomedical Engineer
CDRH/OPEQ/OCVD/PMDT

# Meeting Purpose

- To request Panel feedback on whether the Lutonix 014 DCB provides a reasonable assurance of safety and effectiveness and a favorable benefit/risk profile for the treatment of below-the-knee (BTK) critical limb ischemia (CLI).
- The panel will be asked if:
  - For *safety*, whether the Lutonix 014 DCB is associated with "**the absence of unreasonable risk** of illness or injury associated with the use of the device for its intended uses and conditions of use." (21 CFR 860.7(d)(1))
  - For *effectiveness*, if it has been determined that "based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses… will provide **clinically significant results**." (21 CFR 860.7(e)(1))

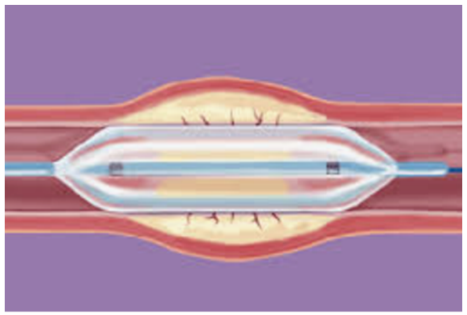
# Clinical Background

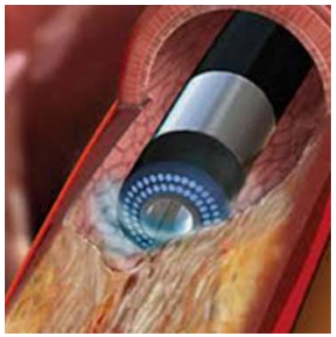
- Peripheral arterial disease (PAD):
  - Narrowing of the blood vessels in the lower extremities
  - Results in inadequate blood flow to downstream tissues
  - Clinical signs and symptoms: Leg pain when walking (claudication)
  - Categorized: Rutherford Classification (RC) 1 to 3
- Critical Limb ischemia (CLI):
  - Clinical signs and symptoms: Limb pain at rest, tissue loss, non-healing wounds, gangrene, and potential amputation
  - Categorized: RC 4 to 6

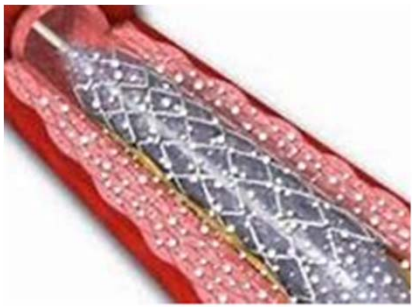


# Clinical Background

- Available treatment strategies for BTK CLI include:
  - Surgical
    - Bypass
  - Intravascular
    - PTA
    - Atherectomy
    - Off-label device use



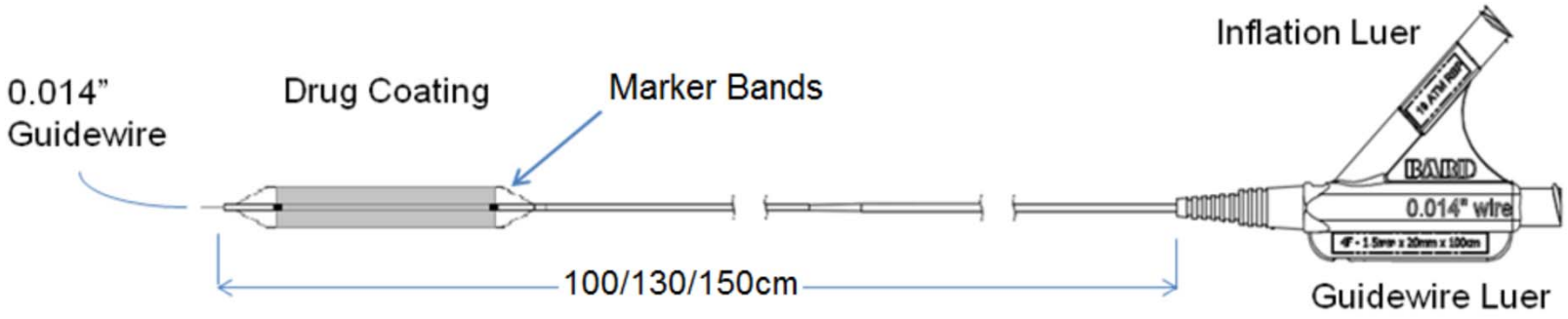




- If approved, the Lutonix 014 DCB would be the first-of-a-kind device for the treatment of BTK CLI in the US beyond vessel preparation strategies (PTA and atherectomy).

# Device Description

- The Lutonix 014 DCB is an over-the-wire PTA catheter with a paclitaxel drug coating on the surface of the balloon.
- 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 the ancillary benefit of preventing restenosis.



# Device Description

- The Lutonix drug coating contains the anti-proliferative drug Paclitaxel as well as various excipients and solvents.
- The balloon is coated with a constant 2 μg/mm$^2$ of paclitaxel; thus the total drug dosage is correlated to the balloon surface area.
- Available balloon diameters 2-4 mm, and available balloon lengths 40-150 mm.

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

# 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.*

# Regulatory History – IDE Approval

Original Investigational Device Exemption (IDE) approved May 30, 2013 for:

- 480 subjects
- Randomized 2:1 to the Lutonix 014 DCB or PTA
- Primary safety endpoint: Freedom from below-the-knee (BTK) major adverse limb event (MALE) + perioperative death (POD) at 30 days
- Primary effectiveness endpoint: A composite of limb salvage and primary patency at 12 months

# Regulatory History

- After IDE approval in 2013, the study enrolled for 5 years
- Multiple protocol changes were enacted, some to assist in enrollment
  - 34 IDE supplements for various changes, including to the design and manufacturing of the device, clinical protocol modifications, and other administrative changes
  - The two most significant changes were to the primary endpoint analysis and primary endpoint assessment timepoint (to be discussed)
- Trial terminated early and data were submitted to FDA
  - Predefined study success criteria not met
  - FDA concluded that a robust primary endpoint treatment effect was not present and we found no greater benefit of the Lutonix DCB vs. PTA for secondary effectiveness endpoints

# Revision to FD&C Act, July 2012

- FDA will only disapprove an IDE due to concerns related to subject safety and protections
- FDA will not disapprove an IDE because we do not believe that the investigation will support approval of a device
- Feedback or concerns related to the study design can be provided as study design considerations

# Regulatory History – IDE Changes

- Major protocol changes made during course of investigation include:
  - Removal of hemodynamic inclusion criteria
  - Rutherford Classification 3 patient enrollment permitted
  - Increased sample size and addition of interim analyses
  - Shortened primary effectiveness endpoint from 12 months to 6 months
  - Added co-primary effectiveness endpoint for “proximal segment flow pathway”
  - Added secondary effectiveness endpoint excluding early mechanical recoil
  - Early study termination

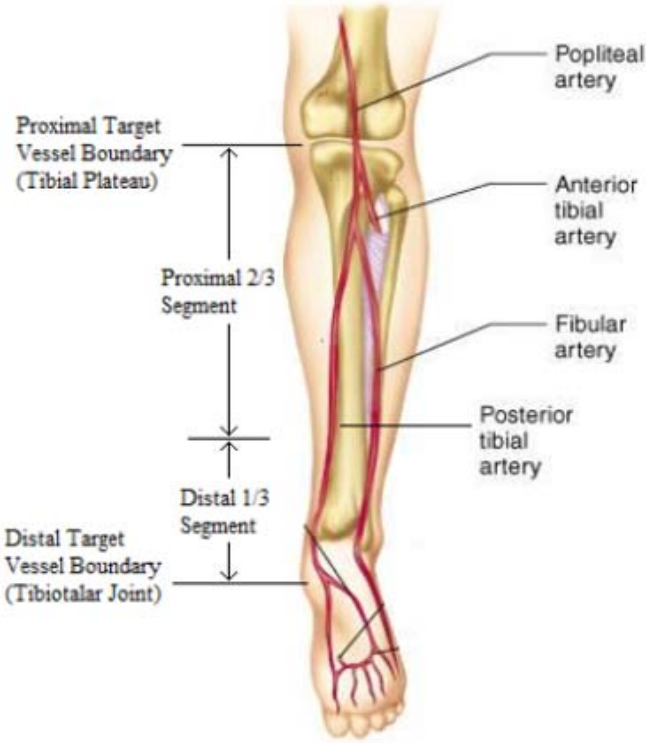
# Primary Effectiveness Endpoint Assessment Change From 12 months to 6 Months

- Change occurred:
  - Approximately 3 years after original IDE approval
  - After enrollment of 325 patients
- Sponsor rationale: Clinical meaningfulness of a 6-month assessment due to aggressive nature of the disease.
- FDA feedback:
  - Acknowledged that an improvement at 6 months may be clinically meaningful
  - **Durability of the treatment effect was also valued by patients and physicians and would be important in demonstrating a reasonable assurance of effectiveness and a favorable benefit-risk profile for the Lutonix 014 DCB.**

# Added Proximal Segment Co-Primary Effectiveness Endpoint

- Change occurred:
  - Approximately 4.5 years after the original IDE approval
  - After enrollment of 440 patients

- Background:
  - "Flow pathway": analysis unit for the primary effectiveness endpoint
  - Includes the following arteries: popliteal, tibioperoneal, anterior tibial, posterior tibial, and peroneal
  - Multiple lesions may be present in a single flow pathway
  - "Proximal segment flow pathway": Vessels that are entirely within the proximal 2/3 segment of the target flow pathway boundary or are split across the 2/3 segment cut-off

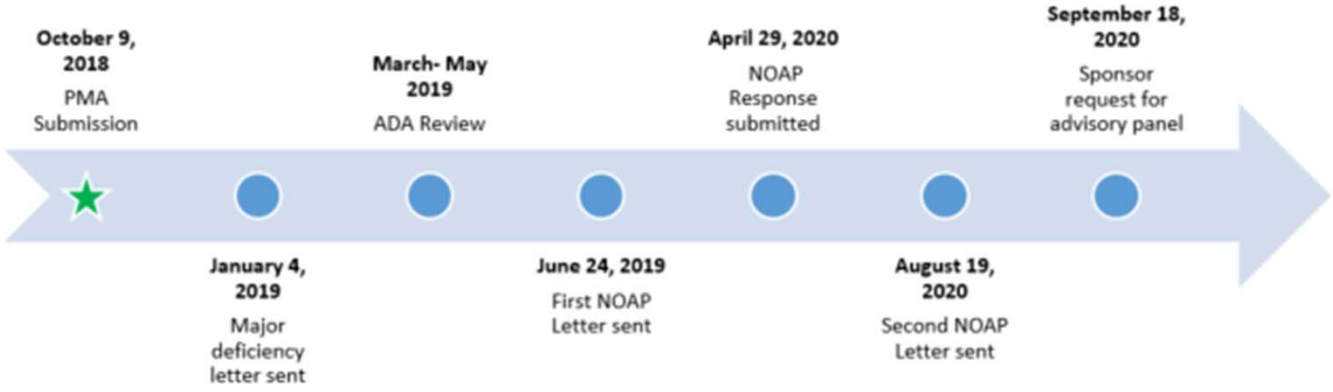


# Proximal Segment Analysis - Background

- The co-primary effectiveness endpoint included two assessments:
  - Assessment 1: For “full flow pathway”
  - Assessment 2: If the “full flow pathway” assessment did not show superiority, the analysis was repeated for the “proximal segment flow pathway”
- Success = either of the analyses reach statistical significance
  - Due to this change, and addition of interim analyses (to be discussed), the alpha level to reach statistical significance was reduced to 0.0085 for both co-primary endpoints in order to control overall study type 1 error rate at 0.025
- Only the full flow pathways analysis is presented

# Regulatory History – PMA Timeline

- PMA submission after early IDE termination
- Major Deficiency Letter – questions regarding effectiveness
- Agency Directed Assignment (ADA) - requested input on effectiveness
- Two Not Approvable (NOAP) letters issued
- Sponsor request for an  Advisory Committee Meeting



## IDE Study Design and Statistical Analysis Plan (SAP)

Rong (Rona) Tang, Ph.D.
*Statistical Reviewer*
CDRH/OCEA/DCEAII

# Pivotal Clinical Trial Design

- Prospective, multicenter, 2:1 randomized, controlled trial
- Compared the Lutonix 014 DCB (test group) vs. standard balloon angioplasty (control group) for treatment of BTK arteries
- Sample Size: Approved for up to 1000 subjects to obtain 840 flow pathways evaluable for the primary effectiveness endpoint
- Sites: 75 Global Sites

# Primary Safety Endpoint

Definition: Freedom from both BTK MALE (major adverse limb event) + POD (peri-operative death ) at 30 days

- MALE:
  - —Above ankle amputation; or
  - —Major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) of the index limb involving a BTK artery
- POD: All-cause mortality

# Primary Safety Endpoint
# Statistical Hypothesis and Analysis

- Hypothesis:

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

where p is the success rate in each treatment group arm through 30 days and δ is the non-inferiority margin of 12%

- Pre-Specified Statistical Analysis:
  - Primary analysis population: Intent-to-Treat
  - Analysis unit: Per-Patient
  - Farrington and Manning test with one-sided alpha = 0.025

# Primary Effectiveness Endpoint

Definition: Limb Salvage + Primary Patency at 6 months

- Limb Salvage: Freedom from above ankle amputation in index limb
- Primary Patency: Freedom from target lesion occlusion and freedom from clinically driven target lesion revascularization (CD-TLR)*

*CD-TLR defined as CEC-adjudicated reintervention due to worsening Rutherford class, stagnant or worsening wound healing, or a new or recurrent wound

# Co-Primary Effectiveness Endpoint Statistical Hypothesis

- Hypothesis :

$$H_0: \beta \leq 0 \text{ vs } H_1: \beta > 0$$

  Where $\beta$ is the increment in log odds of success in the treatment group

- Up to two hypotheses may be tested
  - Full flow pathway analysis
  - If not successful, proximal segment flow pathway population

# Co-Primary Effectiveness Endpoint Statistical Analysis

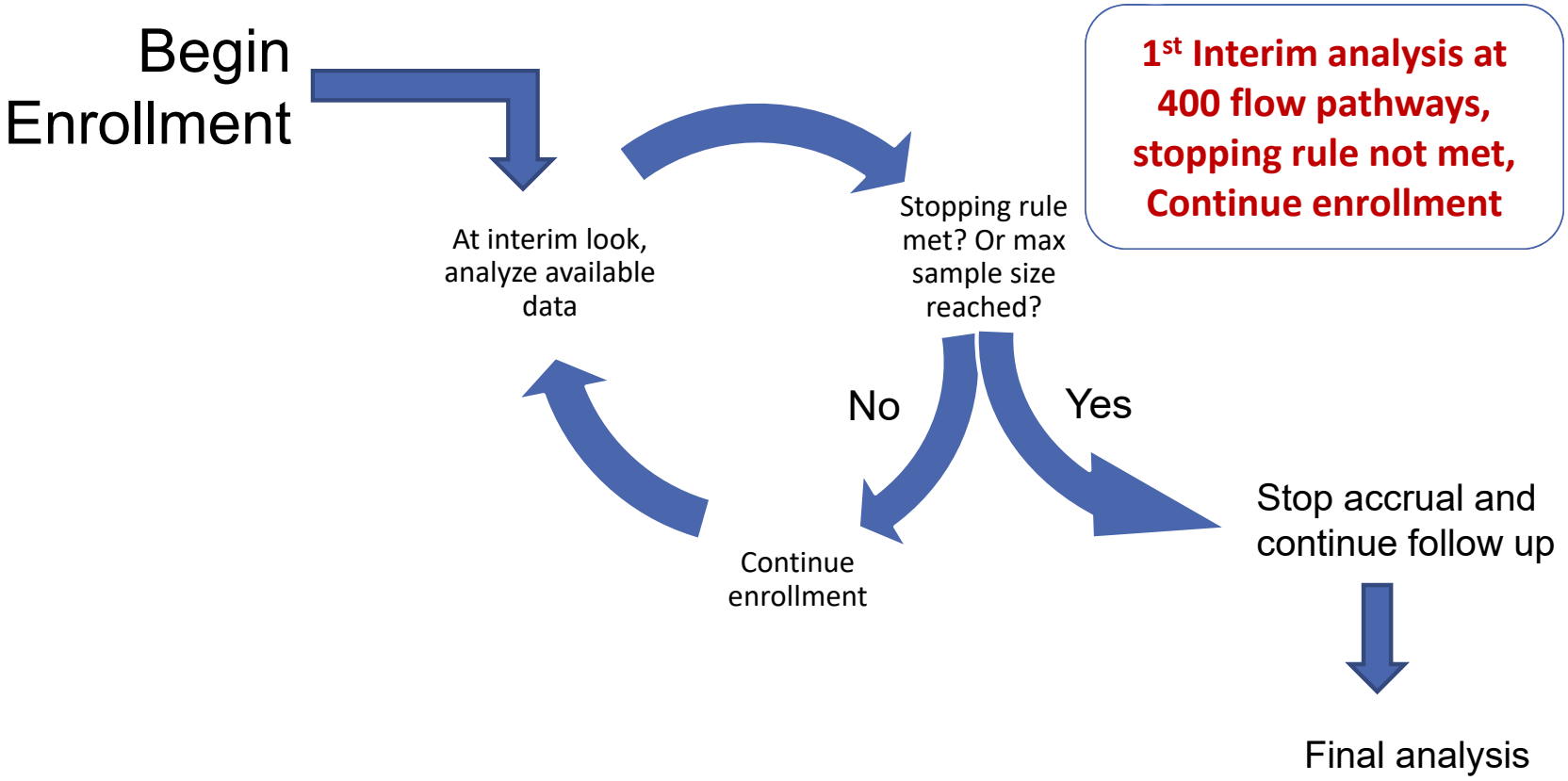
Pre-Specified Statistical Analysis

- Primary analysis population: intent-to-treat
- Analysis unit: per-flow pathway
- Two hypotheses each tested at an alpha = 0.0085
  - First test the full flow pathway
  - If the full flow pathway test is not successful, retest the hypothesis for the proximal segment flow pathway
- Logistic regression with random effects

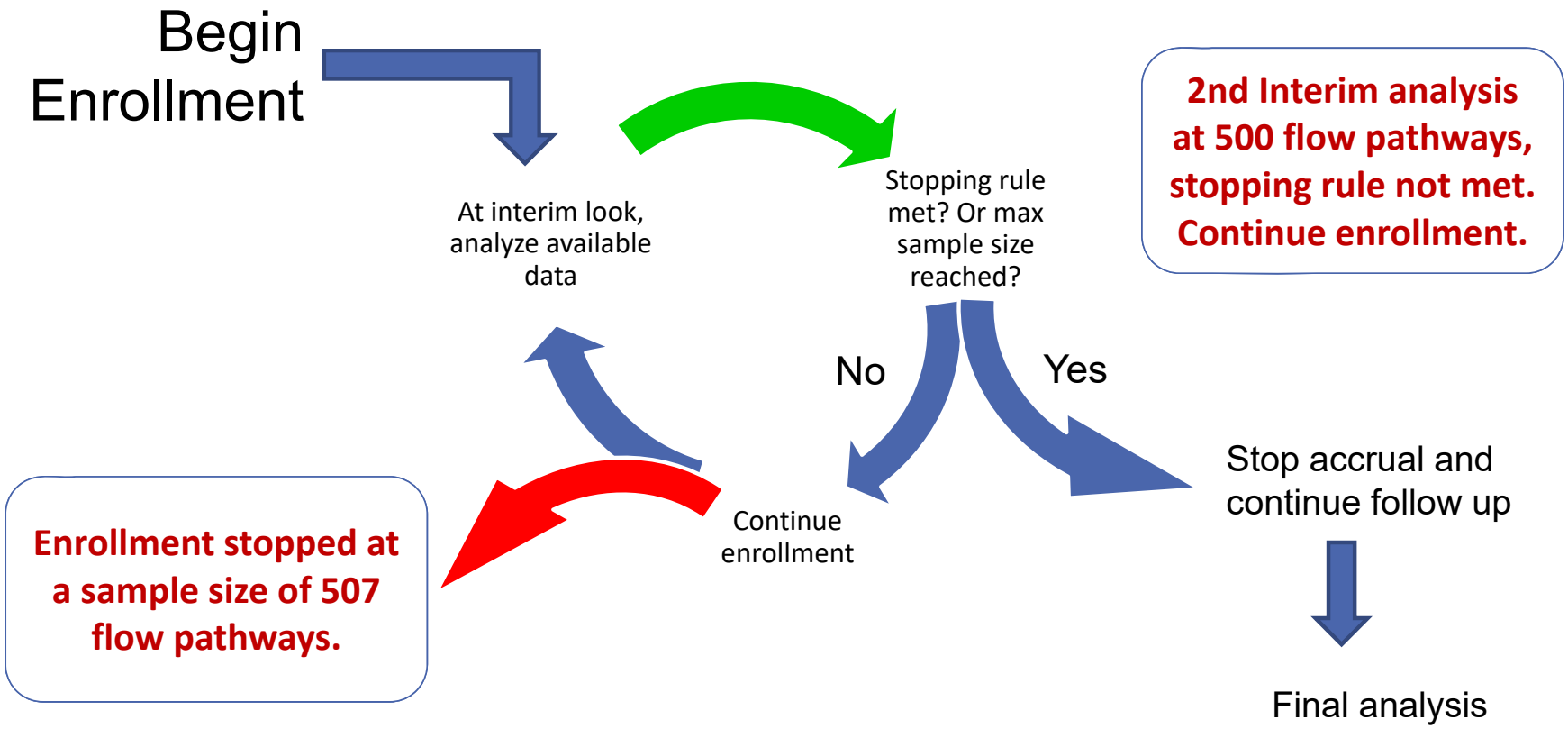
# Interim Analyses

- Bayesian decision process was used to adjust the sample size to a maximum  of 840 flow pathways.
- May occur when 400, 500, 600, and 700 randomized flow pathways are treated.

# Adaptive by Design Process for Primary Effectiveness Endpoint

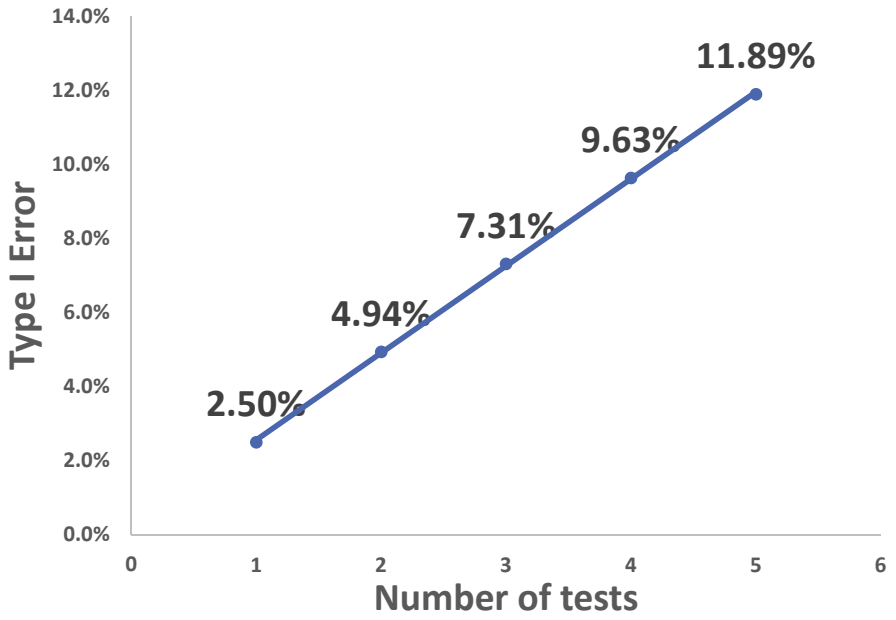


# Adaptive by Design Process for Primary Effectiveness Endpoint



# Interim Analysis and False Positive Rate Inflation

- Without interim analysis:
  - Comparing p-value to 0.025
- With interim analyses to allow for early stopping for effectiveness:
  - Increased chance of type I error (false positive rate)
  - Reduce significance level required to maintain an overall 0.025 false positive rate



# Alpha Level Determination

Pre-specified alpha allocation for the primary effectiveness endpoint

Two final hypothesis tests with significance level = 0.0085 each

Interim analysis with early stopping for potential efficacy (up to 4 analyses)

Overall one-sided type I error rate controlled at 0.025 (via simulation)

# Pre-Specified Hypothesis Testing for Secondary Endpoints

- Superiority may be tested at 6 months for the following:
  - Primary patency with exclusion of early mechanical recoil
  - Primary patency
  - Freedom from clinically-driven TLR
  - Composite of freedom from above-ankle amputation, unhealed wound, ischemic rest pain, target vessel occlusion, and clinically-driven target vessel revascularization (TVR)
- Sequential testing performed only if the study showed success for the primary endpoints

**Since the primary effectiveness endpoint was not met, secondary endpoint hypotheses were not tested**

## IDE Study Design and Clinical Data Review

Donna Buckley, M.D., M.S.
*Interventional Radiologist/Medical Officer*
CDRH/OPEQ/OCVD/PIDT

# Key Selection Criteria

- Rutherford Classification
  - Rutherford 5 (minor tissue loss)
  - Rutherford 4 (ischemic rest pain)
  - Rutherford 3 (severe claudication)
    - Added to increase enrollment; accounted for ~10% of enrolled patients
- Stenosis >70% in one or two BTK arteries
- Lesion Dimensions
  - Total length of all target lesions <320 mm
  - 2-4 mm diameter
- Reconstitution of flow at or above the ankle
- Hemodynamic criteria were removed to increase enrollment

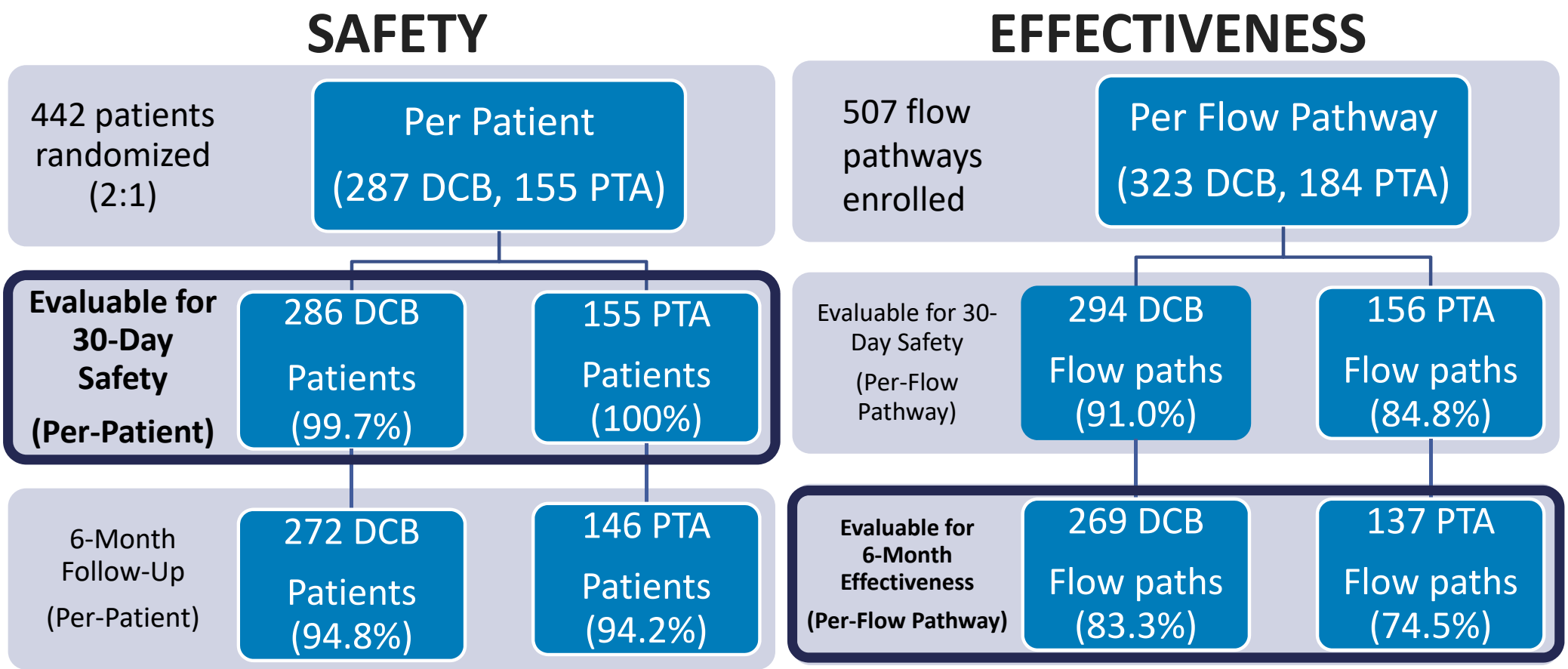
# Design Elements

- Third Party Review
  - Data Monitoring Committee (DMC)
  - Clinical Events Committee (CEC)
  - Core Laboratories: Duplex Ultrasound (DUS) and angiography
- Blinding
  - Patient was blinded to 6 months
  - CEC, Core Labs, and Sponsor were blinded
  - Physicians performing the index procedure and follow-up clinical evaluations were *not blinded*

# Select Secondary Endpoints

- Primary Safety Endpoint Evaluated Longer Term
- Primary Effectiveness Endpoint Evaluated Longer Term
- Wound Healing
- Amputation: Major (above ankle) and minor (below ankle)
- Freedom from clinically-driven target lesion revascularization (CD-TLR)
- Primary Patency (both including and excluding early mechanical recoil)
- Secondary Patency
- Hemodynamic outcomes (ABI, TBI)
- Change in Rutherford Classification
- Quality of Life (EQ-5D; Change in Walking Impairment Questionnaire (WIQ))
- All-Cause Mortality

# Enrollment and Accountability



# Baseline Demographics and Lesion Characteristics

## Baseline Demographics

| | DCB Subjects (N=287) | PTA Subjects (N=155) |
|---|---|---|
| Mean Age, Years | 72.9 | 72.9 |
| Gender, n/N (%) | | |
| Male | 202/287 (70.4%) | 104/155 (67.1%) |
| Female | 85/287 (29.6%) | 51/155 (32.9%) |
| Race, n/N (%) | | |
| American Indian/Alaska Native | 1/287 (0.3%) | 0/155 (0.0%) |
| Asian | 25/287 (8.7%) | 15/155 (9.7%) |
| Black or African American | 33/287 (11.5%) | 12/155 (7.7%) |
| White | 226/287 (78.7%) | 127/155 (81.9%) |
| Other | 2/287 (0.7%) | 1/155 (0.6%) |
| Rutherford Category, n (%) | | |
| 3 | 26 (9.1%) | 16 (10.3%) |
| 4 | 100 (34.8%) | 52 (33.5%) |
| 5 | 161 (56.1%) | 87 (56.1%) |
| History of Risk Factors, n/N (%) | 285 / 287 (99.3%) | 155 / 155 (100.0%) |
| Diabetes | 204 / 287 (71.1%) | 106 / 155 (68.4%) |
| Dyslipidemia | 225 / 287 (78.4%) | 116 / 155 (74.8%) |
| Hypertension | 264 / 287 (92.0%) | 148 / 155 (95.5%) |
| Cigarette Smoking | 170 / 287 (59.2%) | 89 / 155 (57.4%) |
| Current | 43 / 287 (15.0%) | 19 / 155 (12.3%) |
| Former | 127 / 287 (44.3%) | 70 / 155 (45.2%) |

## Lesion Characteristics

| | DCB Lesions (N=352) | PTA Lesions (N=212) |
|---|---|---|
| Lesion Type, n (%) | | |
| 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) | | |
| Mean (SD) | 111.8 (92.64) | 94.7 (85.36) |
| Any Calcification, n/N (%) | 211/352 (59.9%) | 115/212 (54.2%) |
| Severe Calcification, n/N (%) | 53/352 (15.1%) | 28/212 (13.2%) |
| TASC Lesion Type, n (%) | | |
| A | 182 (51.9%) | 131 (62.7%) |
| B | 61 (17.4%) | 32 (15.3%) |
| C | 62 (17.7%) | 28 (13.4%) |
| D | 46 (13.1%) | 18 (8.6%) |

**Similar**

- **Demographics & Medical Conditions**
- **Lesion Characteristics**
- **Medication Usage**

# Primary and Long-Term Safety Outcomes

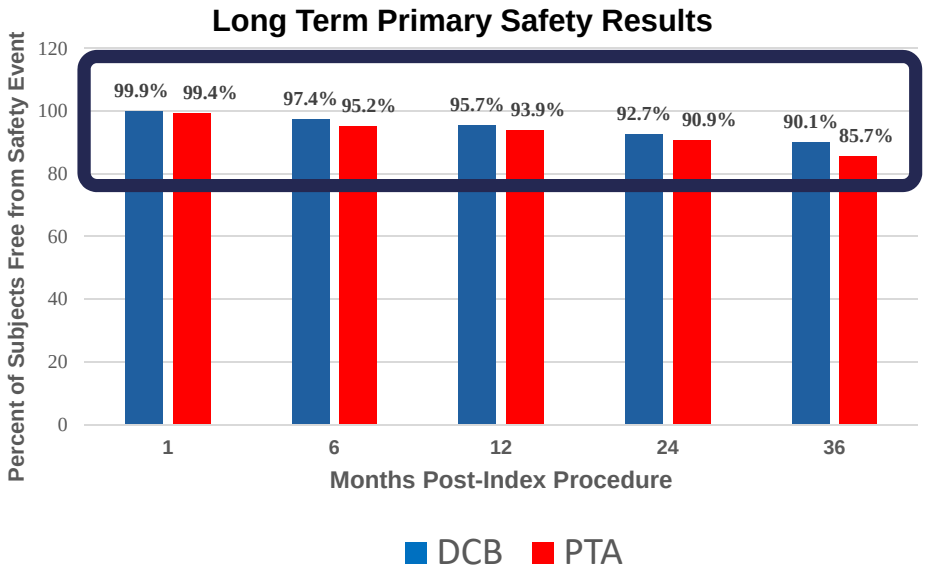
# Primary Safety Endpoint Results

## Freedom from both BTK MALE (major adverse limb event) + POD (peri-operative death ) at 30 days (ITT Per-Patient)

| | DCB Subjects (N=287) | PTA Subjects (N=155) | Difference | P value |
|---|---|---|---|---|
| Free from Primary Safety Events through 30 Days | 284 / 286 (**99.3%**) (97.5%, 99.9%) | 154 / 155 (**99.4%**) (96.5%, 100.0%) | -0.1% (-3.9%, 3.8%) | < 0.0001 |
| Primary Safety Events | | | | Non-inferiority margin = 12% |
| Above Ankle Amputation ≤ Day 30 | 0 | 0 | | |
| Major Re-intervention ≤ Day 30 | 1 | 0 | | **SAFETY ENDPOINT MET** |
| Death ≤ Day 30 | 1 | 1 | | |

# Long-Term (36-Months) Safety Results

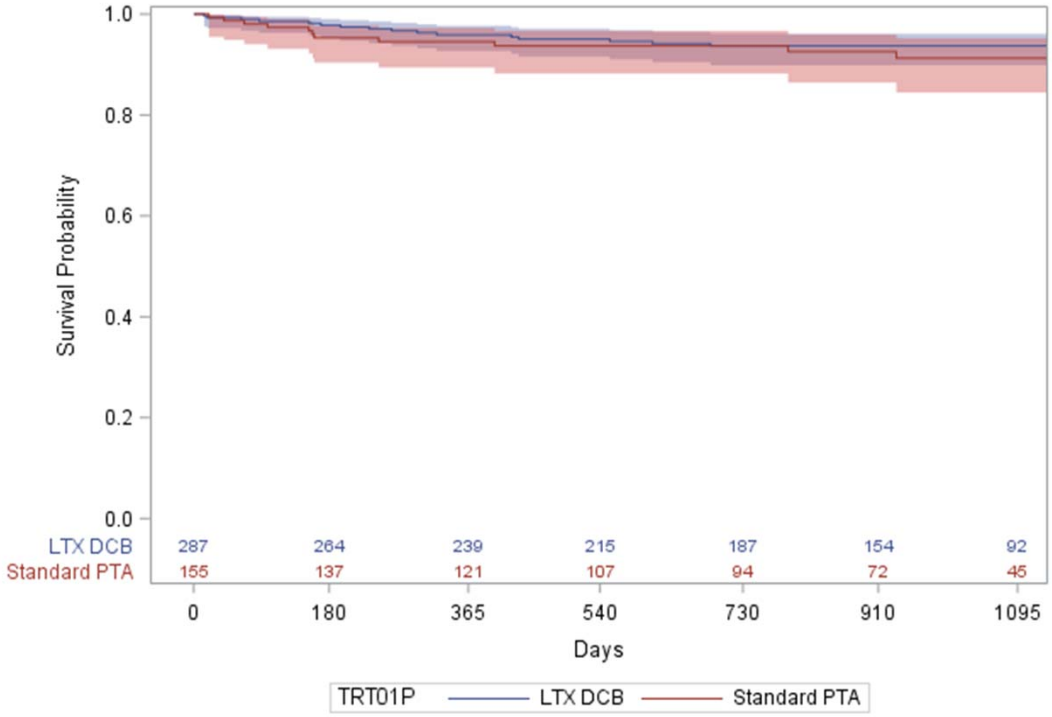
**Freedom from BTK MALE (Major Adverse Limb Event)**
**+ POD (Peri-Operative Death ) through 36 Months**
(ITT Per-Patient; Binary Outcome )




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

# Long-Term (36-Months) Safety Results

**Freedom from BTK MALE (Major Adverse Limb Event)**
**+ POD (Peri-Operative Death ) through 36 Months**
(ITT Per-Patient; KM Estimates)



# Primary and Long-Term Effectiveness Outcomes

# Primary Effectiveness Endpoint Results

## Limb Salvage + Primary Patency at 6 months (ITT Per-Flow Pathway)

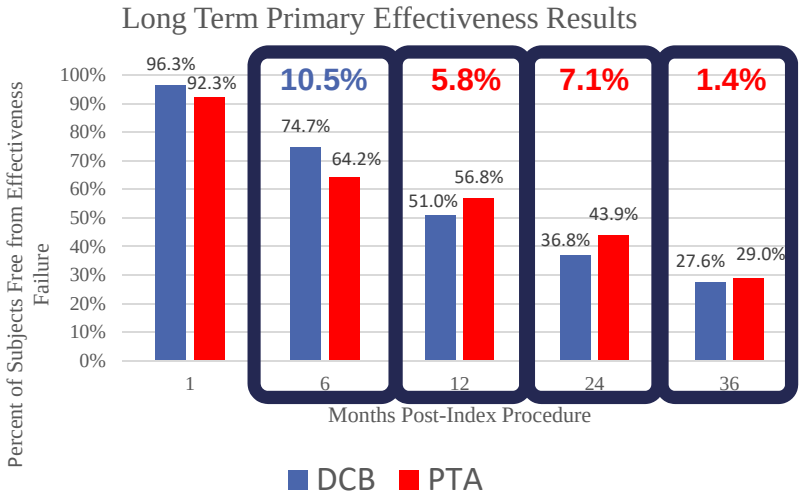
| | DCB n/N (%) (95% CI) | PTA n/N (%) (95% CI) | Difference in Response (95% CI) | P-value |
|---|---|---|---|---|
| **Free from Primary Effectiveness Failure at 6 Months** | 201/269 (**74.7%**) (69.1%, 79.8%) | 88/137 (**64.2%**) (55.6%, 72.2%) | 10.5% (0.3%, 18.8%) | **0.0222** P-value **not** <0.0085 for superiority |
| **Composite Endpoint Failure Events ≤ Day 210, n** | | | | **EFFECTIVENESS ENDPOINT NOT MET** |
| Patients with major amputation | 4 (1.4%) | 3 (2.0%) | | |
| Pathways with clinically driven TLR | 28 (10.4%) | 30 (21.9%) | | |
| Pathways with total occlusion on imaging | 42 (15.6%) | 21 (15.3%) | | |

| | DCB n/N (%) | PTA n/N (%) |
|---|---|---|
| All evaluable pathways with clinically driven TLR | 28/303 (9.2%) | 30/172 (17.1%) |

# Long-Term (36-Months) Effectiveness Results

## **Limb Salvage + Primary Patency through 36 Months**

(ITT Per-Flow Pathway; Binary Outcome)

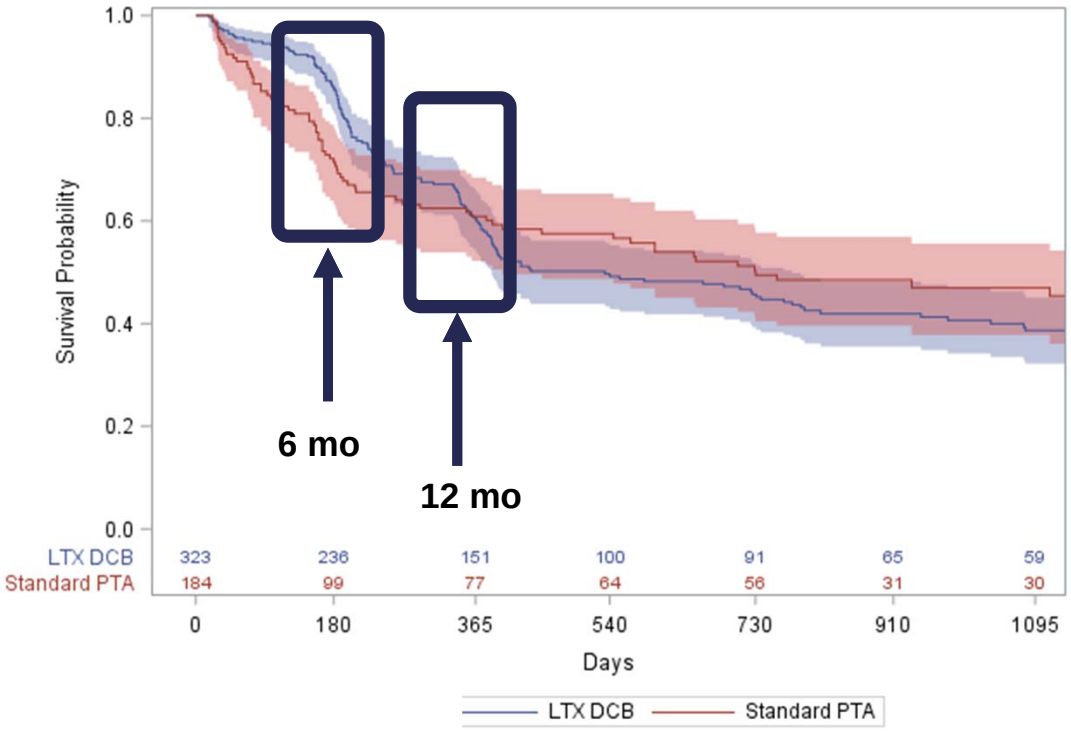



| Visit | DCB Pathways (N=323) Response Rate | PTA Pathways (N=184) Response Rate | Difference (95% CI) |
|---|---|---|---|
| 30 Days | 283 / 294 (96.3%) | 144 / 156 (92.3%) | 4.0% (-1.0%, 7.9%) |
| 6 Months | 201 / 269 (74.7%) | 88 / 137 (64.2%) | 10.5% (0.3%, 18.7%) |
| 12 Months | 128 / 251 (51.0%) | 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% |

# Long-Term (36-Months) Effectiveness Results

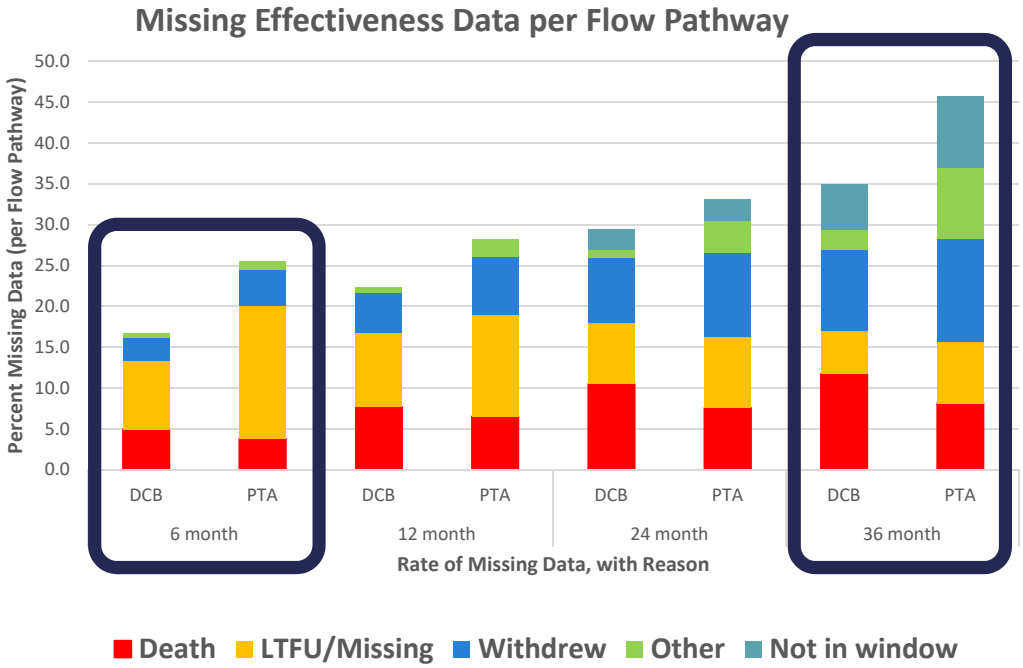
**Limb Salvage + Primary Patency through 36 Months**

(ITT Per-Flow Pathway; KM Estimates)



# Missing Effectiveness Outcome Data

# Missing Data (ITT Effectiveness)



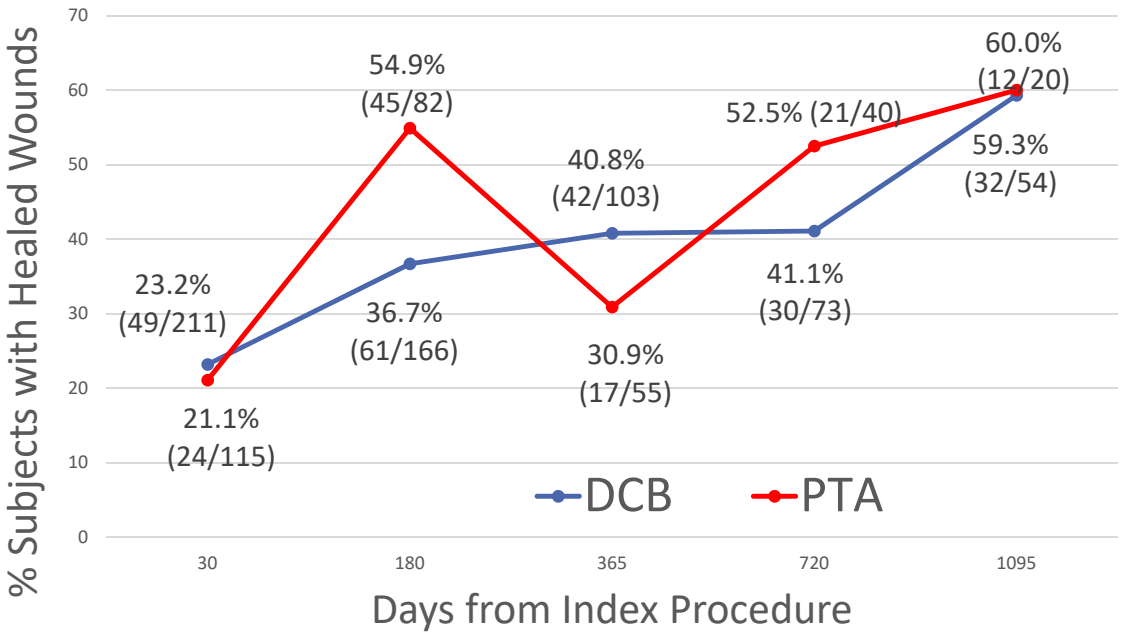

- Missing data higher for the PTA group at all time points
- Even at the 6 month time point, there is substantial amount of missing data, notably LTFU in the PTA group
- High rates of missing data present across all follow-up time points

High rates of missing data add uncertainty regarding study conclusions

# Secondary Endpoints
# Wounds

# Wound Healing

## Percentage of Healed Wounds (ITT Per Patient)

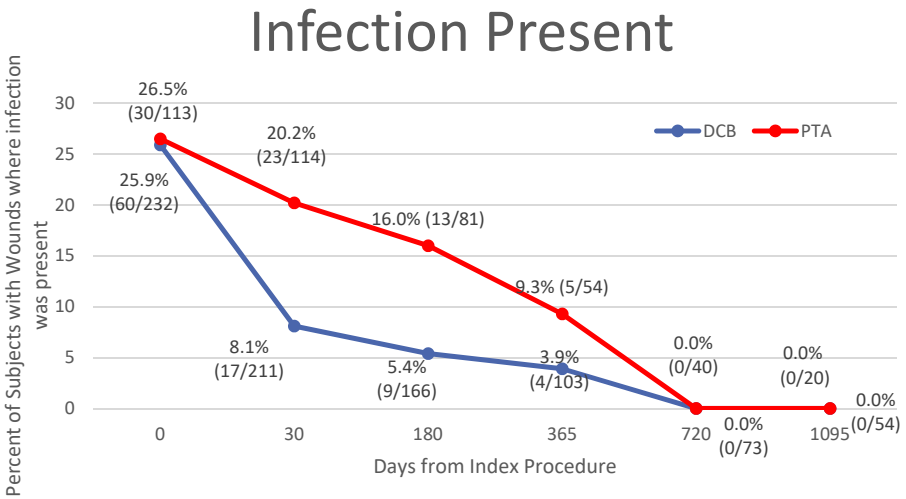


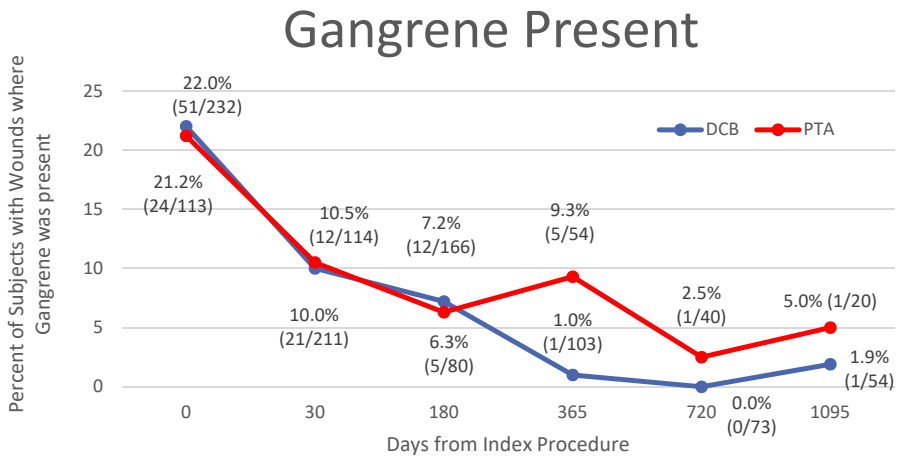

**Limitations**

- No uniform wound assessment or healing scale used
- Wounds assessed by the unblinded physicians performing treatment
- Wound photographs did not undergo third-party independent review
- No photo required if a wound was deemed healed

# Wound Healing

## Percentage of Healed Wounds (ITT Per Patient)



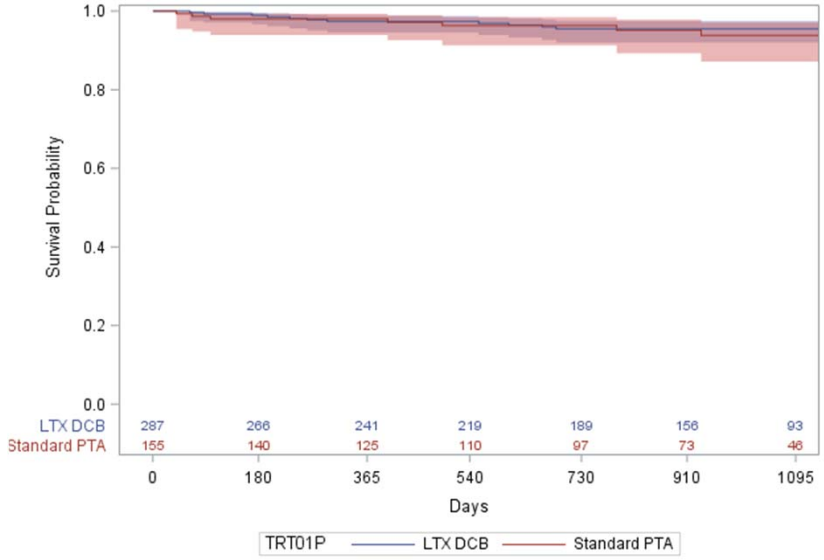



# Secondary Endpoints

# Freedom From Amputation

# Amputation

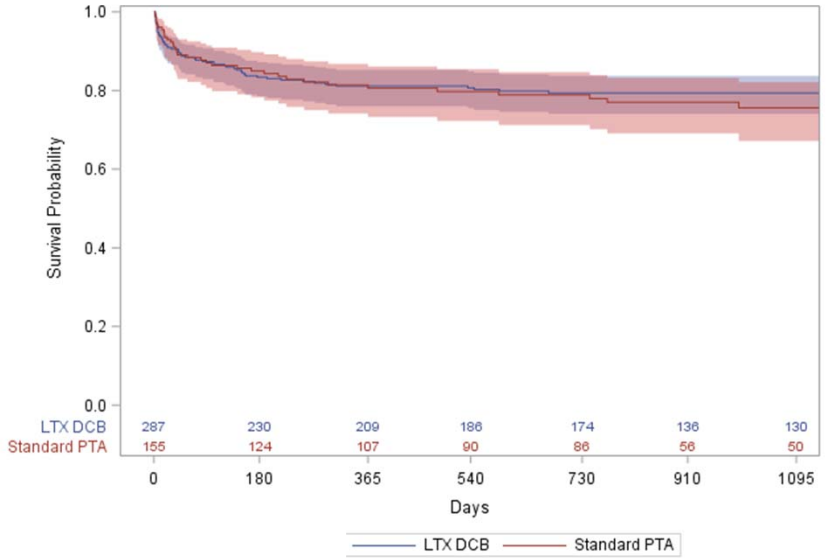
**Freedom From Major Amputation**
(ITT Per-Patient KM Estimates)




**Freedom from Major Amputation (ITT Per-Patient Binary Outcomes)**

| Visit | DCB Response Rate | PTA Response Rate | Difference 95% CI |
|---|---|---|---|
| 30 Days | 286/286 (100.0%) | 154/155 (99.4%) | 0.6% (-0.6%, 1.9%) |
| 6 Months | 267/271 (98.5%) | 142/145 (97.9%) | 0.6% (-2.1%, 3.3%) |
| 12 Months | 244/251 (97.2%) | 127/130 (97.7%) | -0.5% (-3.8%, 2.8%) |
| 24 Months | 204/215 (94.9%) | 103/109 (94.5%) | 0.4% (-4.8%, 5.6%) |
| 36 Months | 148/159 (93.1%) | 67/ 74 (90.5%) | 2.5% (-5.2%, 10.3%) |

**Freedom From Minor Amputation**
(ITT Per-Patient KM Estimates)




**Freedom from Minor Amputation (ITT Per-Patient Binary Outcomes)**

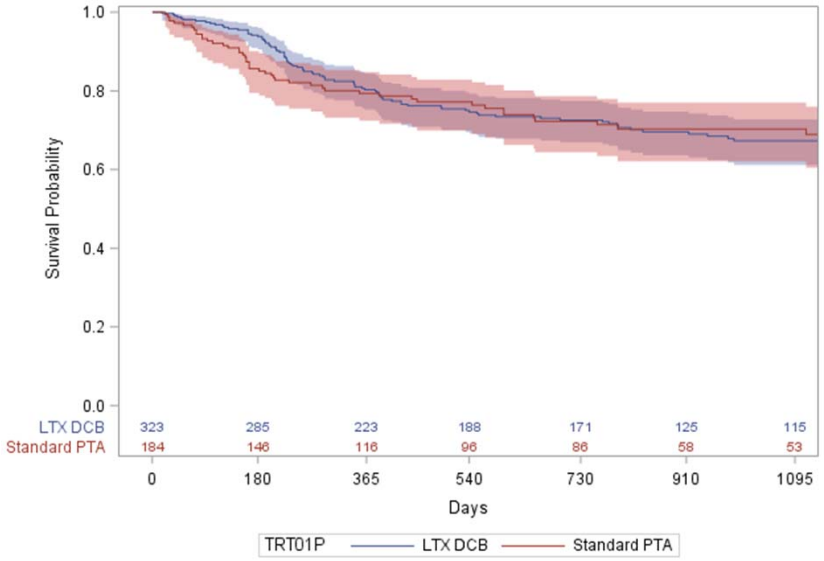
| Visit | DCB Response Rate | PTA Response Rate | Difference (95% CI) |
|---|---|---|---|
| 30 Days | 272 / 286 (95.1%) | 143 / 155 (92.3%) | -2.8% (-7.7%, 2.0%) |
| 6 Months | 241 / 274 (88.0%) | 128 / 147 (87.1%) | -0.9% (-7.5%, 5.8%) |
| 12 Months | 219 / 257 (85.2%) | 110 / 135 (81.5%) | -3.7% (-11.6%, 4.1%) |
| 24 Months | 183 / 226 (81.0%) | 88 / 117 (75.2%) | -5.8% (-15.1%, 3.6%) |
| 36 Months | 135 / 178 (75.8%) | 53 / 83 (63.9%) | -11.9% (-24.1%, 0.1%) |

# Secondary Endpoints

# Freedom From Clinically-Driven Target Lesion Revascularization (CD-TLR)

# CD-TLR

## Freedom From CD-TLR
(ITT Per-Flow Pathway; KM Estimates)




## Freedom From CD-TLR
(ITT Per Plow-Pathway; Binary Outcomes)

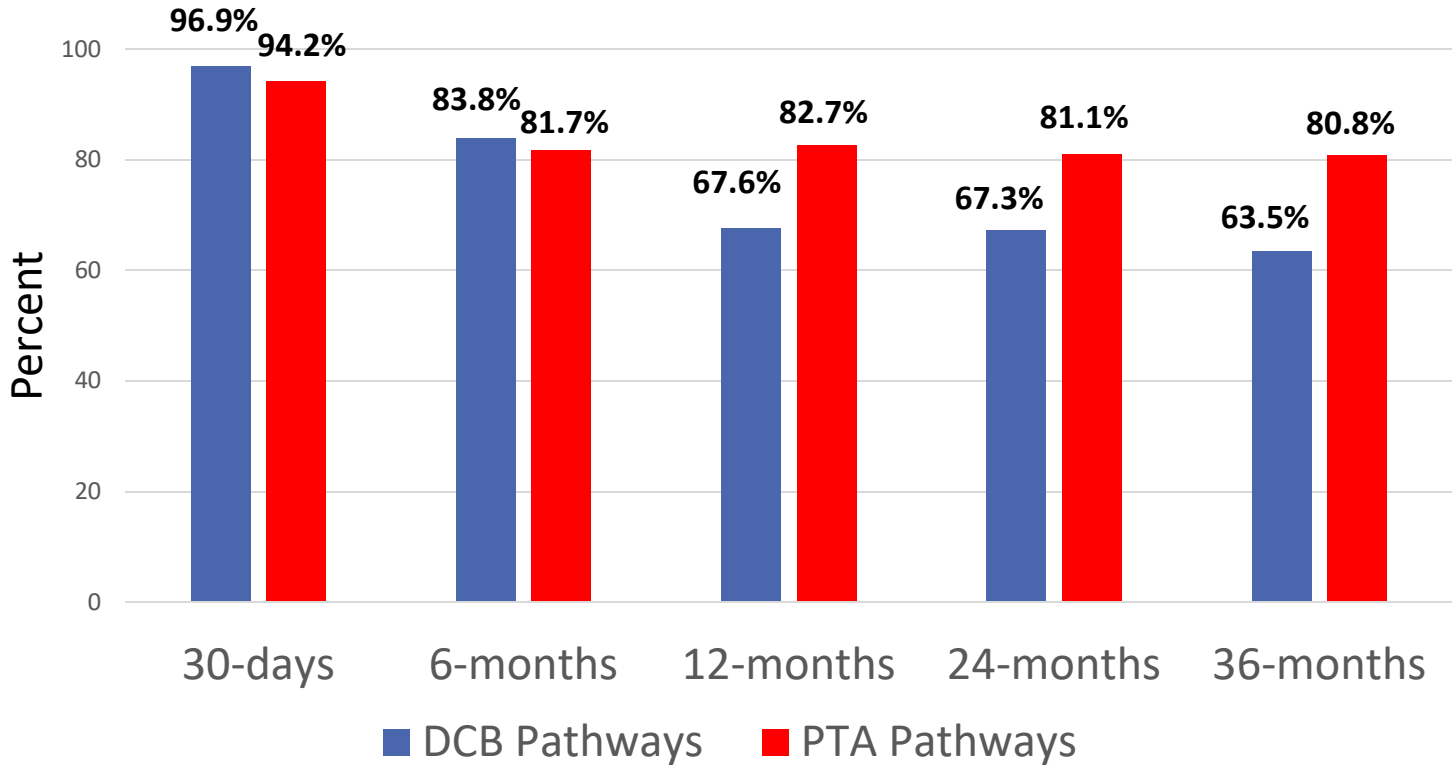
| Visit | DCB (N=323) Response Rate | PTA (N=184) Response Rate | Difference (95% CI) |
|---|---|---|---|
| 30 Days | 317/321 (98.8%) | 179/184 (97.3%) | 1.5% (-2.0%, 4.1%) |
| 6 Months | 275/303 (90.8%) | 142/172 (82.6%) | 8.2% (1.5%, 13.3%) |
| 12 Months | 216/281 (76.9%) | 116/152 (76.3%) | 0.6% (-9.8%, 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%) |

# Secondary Endpoints

# Secondary Patency

# Secondary Patency

**Definition:** Freedom from total occlusion independent of whether or not patency was re-established via an endovascular procedure

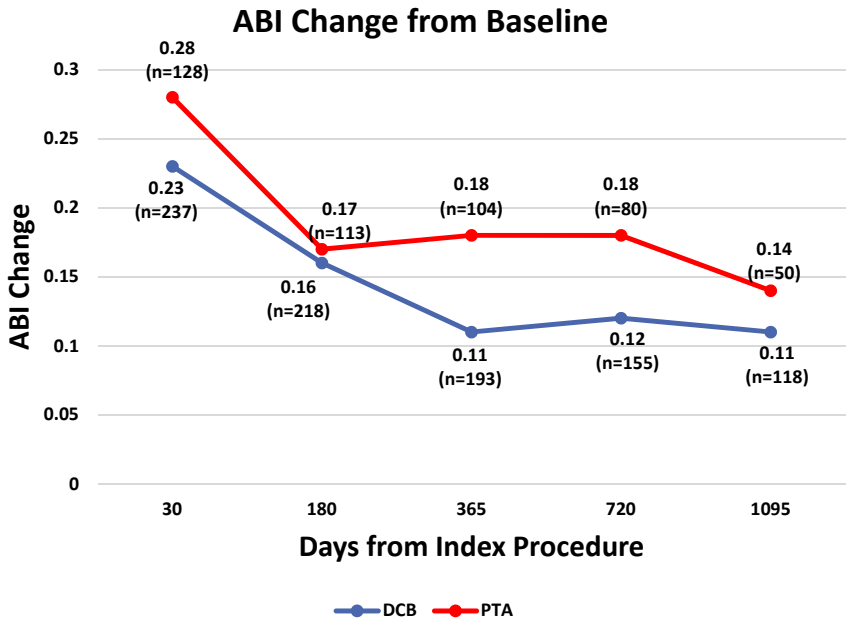


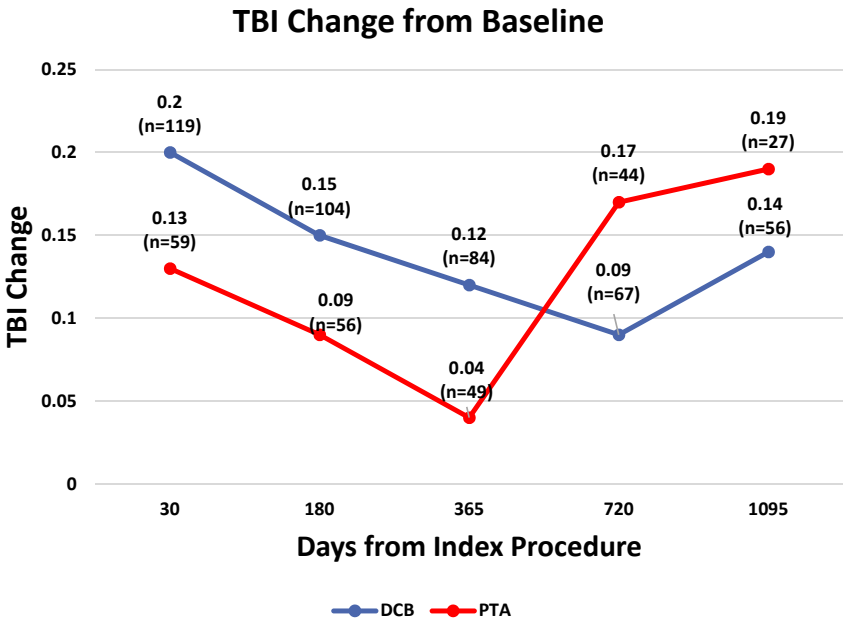
# Secondary Endpoints

# Ankle Brachial Index (ABI) and Toe Brachial Index (TBI)

# ABI and TBI

## Change in Hemodynamic Outcomes (ITT Per-Patient)

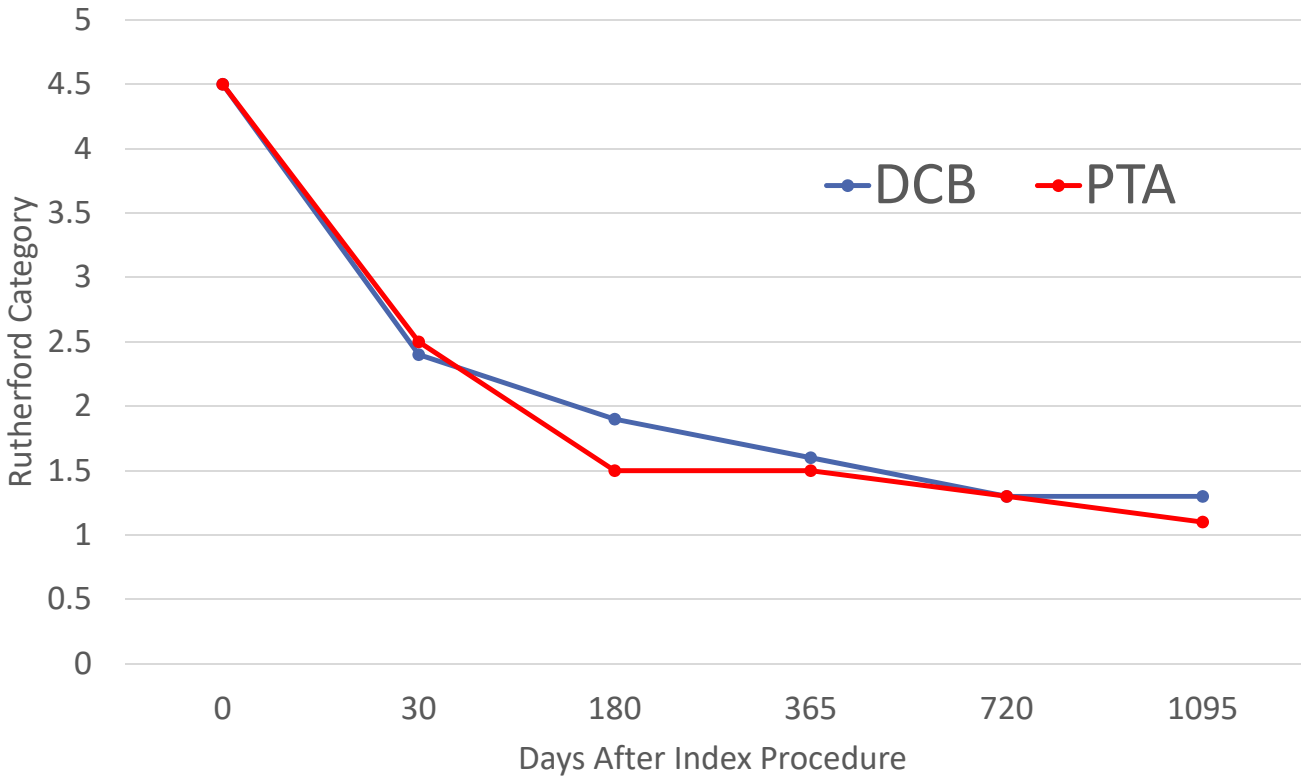


# Secondary Endpoints
# Rutherford Classification

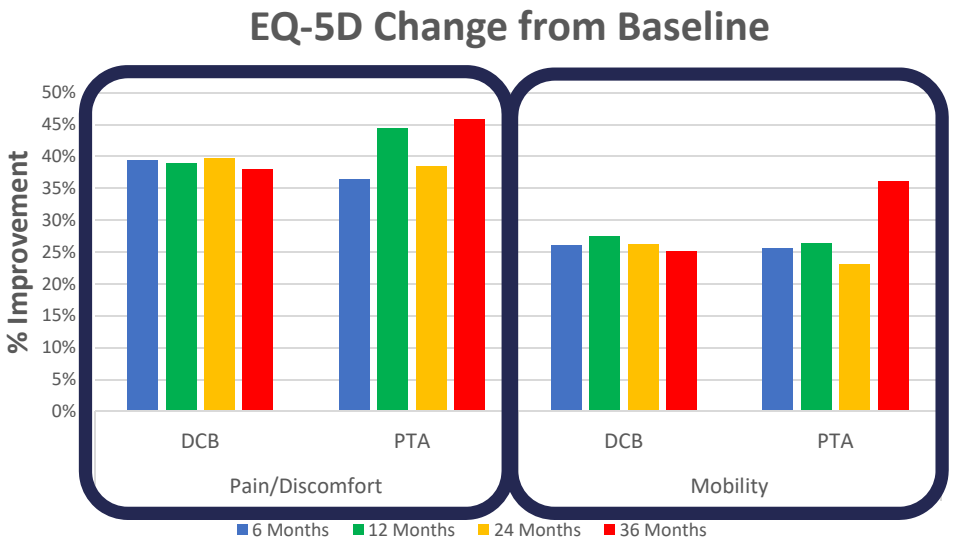
# Rutherford Classification

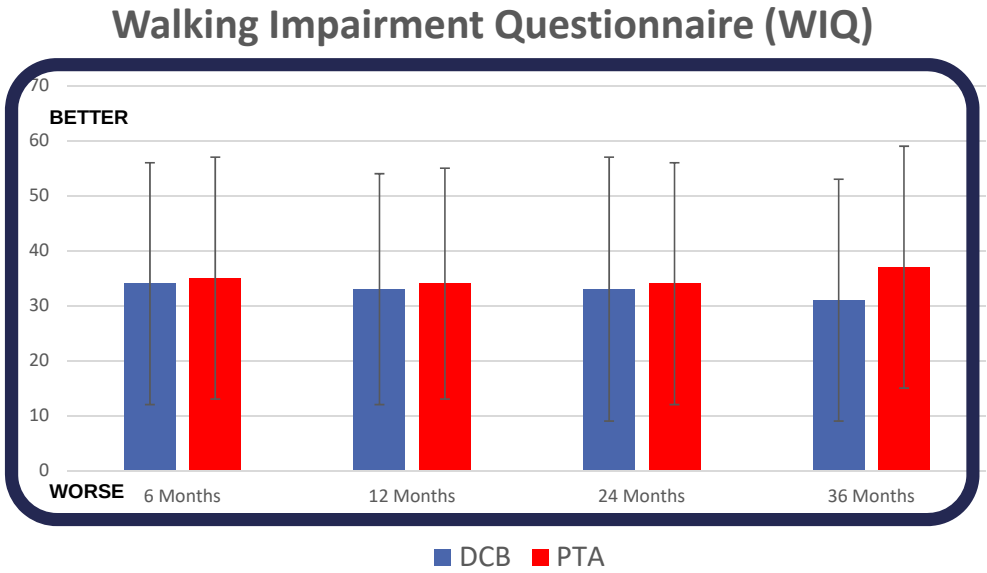
## Rutherford Classification Through 36 Months (ITT Per-Patient)



# Secondary Endpoints
# Quality of Life (QoL) Assessment

# EQ-5D and WIQ

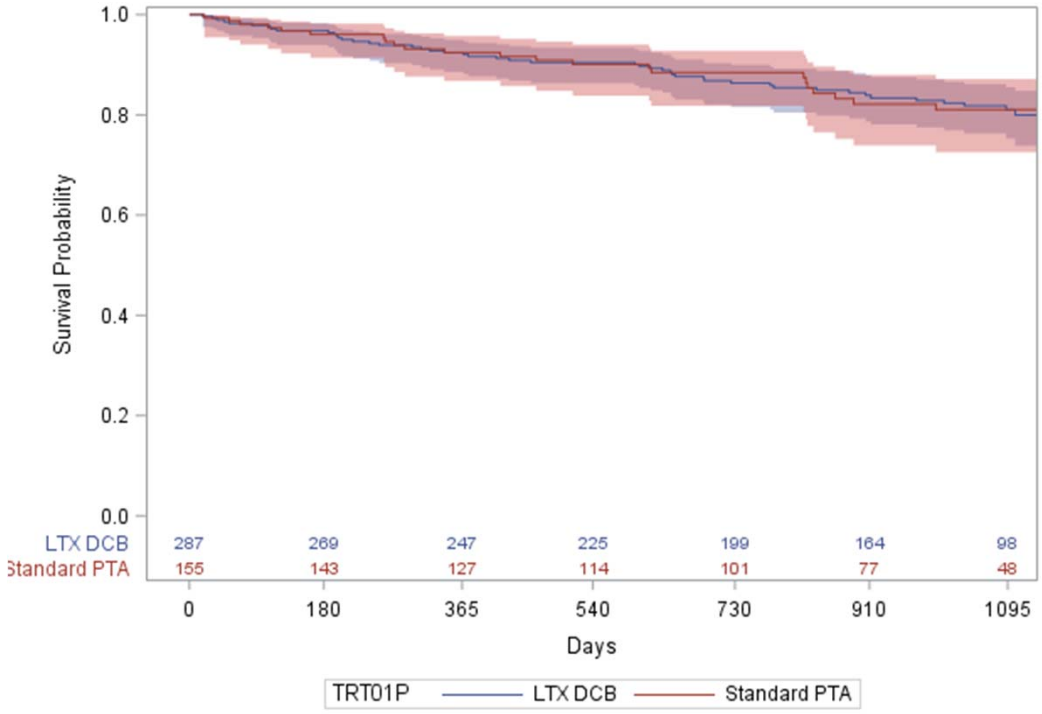

EQ-5D Change from Baseline
% Improvement
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
DCB
PTA
Pain/Discomfort
DCB
PTA
Mobility
6 Months
12 Months
24 Months
36 Months


Walking Impairment Questionnaire (WIQ)
70
BETTER
60
50
40
30
20
10
0
WORSE
6 Months
12 Months
24 Months
36 Months
DCB
PTA

# Secondary Endpoints
# All-Cause Mortality

# Mortality

## **All-Cause Mortality Through 36 Months** (ITT Per-Patient)




| Visit | DCB Pathways (N=287) Response Rate | PTA Pathways (N=155Response Rate | Difference (95% CI) |
|---|---|---|---|
| 30 Days | 3 / 286 (1.0%) | 1 / 155 (0.6%) | 0.4% (-1.3%, 2.1%) |
| 6 Months | 14 / 280 (5.0%) | 6 / 150 (4.0%) | 1.0% (-3.0%, 5.0%) |
| 12 Months | 23 / 270 (8.5%) | 11 / 139 (7.9%) | 0.6% (-5.0%, 6.2%) |
| 24 Months | 38 / 247 (15.4%) | 16 / 124 (12.9%) | 2.5% (-4.9%, 9.9%) |
| 36 Months | 47 / 200 (23.5%) | 23 / 94 (24.5%) | -1.0% (-11.5%, 9.5%) |

# Subgroup Analyses

# Subgroup Analyses

- For most subgroups, there was no statistically significant interaction effect (p-value threshold of 0.15) for key variables
- No interaction for:
  - Gender
  - Geographic & Site Location (US vs. non-US; EU vs. Japan vs. OUS)
  - Rutherford Category (3 vs. 4 vs. 5)
- FDA did not identify baseline patient or lesion characteristic subgroups in which the Lutonix DCB demonstrated a differential benefit vs PTA

# Pivotal Study Summary

# Pivotal Trial Summary (1)

- Primary Safety Endpoint - Met
  - Freedom from BTK MALE (major adverse limb event) + POD (peri-operative death) at 30 days (ITT Per-Patient) was 99.3% for DCB vs. 99.4% for PTA meeting the 12% non-inferiority margin ($p<0.0001$).
- Primary Effectiveness Endpoint - Not Met
  - Limb salvage + primary patency at 6 months (ITT per-flow pathway) was 74.7% for DCB vs. 64.2% for PTA ($p=0.0222$; $p \leq 0.0085$ required for superiority).
    - 10.5% effect size in favor of the DCB

# Pivotal Trial Summary (2)

- Longer-term primary effectiveness endpoint rates favored the PTA group at 12 months through 36 months
- FDA did not observe trends in favor of the Lutonix DCB vs. PTA for:
  - Freedom from CD-TLR at 12 months and beyond
  - Mortality
  - Major amputations
  - Wound healing and infections
  - Hemodynamic parameters: ABI & TBI
  - Rutherford Classification
  - Quality of life and walking impairment

# Pivotal Trial Summary (3)

## Study execution and design limitations

- Trial terminated early prior to enrolling the required sample size
- Multiple protocol modifications during the ongoing study
- High rate of missing primary effectiveness endpoint data
- Wound healing assessments flawed by important methodologic limitations

# Pivotal Study Conclusions

The Lutonix 014 DCB was associated with:

- A short-term lower rate of target lesion revascularization vs. PTA, which is of uncertain clinical significance
- No clear evidence to FDA for additional clinical benefits vs. PTA for a durable reduced repeat revascularization rate, target lesion patency, arterial hemodynamics, major amputations, wound healing, Rutherford classification, or quality of life

## Summary of Adjunctive Data Sources

Eleni Whatley, Ph.D.
Biomedical Engineer
CDRH/OPEQ/OCVD/PMDT

# Adjunctive Data Sources

- The Sponsor provided additional datasets intended to support the safety and effectiveness of the Lutonix 014 DCB:
  - 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 Surgery (SVS) Vascular Quality Initiative (VQI) Database
  - Japan HD RCT
- The sponsor provided literature sources from small, single center studies.

# Global BTK Real-World Registry

- Primary safety endpoint: Composite all-cause death, above-ankle amputation, or major re-intervention at 30 days
- Primary effectiveness endpoint: Freedom from CD-TLR at 6 months
- Results:

| 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

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

[1] Exact binomial confidence interval

| Measure | 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.

# Global BTK Real-World Registry

- Strengths: Large sample size, real world subjects, prospectively designed, CEC Adjudicated
- Limitations: No active control, limited objective evaluations (e.g., no imaging with patency being determined by investigator), and high rates of missing data

# Pooled analysis - IDE Trial and Global BTK Registry

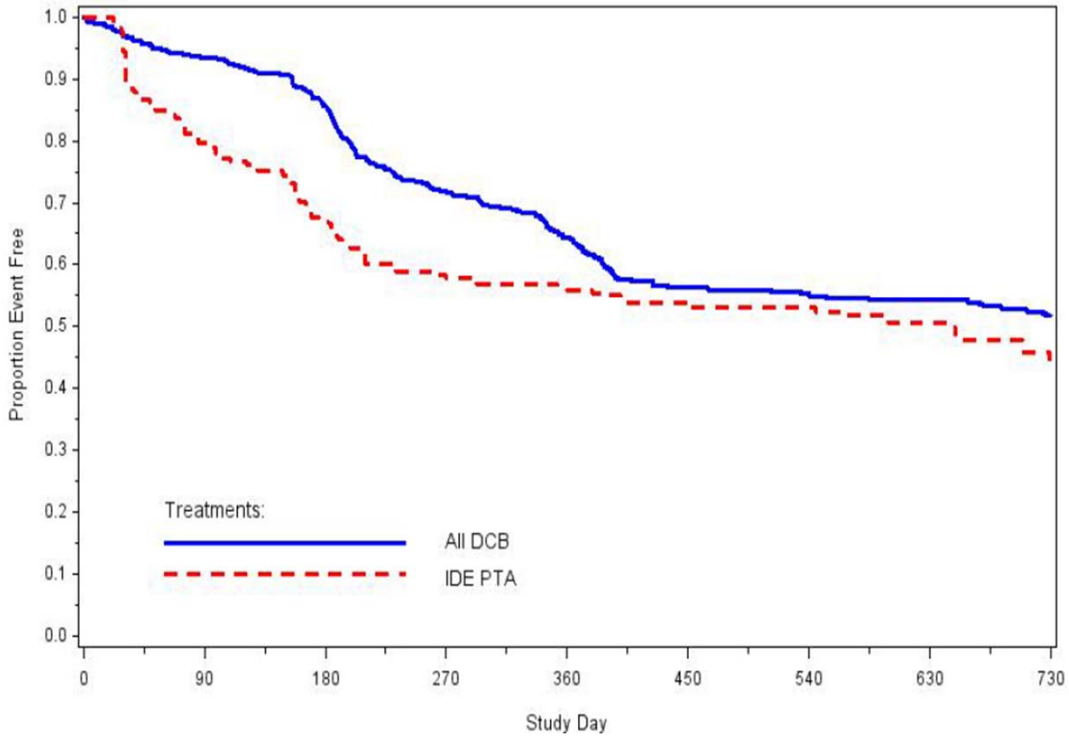
**Pooled DCB data (BTK IDE Trial + BTK Global Registry)** vs. **PTA data (BTK IDE Trial )**

- The pooled dataset included 658 DCB subjects and 155 PTA subjects
- Primary endpoints:
  - Safety: Composite all-cause death, above-ankle amputation, or major re-intervention at 30 days
  - Effectiveness: Composite of Limb Salvage and Primary Patency at 6 months

# Pooled analysis - IDE Trial and Global BTK Registry

| | Freedom from Primary Effectiveness Event | |
|---|---|---|
| **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%)** |

**Limb Salvage and Primary Patency**



# Pooled analysis - IDE Trial and Global BTK Registry

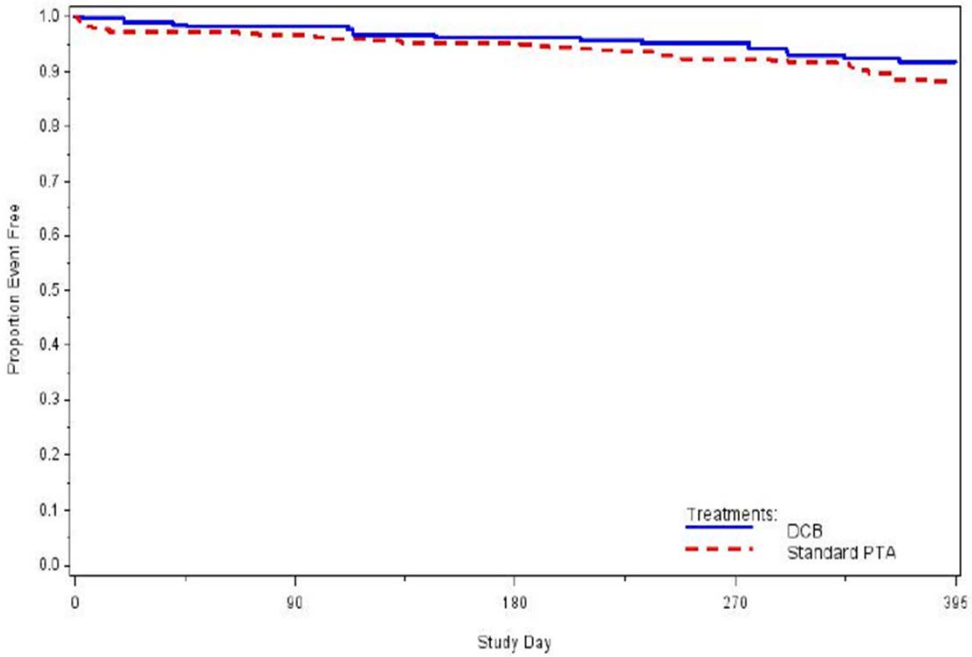
- Strengths:
  - Larger sample size that includes real world subjects
  - PTA control group from the IDE trial
- Limitations:
  - Retrospective analysis of known data from IDE trial and global registry
  - Important differences in study oversight, eligibility criteria, and primary endpoint definitions
  - Concerns with propensity score methodology
    - Final SAP did not contain sufficient details for the propensity score method
    - Insufficient overlap present in the propensity score distribution between treatment groups
    - Subjects with missing outcome data excluded

# Real-world data from the SVS VQI Database

- Real-world and off-label use of the 4 mm diameter SFA product that is approved in the US utilizing the VQI Peripheral Vascular Reintervention database
- Included 167 consecutive Lutonix DCB cases and 397 consecutive PTA cases who were propensity matched
- The primary endpoint assessment was freedom from TLR at 6 months.

# SVS VQI Data

| Day | DCB TLR Free Estimate (95% CI) | PTA TLR Free Estimate (95% CI) |
|---|---|---|
| 0 | 100.0% (100.0%, 100.0%) | 100.0% (100.0%, 100.0%) |
| 30 | 98.9% (94.7%, 99.8%) | 97.2% (94.9%, 98.5%) |
| 180 | 96.1% (91.0%, 98.4%) | 95.2% (92.5%, 97.0%) |
| 365 | 91.8% (85.1%, 95.6%) | 88.6% (84.3%, 91.7%) |




- Strengths: Real world subjects, non-randomized comparator
- Limitations: Off-label use of one device size, protocol concerns, and statistical issues (e.g., ambiguity regarding patient selection, protocol changes to primary analysis method, and issues with how missing data were handled)

# Adjunctive Data Sources

- The robustness of these studies were hindered by one or more of the following limitations:
  - Small sample sizes
  - No active controls
  - Retrospective analyses of known data
  - Unresolved statistical concerns
  - Short term follow up

**FDA considered these additional studies in the totality of the data, but they did not result in any different findings or new conclusions, and they did not provide additional support beyond the pivotal IDE trial**

# Post Approval Study Proposal

# Regulatory Purpose

- The requirement for a post-approval (PAS) study does not alter the requirements for premarket approval
- Pre-market data must reach the threshold for providing a reasonable assurance of safety and effectiveness
- Discussion regarding the proposed PAS does not indicate that FDA has made a decision or is making a recommendation on the approvability of this PMA

# Post Approval Study (PAS) Proposal

- Continued follow-up PAS for their pivotal and global cohorts
- New Enrollment:
  - Vascular Quality Initiative (VQI) prospective data collection
  - Approximately 200 subjects
  - 1 year primary endpoint of TLR and vital status through 5 years
  - Success criteria and questions to be addressed are unclear

# Benefit/Risk Considerations and Conclusions

# Benefit/Risk Considerations

FDA determines whether the totality of the data provide a "reasonable assurance of safety and effectiveness" by weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.

- A reasonable assurance of safety occurs when "it can be determined, based upon valid scientific evidence, that the probable benefits… outweigh any probable risks," and can be demonstrated by establishing "**the absence of unreasonable risk of illness or injury** associated with the use of the device for its intended uses and conditions of use." (21 CFR 860.7(d)(1))
- A reasonable assurance of effectiveness occurs when "it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses… will provide **clinically significant results**." (21 CFR 860.7(e)(1))

# Benefit/Risk Considerations

Some factors that should be considered when evaluating benefits and risk of a medical device include:

- Benefits
  - Type of benefit
  - Magnitude of benefit
  - Likelihood of patients experiencing one or more benefit
  - Duration of effects
  - Patient perspective on benefit
  - Medical Necessity
- Risks
  - Severity of harm
  - Likelihood of risk
  - Duration of exposure to population
  - Patient tolerance of risk

# Uncertainty in Benefit-Risk Determinations

- The appropriate extent of uncertainty regarding the benefits and risks in a given case will depend on consideration of multiple factors and other relevant information concerning the device, including:
  - The extent of the probable benefits and risks of the device
  - The extent of the public health need
  - The probable benefits of earlier patient access to the device
  - The ability to reduce uncertainty post-market
  - The likely effectiveness of mitigations, such as labeling, and other tools

Consideration of Uncertainty in Making Benefit- Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions. (Section V, Page 16)

# Discussion of Benefits

- A 10.5% numerical improvement for the Lutonix 014 DCB was observed for the primary effectiveness endpoint at 6 months
  - This improvement was no longer evident by 12 months and the event rate numerically favored PTA at 12 months and beyond
  - FDA did not observe any evidence of added benefit of the Lutonix 014 DCB vs. PTA from pre-specified and post hoc secondary effectiveness endpoint evaluations including for:
    - Freedom from CD-TLR at 12 months and beyond
    - Major amputations
    - Wound healing and infections
    - ABI & TBI
    - Rutherford Classification
    - Quality of life and walking impairment

# Discussion of Risks

- No additional safety risks associated with the Lutonix DCB vs. PTA identified in the current study data
- A safety signal for increased late mortality has been observed in patients treated with paclitaxel-coated devices in the superficial femoral artery
  - This trend was not seen in the current BTK study
- Potential concerns associated with paclitaxel-coated devices, including mortality, should be considered if there is uncertainty regarding clinical benefits

# Benefit Risk Considerations for the Panel

FDA is requesting Panel input on whether:

- The data demonstrate a reasonable assurance of effectiveness for the Lutonix 014 DCB
  - A reasonable assurance of effectiveness occurs when "it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses… will provide **clinically significant results**."
- The type, magnitude, and duration of the probable benefits of the Lutonix 014 DCB outweigh the known and probable risks

Thank you!

Questions?