Lutonix BTK IDE Study: 12-Month Results & Interim Safety Analyses at Three Years

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On behalf of the Lutonix BTK Study Investigators

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Disclosure

Patrick Geraghty:

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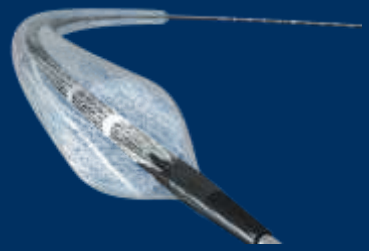
I have the following potential conflicts of interest to report:

- [x] Consulting- BD/Bard Peripheral Vascular, Boston Scientific
- [ ] Employment in industry
- [x] Stockholder of a healthcare company- Euphrates Vascular
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [ ] I do not have any potential conflict of interest

Lutonix BTK Study Device & Design



- **Device:** Lutonix® 014 Drug Coated PTA Dilatation Catheter
  - Active Drug: Paclitaxel (2 µg/mm2)
  - Carrier: Polysorbate and sorbitol
- **Design:** Prospective, Multicenter, Randomized, Single Blind
  - Randomization Scheme: 2 (DCB) : 1 (PTA)
  - Blinding Protocol: Patients, core laboratory, and clinical events committee
- **Independent Analysis:**
  - Angiographic & radiographic assessment: SynvaCor
  - Duplex Ultrasound (DUS) evaluation: VasCore
  - Clinical Events Committee (CEC): adjudicated serious adverse events
  - Data Monitoring Committee (DMC): assessed overall patient safety

Lutonix BTK Study
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Lutonix BTK Study
Investigators and Study Sites

51 Sites: USA, Europe, Canada, Japan, and Australia

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Lutonix BTK Study Enrollment

Patient Enrollment	DCB (N=287)	PTA (N=155)	Total (N=442)
United States: 32 Sites	178	97	275 (62%)
Europe/Canada: 14 Sites	84	43	127 (29%)
Japan: 5 Sites	25	15	40 (9%)

Lutonix BTK Study Criteria

Key Inclusion Criteria

- Arterial stenosis (≥70%) below the tibial plateau & above the tibiotalar joint
- Appropriate for angioplasty per operator visual assessment
- Rutherford Category 3-5
- Cumulative lesion length ≤ 320 mm
- Patent inflow artery from the aorta to the target lesion free from significant (≥ 50%) stenosis
- Target vessel reconstitutes at or above ankle with inline flow to at least one patent (<50%) infra-malleolar outflow vessel
- Target vessel diameter 2-4 mm & able to be treated with available device sizes

Key Exclusion Criteria

- Severe medical comorbidities (e.g., untreated CAD/CHF) or metastatic cancer
- Ischemic ulceration extending > 4 cm proximal to digit-metatarsal skin crease (target limb)
- Gangrene extending proximal to the digit-metatarsal skin crease (target limb)
- Neurotropic ulcer or heel pressure ulcer or ulcer potentially involving calcaneus (target limb)
- Planned major amputation, or prior major amputation if the patient is not independently ambulating
- Acute limb ischemia, in-stent restenosis, or presence of thrombosis (target lesion)

Lutonix BTK Study
Demographics & Risk Factors

Demographic Criteria	DCB N=287	PTA N=155	P-Value[1]
Mean Age, years ± SD	72.9 ± 9.7	72.9 ± 9.6	0.96
Male/Female	70.4%/29.6%	67.1%/32.9%	0.52
Mean BMI, kg/m^2 ± SD	28.4 ± 6.3	28.0 ± 5.7	0.61
Rutherford Category			0.92
3	9.1%	10.3%	
4	34.8%	33.5%	
5	56.1%	56.1%	
Co-Morbidities/Medical History			0.54
Smoker Current/Former	15.0%/44.3%	12.3%/45.2%	
Hypertension	92.0%	95.5%	
Dyslipidemia	78.4%	74.8%	
Diabetes (Type 2)	71.1%	68.4%	
Previous Peripheral Intervention	53.7%	54.2%	0.92

[1] Wilcoxon Rank-Sum Test for continuous data or Fisher's Exact Test for categorical data

Lutonix BTK Study
Lesion Characteristics

Lesion Criteria	DCB	PTA	P-value[1]
Total Number of Lesions	380	225	
Lesion Morphology			
Mean Lesion Length, mm ± SD	111.8 ± 92.6	94.7 ± 85.4	0.03
Mean Baseline Stenosis, % ± SD	86.7 ± 14.5	84.8 ± 14.5	0.09
Calcification (any)	59.9%	54.2%	0.19
Severe Calcification	15.1%	13.2%	0.54
Occlusion or re-occlusion	37.7%	35.5%	
Lesion Pathway Locations			
Popliteal Artery	10.2%	9.3%	
Tibioperoneal Trunk	28.0%	31.1%	
Anterior Tibial Artery	41.0%	35.5%	
Posterior Tibial Artery	24.2%	27.3%	
Peroneal Artery	23.6%	24.6%	

[1] Wilcoxon Rank-Sum Test and Likelihood Ratio Chi-Square Test

Lutonix BTK Study
Primary Endpoints

- **Safety:** 30-Day Freedom from Major Adverse Limb Events (MALE, which includes significant re-intervention and above-ankle amputation) and Perioperative Death (POD)

- **Efficacy:** 6-Month Freedom from Major Amputation, Target Vessel Occlusion, and Clinically-Driven Target Lesion Revascularization

6 Month Efficacy Endpoint Analysis

- Prolonged enrolment led to change from frequentist to Bayesian analysis -> interim assessments determined need for continued enrollment
  - Each interim assessment decreased the P value needed for significance
  - Addition of analysis of outcomes by arterial distribution also decreased P value for success
- Composite efficacy measure for the full ITT population did not achieve the pre-specified Bayesian P value of 0.0085
- *Journal of Invasive Cardiology* – Mustapha et al. 2019

Primary Endpoint Results

Binary - Proportional Analyses at 6 Months

Safety: Freedom from MALE-POD

Time Point	DCB % (95% CI)[1]	PTA % (95% CI)[1]	Difference (95% CI)[2]	Non-Inferiority p-value[3]
30 Days	99.3% (97.5%, 99.9%)	99.4% (96.5%, 100.0%)	-0.1% (-3.9%, 3.8%)	<0.0001

Freedom from MALE-POD was non-inferior between groups

Efficacy: Primary Patency & Limb Salvage

Time Point	DCB % (95% CI)[1]	PTA % (95% CI)[1]	Difference (95% CI)[4]	p-value[5]
6 Months	74.7% (69.1%, 79.8%)	64.2% (55.6%, 72.2%)	10.5% (0.3%, 18.8%)	0.02

The composite of primary patency & limb salvage was 10.5% greater for the DCB group than the PTA group

[1] 95% CI based exact binomial distribution

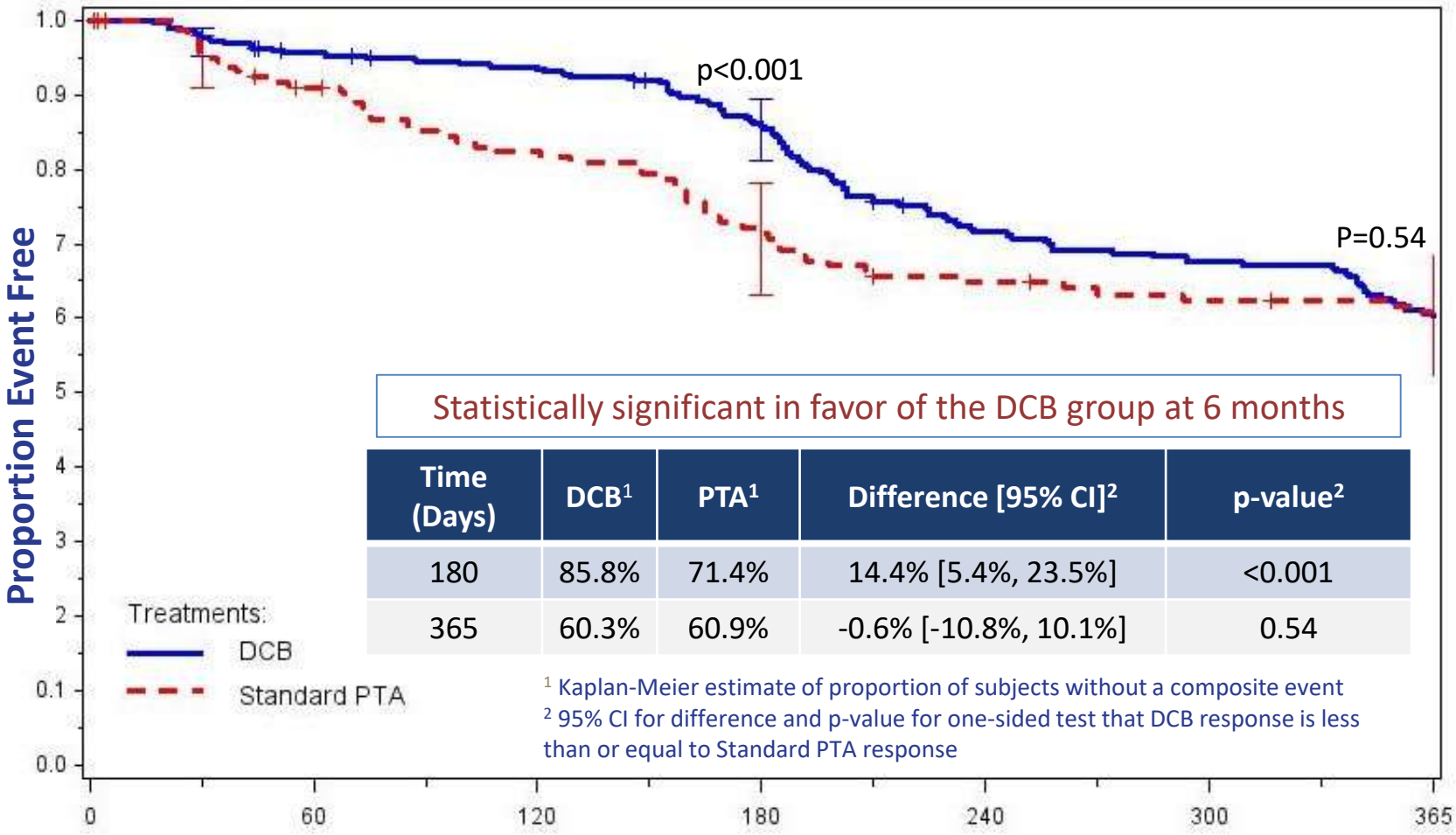
[2] 95% CI is estimated by Farrington-Manning Test

[3] P-value for non-inferiority margin of 12%

[4] Based on the model estimated response rates in both groups

[5] One-sided Wald Test; the p-value of 0.02 did not meet the pre-specified Bayesian p-value for superiority of 0.0085

K-M Efficacy Endpoint at One Year*



Statistically significant in favor of the DCB group at 6 months

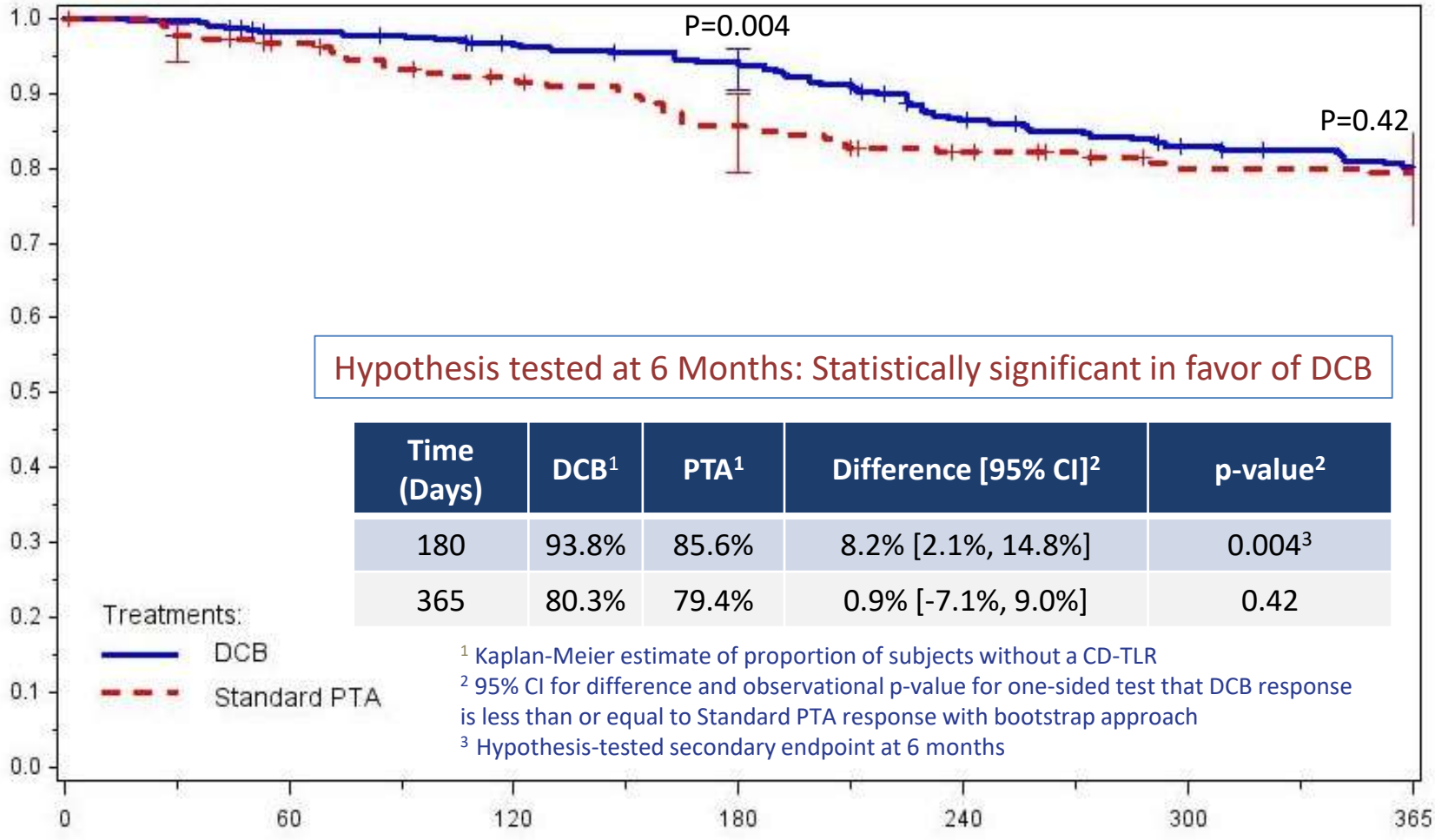
Time (Days)	DCB[1]	PTA[1]	Difference [95% CI][2]	p-value[2]
180	85.8%	71.4%	14.4% [5.4%, 23.5%]	<0.001
365	60.3%	60.9%	-0.6% [-10.8%, 10.1%]	0.54

[1] Kaplan-Meier estimate of proportion of subjects without a composite event
[2] 95% CI for difference and p-value for one-sided test that DCB response is less than or equal to Standard PTA response

* Composite Efficacy Endpoint: Freedom from above ankle amputation, target-lesion occlusion, and clinically-driven target lesion reintervention

Secondary Observations at One Year

Freedom from CD-TLR



Hypothesis tested at 6 Months: Statistically significant in favor of DCB

Time (Days)	DCB[1]	PTA[1]	Difference [95% CI][2]	p-value[2]
180	93.8%	85.6%	8.2% [2.1%, 14.8%]	0.004[3]
365	80.3%	79.4%	0.9% [-7.1%, 9.0%]	0.42

[1] Kaplan-Meier estimate of proportion of subjects without a CD-TLR
[2] 95% CI for difference and observational p-value for one-sided test that DCB response is less than or equal to Standard PTA response with bootstrap approach
[3] Hypothesis-tested secondary endpoint at 6 months

Secondary Observations at One Year

Cumulative Target Lesion Reinterventions (TLR)[1]

Time	DCB	PTA	p-value[2]
1 Month	1.0% (3/293)	2.6% (4/155)	0.22
6 Months	8.5% (22/259)	17.5% (22/126)	0.01
12 Months	17.8% (38/213)	21.8% (24/110)	0.39

6 months: Cumulative TLR rate in the PTA group >2 times the rate in the DCB group

Toe-Brachial Index (TBI)

Criteria	DCB	PTA
TBI $\pm$ SD (6 Months)	0.52 $\pm$ 0.26	0.49 $\pm$ 0.26
TBI $\pm$ SD (12 Months)	0.50 $\pm$ 0.22	0.43 $\pm$ 0.21
TBI change from Baseline + SD (12 Months)	0.12 $\pm$ 0.23	0.04 $\pm$ 0.25

Observational differences at 12 months; not statistically significant

[1] Cumulative TLR: the total number of target lesion re-interventions by pathway in each treatment group. Some pathways had more than one target lesion re-interventions.

[2] p-value of Likelihood Ratio Test based on a Chi-Square distribution – observational p-value

Secondary Clinical Observations at One Year

Wound Assessment

Criteria	DCB	PTA	Difference[1]
Any Wound Present, %			
Baseline	56.5%	56.1%	0.4% [-9.3%, 10.1%]
6 months	41.7%	45.1%	-3.3% [-14.1%, 7.4%]
12 months	29.7%	25.9%	3.8% [-6.5%, 14.1%]

Assessments (6/12 months) based on 242/212 DCB patients and 122/108 PTA patients with wounds - photos assessed: 30-45%

[1] Crude difference in percent or mean values

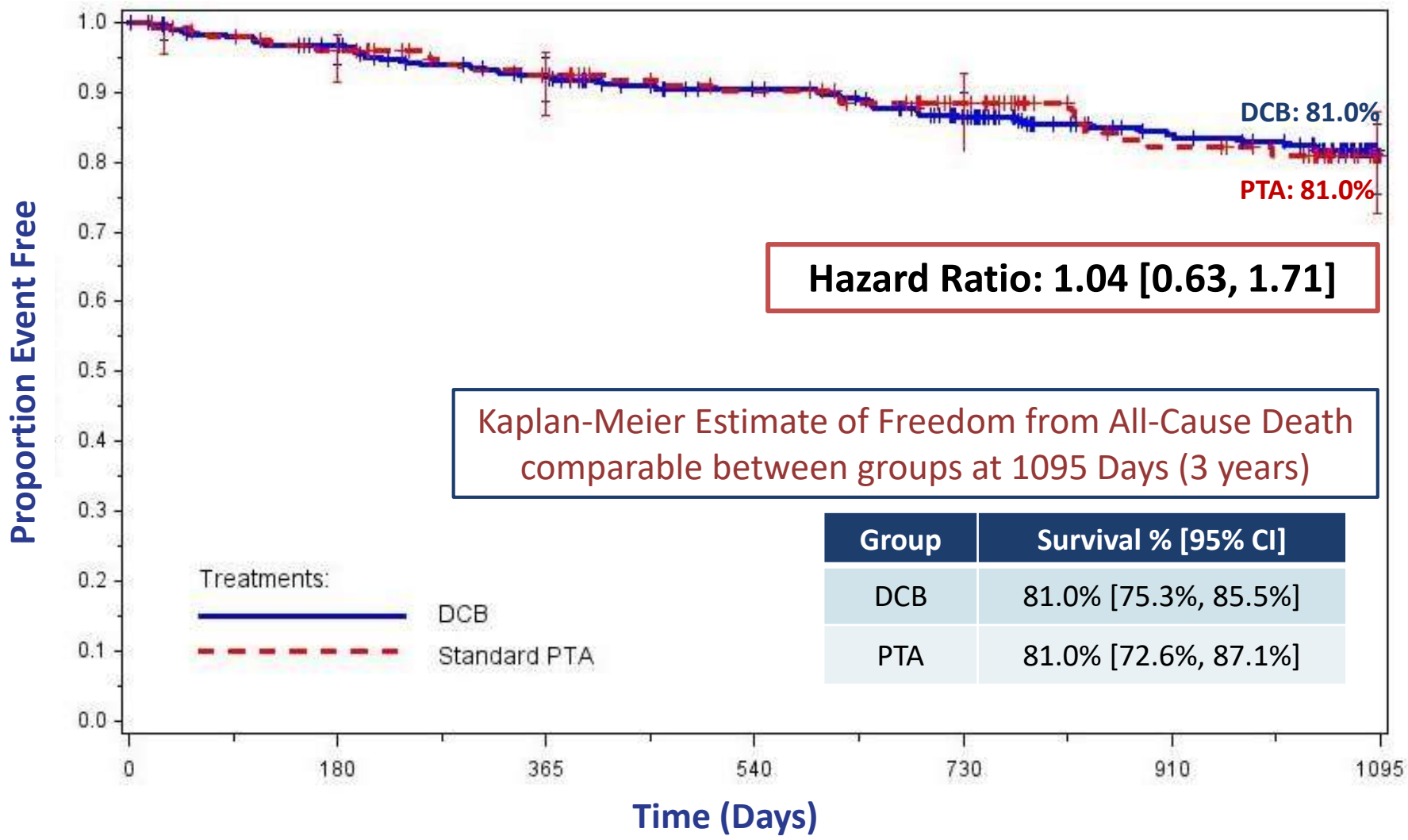
Safety Analyses Through 3 Years

Kaplan-Meier Analysis (Intent-to-Treat Population)
Interim 3-year Safety Data (67% of patients completed)*

- **Freedom from All-Cause Death**
- **Freedom from Major Amputation**
  - ✓ Freedom from above-ankle amputation of the target/treated limb
- **Amputation-Free Survival (AFS)**
  - ✓ Freedom from above-ankle amputation of the target/treated limb and all-cause death

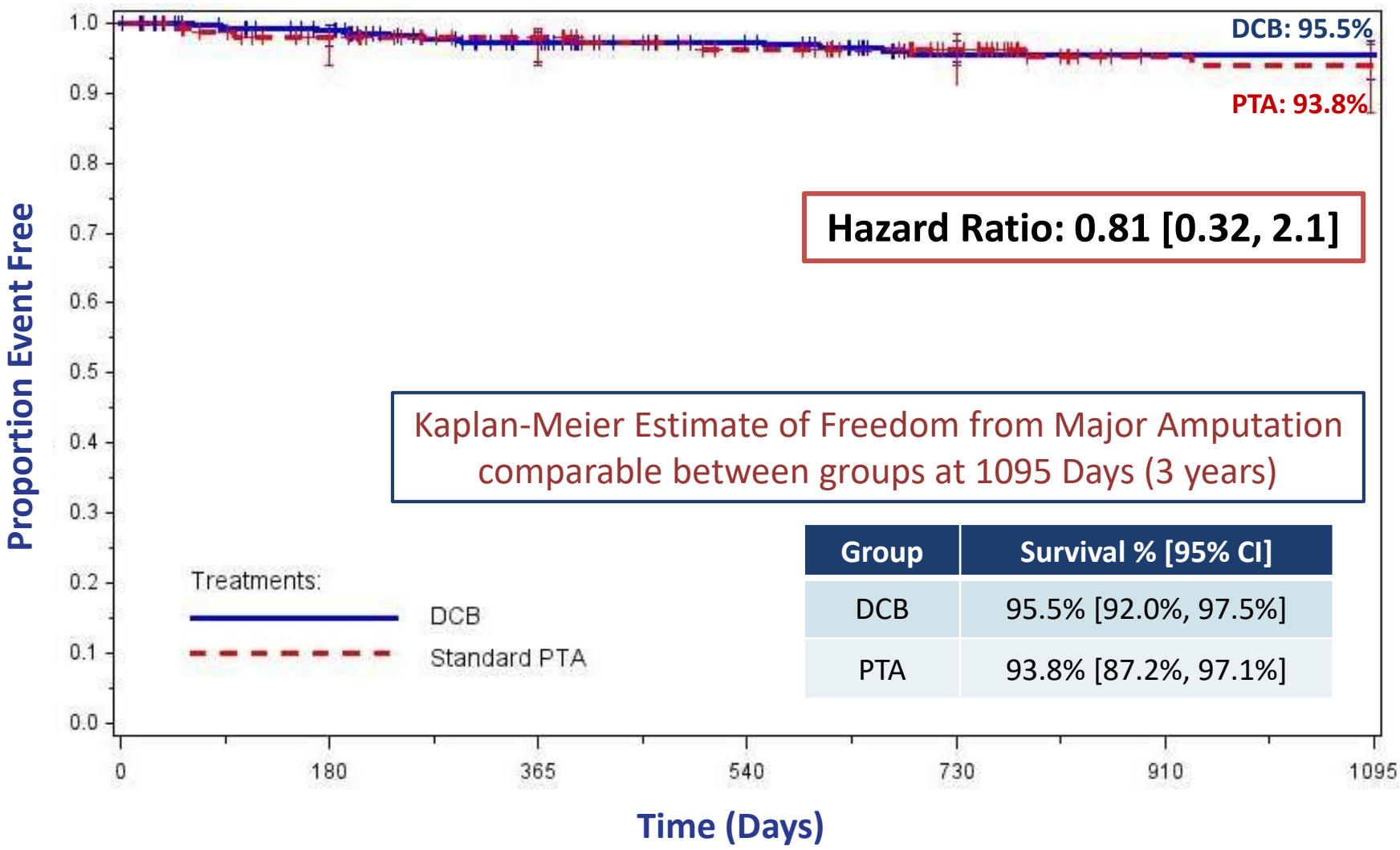
*Three-year data based on 294 patients (66.5%; 294/442) as of Oct 2019 - 57 patients remain to be followed; 91 patients discontinued the trial; 70 patients died prior to three years and were evaluated for this analysis

Freedom from All-Cause Death



Group	Survival % [95% CI]
DCB	81.0% [75.3%, 85.5%]
PTA	81.0% [72.6%, 87.1%]

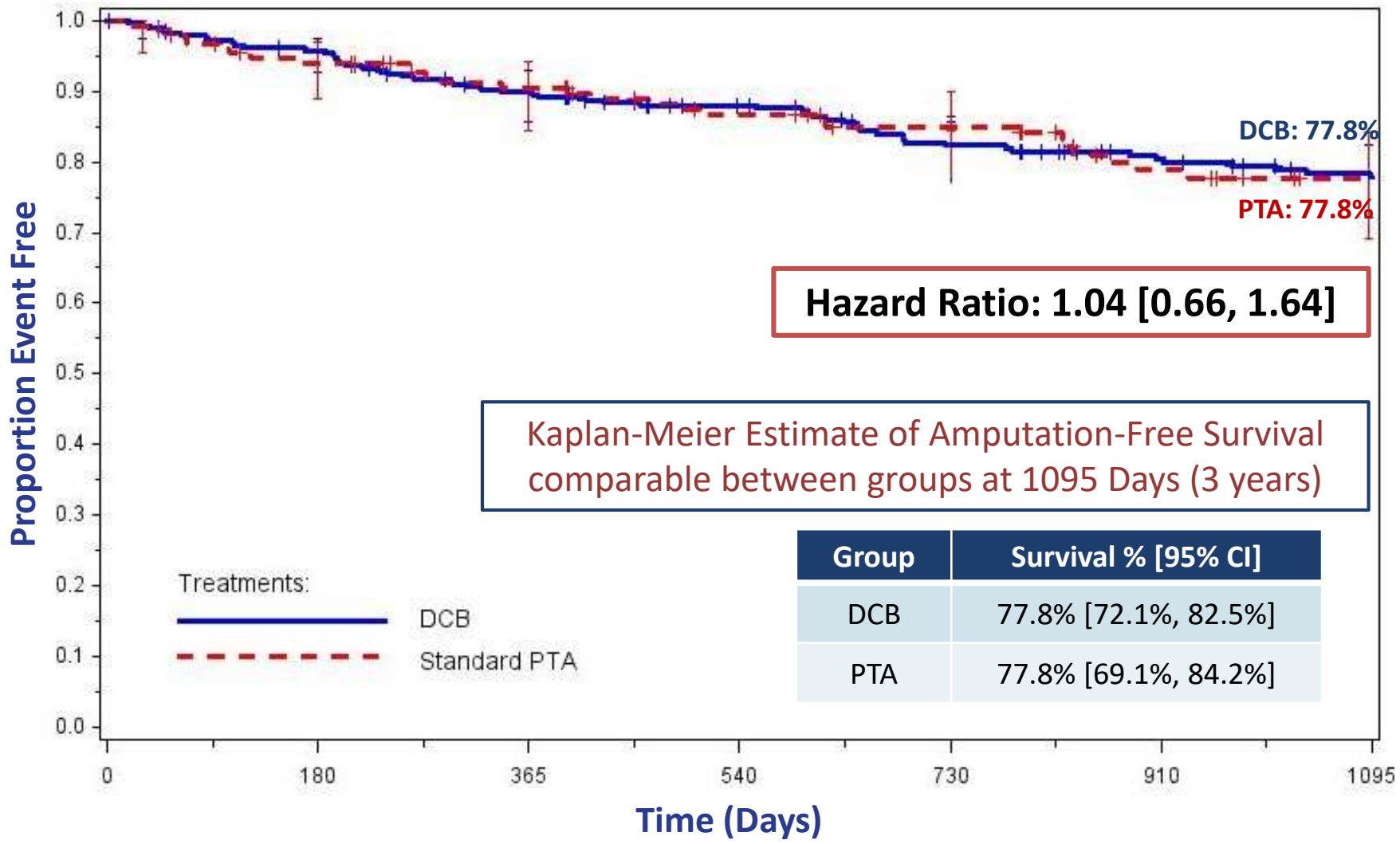
Freedom from Major Amputation



Group	Survival % [95% CI]
DCB	95.5% [92.0%, 97.5%]
PTA	93.8% [87.2%, 97.1%]

Freedom from Major Amputation: Freedom from above-ankle amputation of the target/treated limb

Amputation-Free Survival



Hazard Ratio: 1.04 [0.66, 1.64]

Kaplan-Meier Estimate of Amputation-Free Survival comparable between groups at 1095 Days (3 years)

Group	Survival % [95% CI]
DCB	77.8% [72.1%, 82.5%]
PTA	77.8% [69.1%, 84.2%]

Amputation-Free Survival: Freedom from above-ankle amputation of the target/treated limb and death

Lutonix BTK Study Summary

DCB treatment for symptomatic infrapopliteal arterial lesions produced:

- ✓Non-inferior safety compared to PTA at 30 days,
- ✓10.5% numerical difference in a composite of primary patency and limb salvage in favor of DCB at 6 months (not significant by binary analysis)
- ✓Statistically significant difference in the composite efficacy endpoint and CD-TLR (hypothesis-tested secondary analyses) at 180 days (by K-M analysis)

Lutonix BTK Study Summary

Efficacy Observations Through 12 Months[1]:

- Composite primary efficacy endpoint and freedom from CD-TLR remained greater in the DCB group from 6 - 12 months by K-M analysis, converging at 365 days
- Cumulative TLR rate (>2 times greater in the PTA group than in the DCB group at 6 months) converged but still numerically favored the DCB group at 12 months
- Although there were observed differences between groups in other secondary outcomes (e.g., TBI scores) through 12 months, there were no statistical differences between groups

[1] Observations only - Numerical differences not evaluated for statistical significance

Lutonix BTK Study Summary

Safety at 3 Years*:

Comparable between groups at 1095 days

- Freedom from All-Cause Death (Hazard Ratio: 1.04)
- Major Amputation (Hazard Ratio: 0.81)
- Amputation-Free Survival (Hazard Ratio: 1.04)

First look at 3-Year Efficacy Data*:

- No statistical differences between groups at 1095 days

*Three-year data as of October 2019

MAKING EVAR SAFER IN THE LONG TERM: USING ULTRASOUND TO MEASURE AORTIC SAC DIAMETER ANNUALLY AT HOME

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