Lessons learned from LIFE-BTK

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott, Medtronic, BSC
• Consulting (non-compensated)	• Medtronic, Boston Scientific, Abbott, Phillips
• Major Stock Shareholder/Equity	• Primacea, TissueGen, Orchestra, R3 Vascular, Transit Medical, Syntervention, Cagent
• Royalty Income	• None
• Ownership/Founder	• Innovation Vascular Partners, LLC
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

Why is this difficult?

- Unfortunately, the outcomes for ATK seem dependent upon patency and walking difficulties
- BTK data are mired in endpoints, heterogeneity of subjects, non-uniform nature of wound care and type of patient enrolled (RB3 in RB 4-5-6)

Background

CLTI is a Severe Manifestation of PAD

- Peripheral artery disease (PAD) is estimated to affect more than **230 MILLION** *people*, with **7-12 MILLION** in the United States alone[1,2]
- Chronic limb threatening ischemia **(CLTI)**, characterized by ischemic rest pain and non-healing ulceration or gangrene, is associated with **HIGH RATES OF AMPUTATION**
- *Angioplasty has proven* to be superior to surgery, for infrapopliteal or below-the-knee (BTK) arterial disease, but angioplasty has limitations[3]
- A drug-eluting, **RESORBABLE SCAFFOLD HAS** potential advantages making it suited to treat BTK artery disease and has shown **PROMISING RESULTS** in observational studies[4]

[1] *Allison MA, Ho E, Denenberg JO, et al. Am J Prev Med 2007;32:328-33.*

[2] *Song P, Rudan D, Zhu Y, et al. Lancet Glob Health 2019;7:e1020-e30.*

[3] *Bradbury AW, Moakes CA, Popplewell M, et al. Lancet 2023;401:1798-809.*

[4] *Dia AR, Venturini JM, Kalathiya R, et al. Catheterization and Cardiovascular Interventions 2019;94:1028-33; Ipema J, Kum S, Huizing E, et al. International Angiology 2021;40:42-51; Varcoe RL, Menting TP, Thomas SD, et al. Catheterization and Cardiovascular Interventions 2021;97:142-9; Varcoe RL, Schouten O, Thomas SD, et al. Journal of Endovascular Therapy 2015;22:226-32; Varcoe RL, Thomas SD, Lennox AF. Journal of Endovascular Therapy 2018;25:694-701; Kum S, Ipema J, Chun-Yin DH, et al. J Endovasc Ther 2020;27:616-22; Huizing E, Kum S, Ipema J, et al. Vasc Med 2021;26:195-9.*

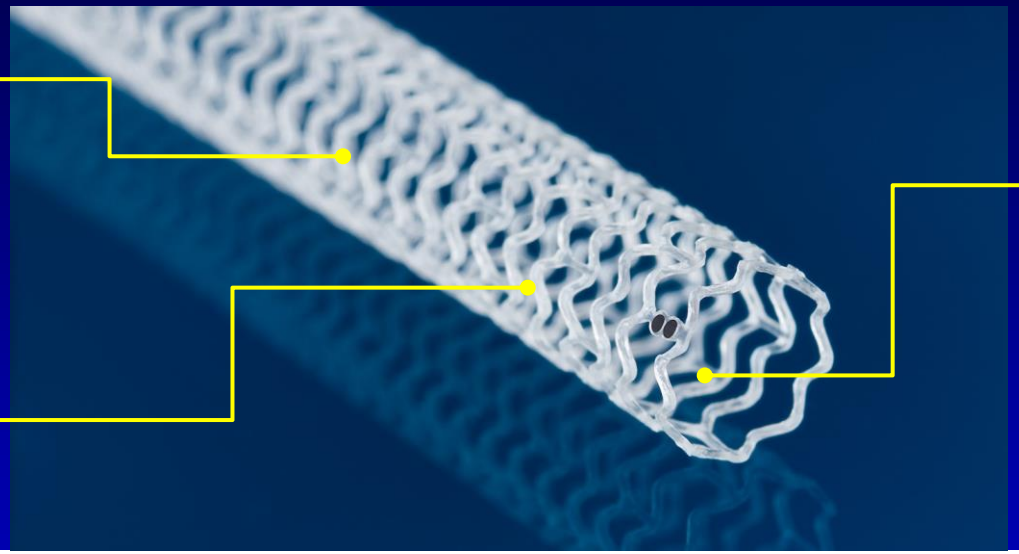
Investigational Device

Design and Components

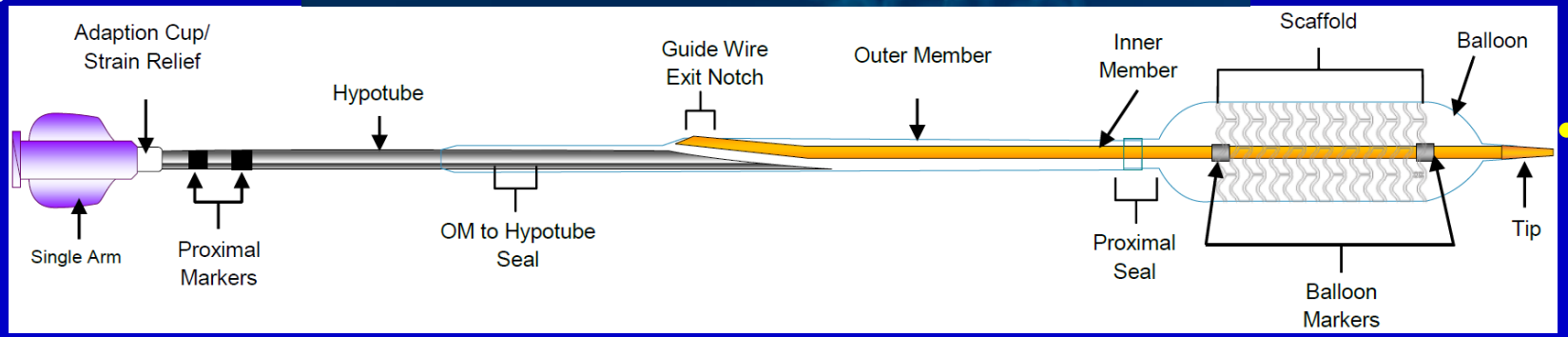
Esprit™ BTK Drug-eluting Resorbable Scaffold (DRS)

Temporary** scaffold that will **resorb over time*

1. *Bioresorbable scaffold backbone comprised of 100% poly(L-lactide) (PLLA) and strut thickness of 99 µm***
2. *Coating comprised of the active pharmaceutical ingredient everolimus and bioresorbable poly (D,L-lactide) (PDLLA)*



3. *Four platinum markers of the same mass, two each embedded at the proximal and distal ends of the scaffold for radiopacity†*



4. *Delivery system*

*The Esprit BTK DRS System is an investigational product not approved by the FDA

*** ≤ 3.0 mm size; 3.5-3.75 mm sizes have 120 µm strut thickness.*

†Platinum markers at proximal and distal ends remain for angiographic visualization

LIFE-BTK Randomized Multicenter Trial*

Evaluate the safety and efficacy of the Esprit BTK DRS System, compared to PTA†, for the treatment of infrapopliteal artery disease in patients with CLTI.

Prospective, randomized, multicenter, US and OUS single-blind trial

***261** patients randomized*

***2:1** Esprit BTK vs. PTA*

DATA EVALUATED AT 12 MONTHS

- ***Primary Safety Endpoint @ 6 Months***
- ***Primary Efficacy Endpoint @ 1 Year***
- ***Powered Secondary Endpoints @ 1 Year***

Clinical Follow-Up:

14 D | **30 D** | **42 D**** | **90 D**** | **6 M** | **1 Y** | **2 Y** | **3 Y** | **4 Y** | **5 Y**

**ClinicalTrials.gov: NCT04227899*
*** Follow up focused on index wound assessment*
† defined as Percutaneous Transluminal Angioplasty

Endpoints

	PRIMARY EFFICACY ENDPOINT	PRIMARY SAFETY ENDPOINT
Endpoint	**Limb Salvage + Primary Patency**	**Freedom from MALE + POD**
Definition	Freedom from above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of target lesion, and CD-TLR* at **12 months**	**MALE** = Above ankle amputation in index limb, major re-intervention at **6 months** **POD** = Perioperative mortality at **30 days**
Test	Superiority of Esprit™ BTK against PTA with a 1-sided α of 0.0249	Non-inferiority of Esprit™ BTK against PTA with a 1-sided α of 0.025
	1ST SECONDARY ENDPOINT	**2ND SECONDARY ENDPOINT**
Endpoint	**Binary restenosis of the target lesion at 1 year**	**Freedom from above ankle amputation in index limb, 100% total occlusion of target vessel and CD-TLR at 1 year**
Test	**Superiority of Esprit™ BTK against PTA with a 1-sided α of 0.025**	**Superiority of Esprit™ BTK against PTA with a 1-sided α of 0.025**

** Defined as clinically-driven target lesion revascularization*

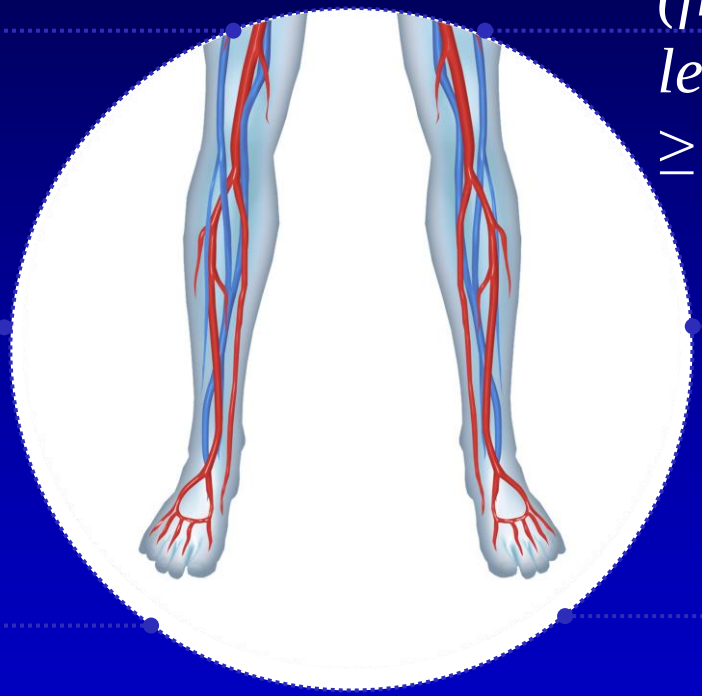
Inclusion Criteria

Study Population LIFE-BTK

Proximal 2/3 of native infrapopliteal arteries (10 cm distance from ankle)

Successful treatment of all inflow artery(ies) through standard of care prior to target lesion treatment*

RVD ≥ 2.5 mm and ≤ 4.0 mm



Maximum 2 de novo/restenotic (from prior PTA) infrapopliteal lesions, each with ≥ 70% stenosis

The total scaffold length per patient ≤ 170 mm (in 1 lesion, or divided among the 2 target lesions)

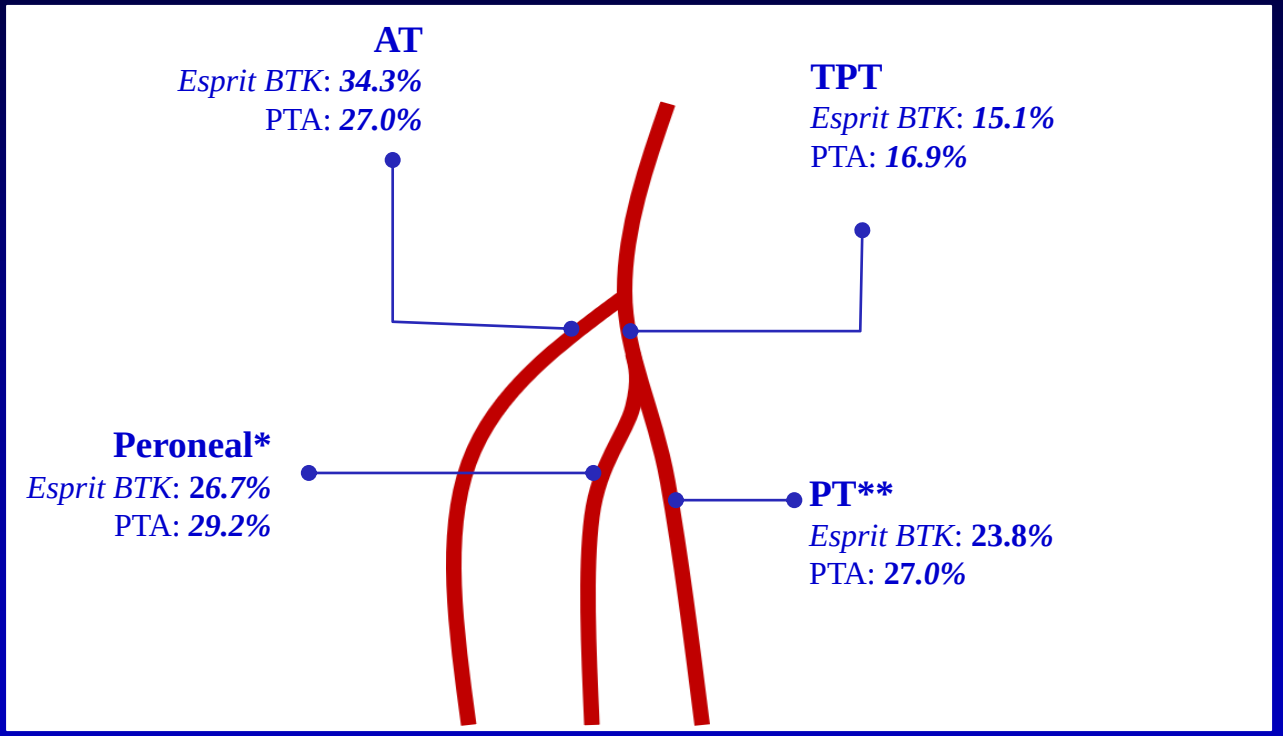
CLTI subjects with RB 4 or 5

*Successful treatment is according to physician's assessment of inflow artery(ies) that are ≥ 50% stenosed

** Tandem lesions are allowed if they are < 3 cm apart and the total scaffold length used to cover the entire diseased segment is ≤ 170 mm. Each tandem lesion is considered one lesion.

Target Lesion Baseline Characteristics

	Esprit BTK	PTA
Lesion length (mm)	**43.78 ± 31.84 (172)**	**44.75 ± 29.07 (89)**
RVD pre-intervention (mm)	**2.94 ± 0.77 (147)**	**2.82 ± 0.74 (80)**
Site-Reported Calcification		
None/Mild	**69.3% (124/179)**	**69.6% (64/92)**
Moderate	**27.4% (49/179)**	**28.3% (26/92)**
Severe	**3.4% (6/179)**	**2.2% (2/92)**
TASC II classification		
A	**48.3% (83/172)**	**52.8% (47/89)**
B	**35.5% (61/172)**	**25.8% (23/89)**
C	**16.3% (28/172)**	**21.3% (19/89)**
D	**0.0% (0/172)**	**0.0% (0/89)**
% DS pre-intervention	**72.6 ± 18.9 (172)**	**73.7 ± 21.0 (89)**



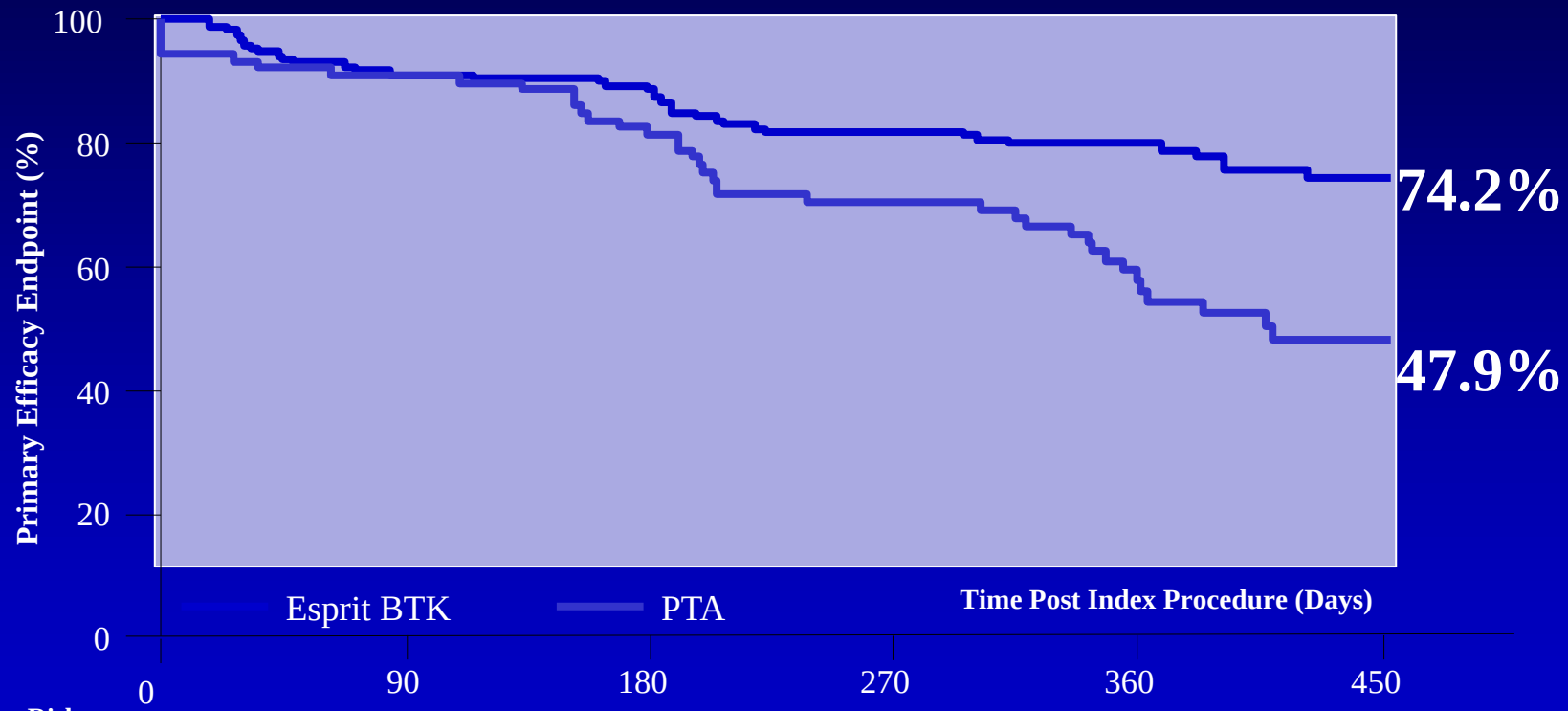
Number of Target Lesions Per Subject
Esprit BTK = 1.0 (*1,2*)
PTA = 1.0 (*1,2*)

* Includes Peroneal and TPT-Peroneal segments
*** Includes PT and TPT-PT segment*

Primary Efficacy Endpoint

Composite of Limb Salvage and Primary Patency at 1 Year – ITT Population

Esprit BTK	PTA	Difference [One-Sided Lower 97.51% CL][2]	P-Value[3]
74.5% (111/149)	43.7% (31/71)	30.8% (17.0%)	<0.0001



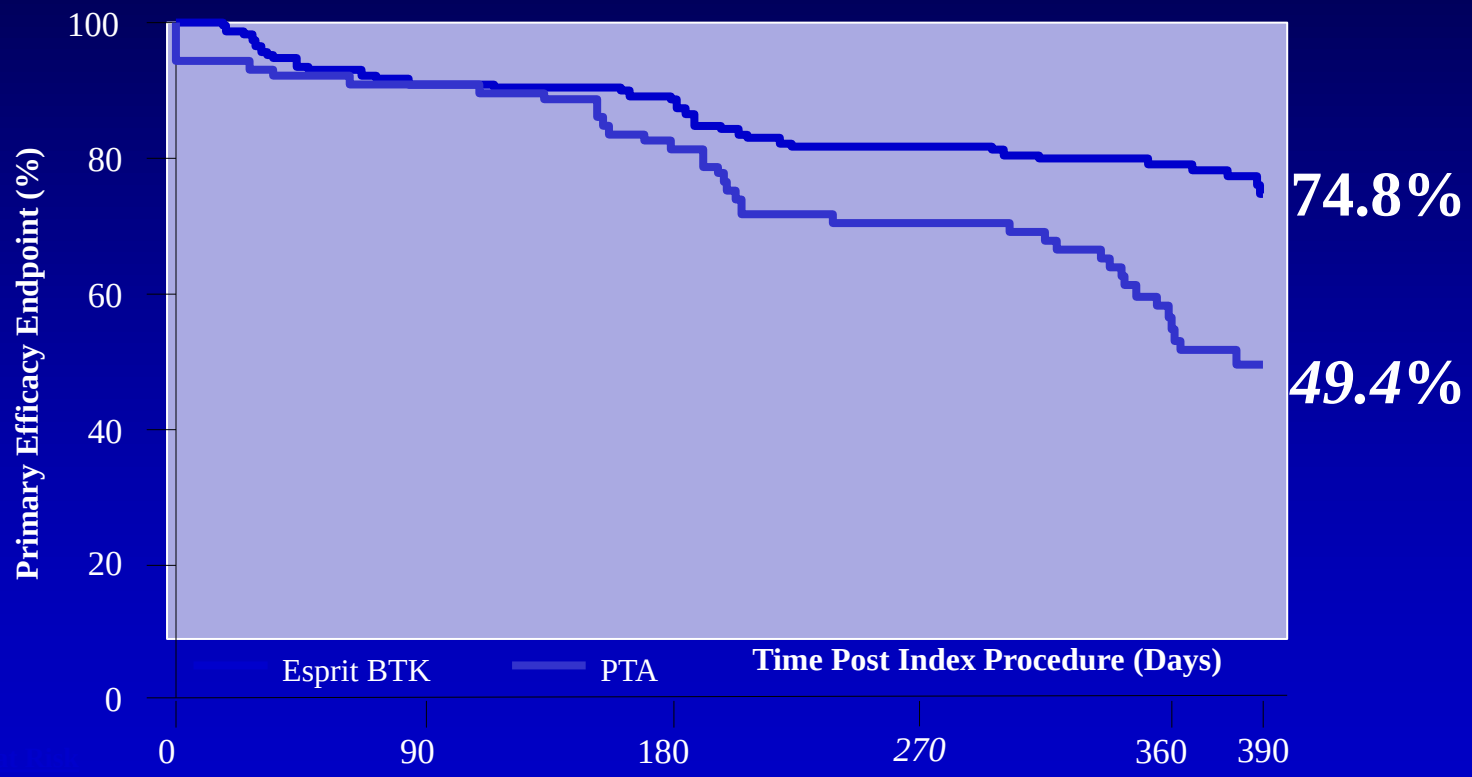
No. at Risk						
Esprit BTK	173	163	152	142	95	42
PTA	88	82	78	67	33	15

[1] *Primary Efficacy Endpoint: Composite of limb salvage and primary patency at 1 year, which includes freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of target lesion, and clinically-driven target lesion revascularization (CD-TLR).*
[2] *By Newcombe score method.*
[3] *From One-sided Chi-square test, to be compared at one-sided significance level of 0.0249.*
Note: The efficacy endpoint denominators of the rates exclude subjects who terminated from the study prior to the lower limit (337 days) of the 1-year primary efficacy endpoint follow-up window without any components of the primary endpoint.

Primary Efficacy Endpoint

Composite of Limb Salvage and Primary Patency at 1 Year (393 Days) – ITT Population

Esprit BTK	PTA	Difference [One-Sided Lower 97.51% CL][2]	P-Value[3]
74.5% (111/149)	43.7% (31/71)	30.8% (17.0%)	<0.0001

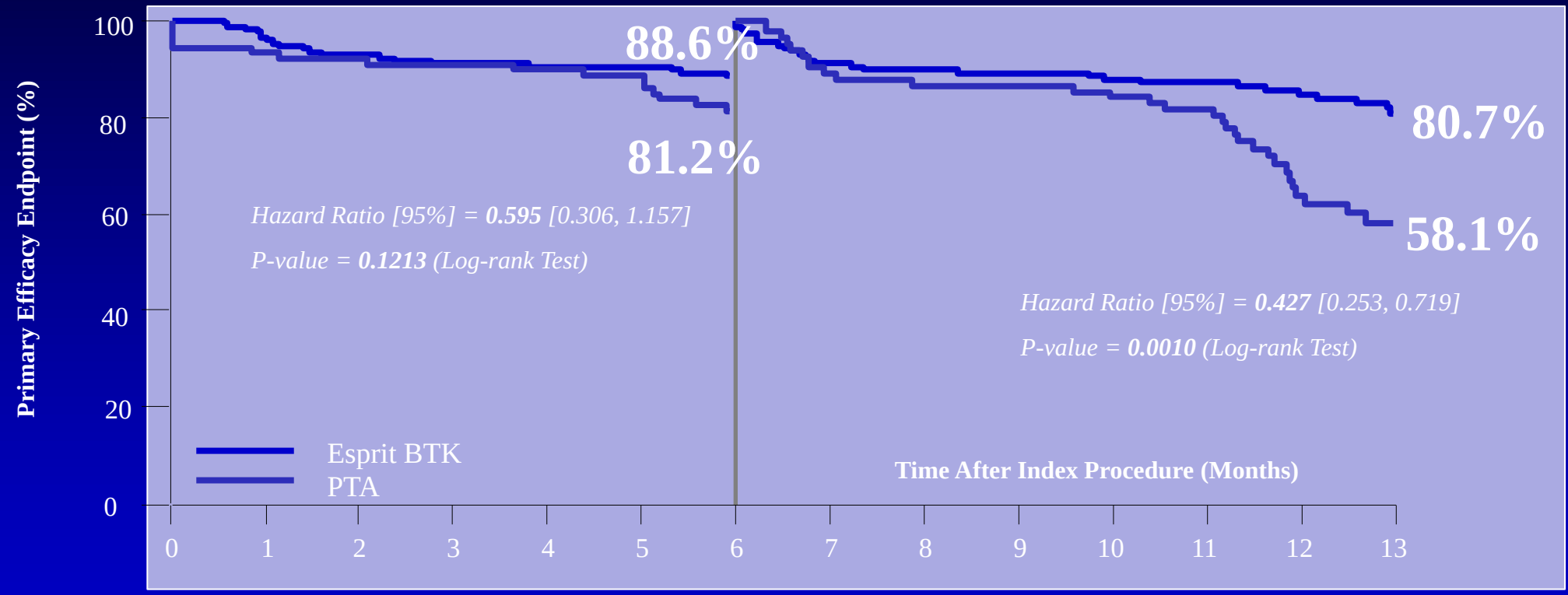


[1] *Primary Efficacy Endpoint: Composite of limb salvage and primary patency at 1 year, which includes freedom from: above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of target lesion, and clinically-driven target lesion revascularization (CD-TLR).*

[2] *By Newcombe score method.*

[3] *From One-sided Chi-square test, to be compared at one-sided significance level of 0.0249.*

Landmark Primary Efficacy Endpoint

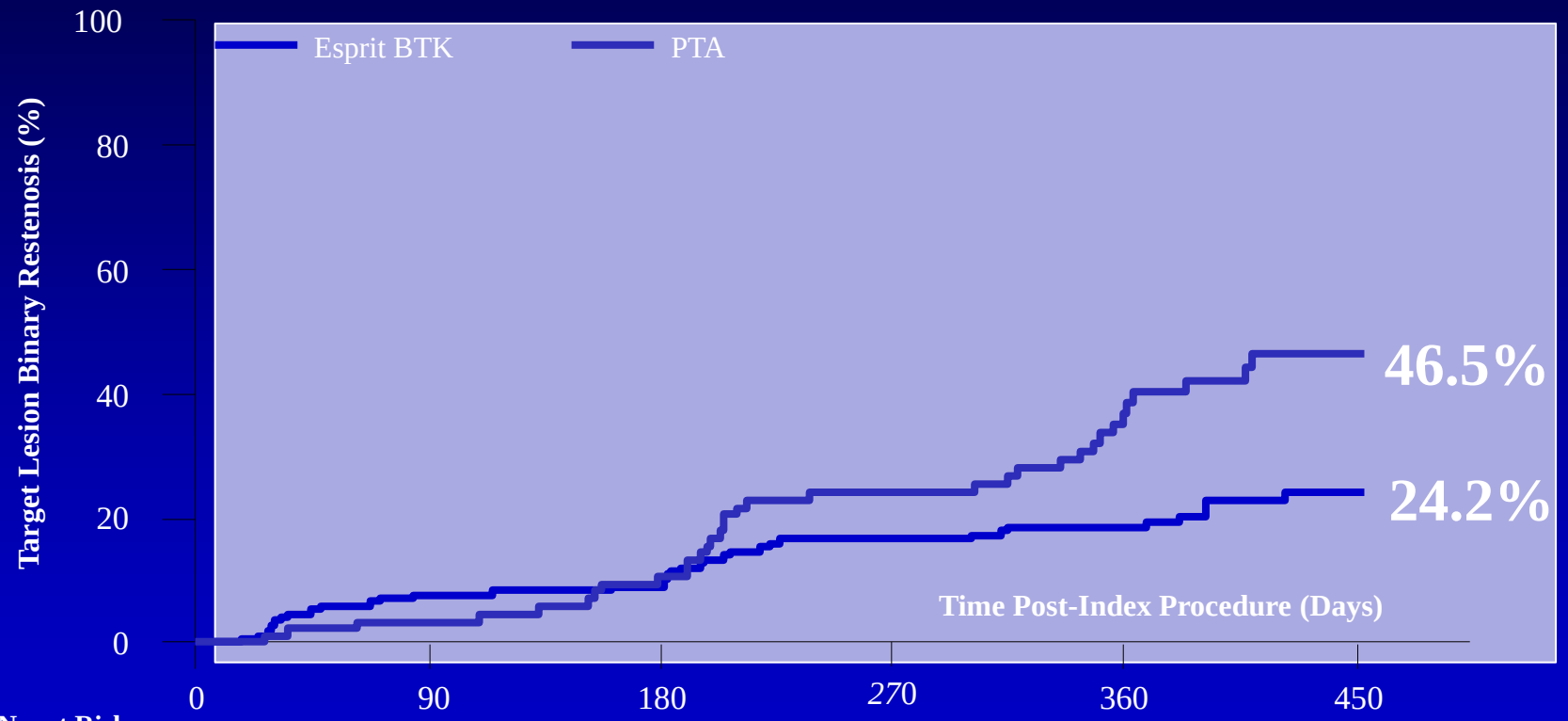


No. at Risk						
Esprit BTK	173			142	157	
PTA	88			67	82	
				100	68	
				37	26	

First Powered Secondary Endpoint

*Binary Restenosis of the Target Lesion at 1 Year – **ITT Population***

Esprit BTK	PTA	Difference [One-Sided Upper 97.5% CL][1]	P-Value[2]
23.5% (35/149)	49.3% (35/71)	-25.8% (-12.3%)	<0.0001



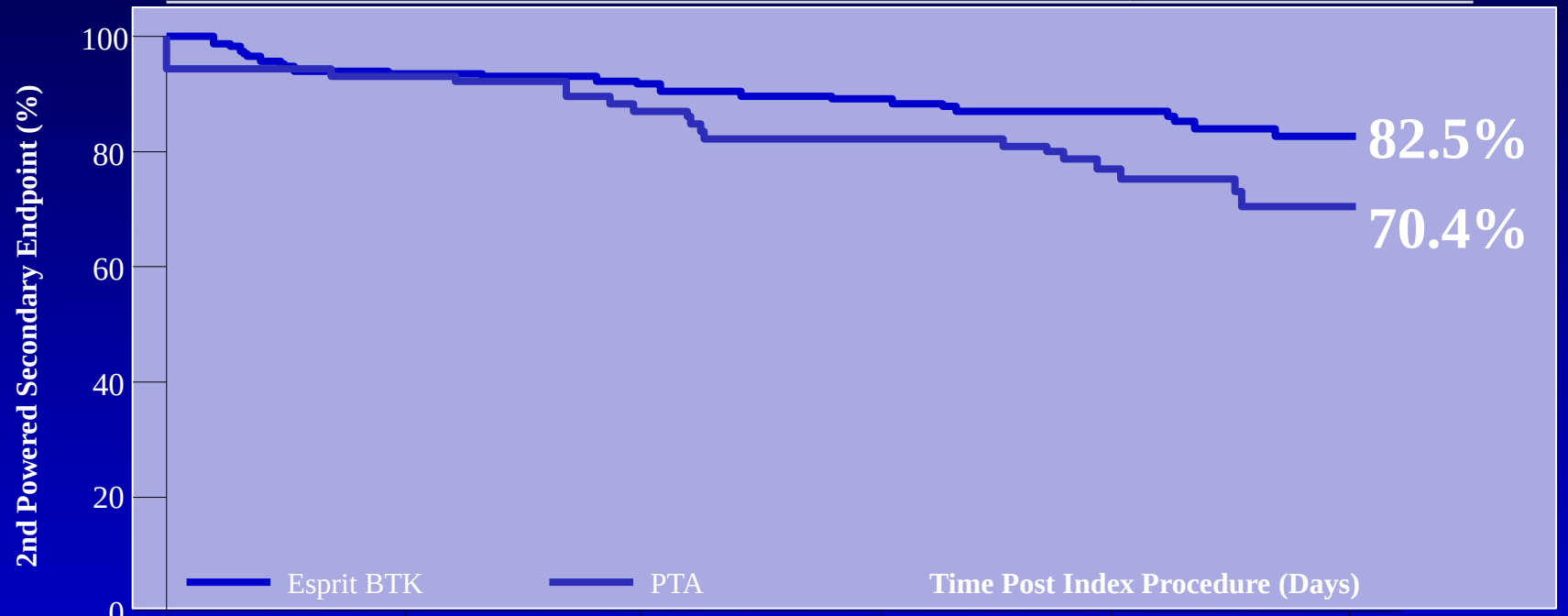
No. at Risk						
Esprit BTK	173	164	153	145	95	72
PTA	88	87	82	73	37	18

[1] *By Newcombe score method.*
[2] *From One-sided Chi-square test, to be compared at one-sided significance level of 0.025.*

Second Powered Secondary Endpoint

Freedom from Above Ankle Amputation in Index Limb, 100% Total Occlusion of Target Vessel, and CD-TLR at 1 Year – ITT Population

Esprit BTK	PTA	Difference [One-Sided Lower 97.5% CL][1]	P-Value[2]
83.2% (124/149)	69.0% (49/71)	14.2% (2.5%)	0.0081



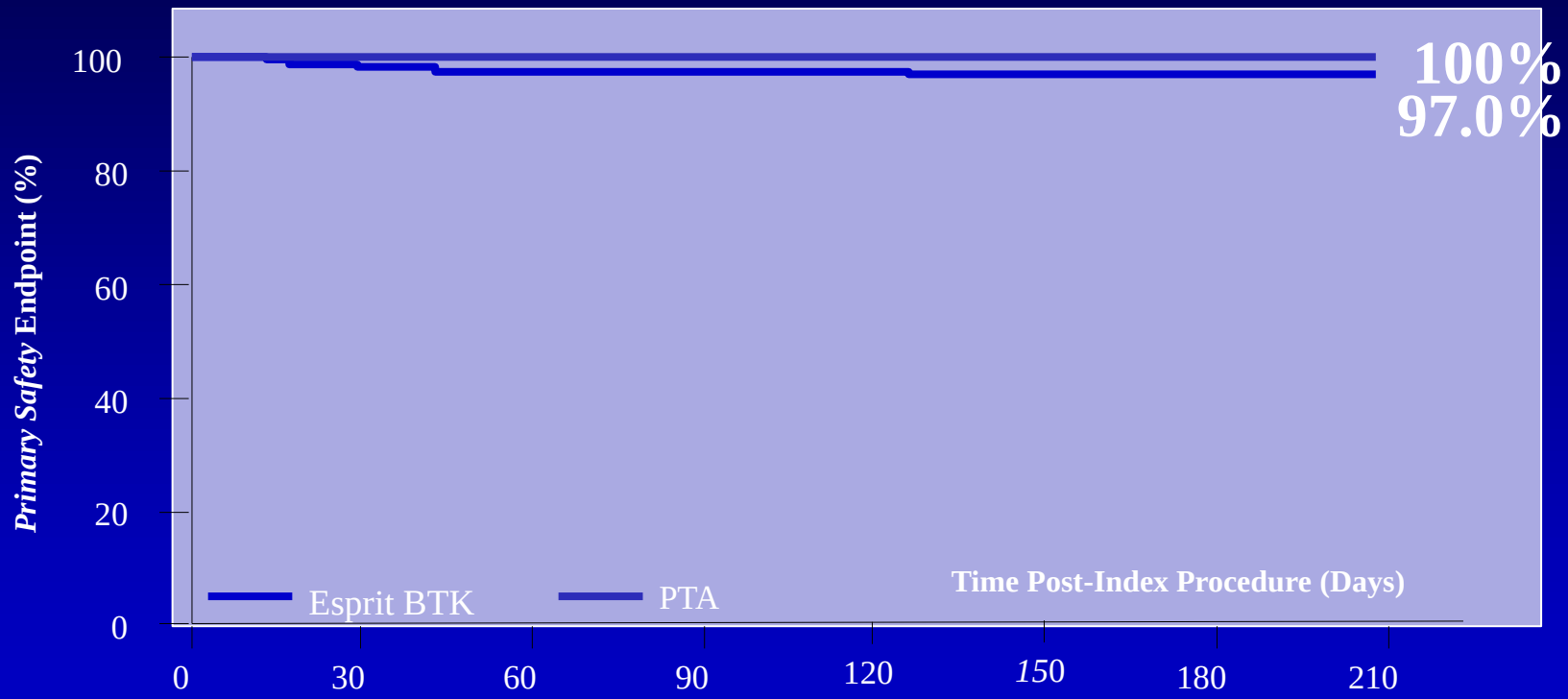
No. at Risk						
Esprit BTK	173	164	156	145	101	47
PTA	88	83	80	72	45	22

[1] *By Newcombe score method.*
[2] *From One-sided Chi-square test, to be compared at one-sided significance level of 0.025.*

Primary Safety Endpoint

*Freedom from Major Adverse Limb Event + Peri-Operative Death – **AT* Population***

Esprit BTK	PTA	Difference [One-Sided Lower 97.5% CL][1]	P-Value[2]
96.9% (155/160)	100.0% (85/85)	-3.1% (-7.1%)	0.0019

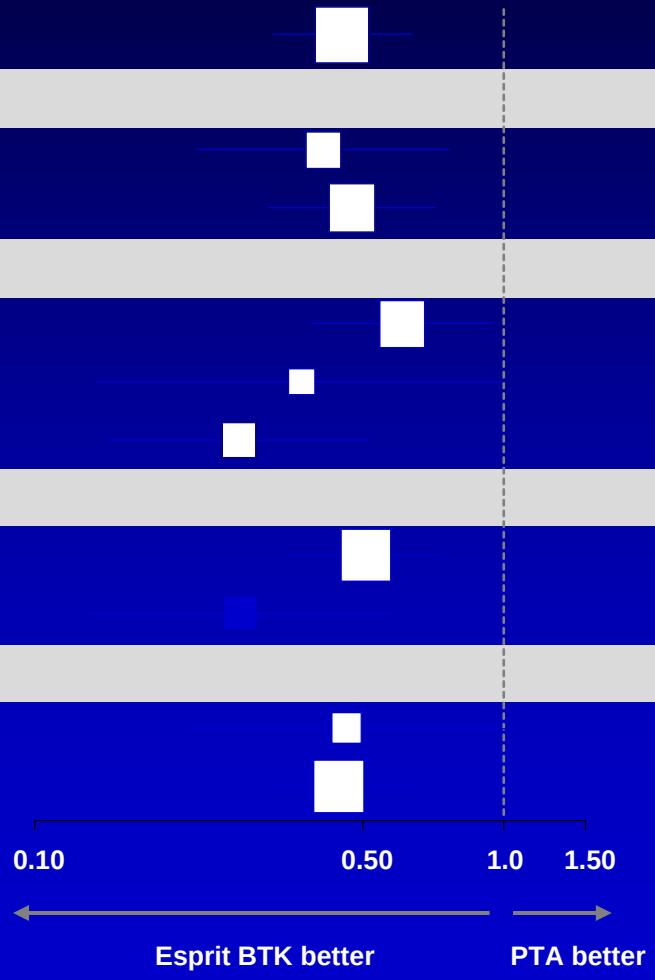


No. at Risk							
Esprit BTK	170	166	162	162		153	152
PTA	90	90	89	87		84	84

** AT defined as As-Treated*
[1] By Newcombe score method.
[2] Farrington-Manning non-inferiority (NI) test, with NI margin of δ set at -10%, to be compared at one-sided significance level of 0.025.
Note: The safety endpoint denominators of the rates exclude subjects who terminated from the study prior to the lower limit (152 days) of the 6-month primary safety endpoint follow-up window without any components of the primary endpoint.

Subgroup Analyses of Composite Primary Efficacy Endpoint at 1 Year

Subgroup	Esprit BTK (%)	PTA (%)	Relative Risk (CI)	Interaction p value
All patients	38/149 (25.5)	40/71 (56.3)	0.45 (0.32-0.64)	
Sex				**0.7709**
Female	12/51 (23.5)	12/21 (57.1)	0.41 (0.22-0.76)	
Male	26/98 (26.5)	28/50 (56.0)	0.47 (0.31-0.71)	
Race				**0.1055**
White	24/79 (30.4)	22/44 (50.0)	0.61 (0.39-0.95)	
African American	4/18 (22.2)	6/10 (60.0)	0.37 (0.14-1.01)	
Others	10/52 (19.2)	12/17 (70.6)	0.27 (0.14-0.51)	
Region				**0.1247**
US	31/114 (27.2)	32/60 (53.3)	0.51 (0.35-0.75)	
OUS	7/35 (20.0)	8/11 (72.7)	0.28(0.13-0.59)	
Age				**0.6159**
< 65 years old	7/32 (21.9)	9/19 (47.4)	0.46 (0.21-1.04)	
≥ 65 years old	31/117 (26.5)	31/52 (59.6)	0.44 (0.31-0.65)	



Lessons learned

- LIFE BTK re-defined the BTK space
  - Principal defined patient population
  - Principal defined primary outcome
  - Principal defined posered secondary outcomes
- LIFE BTK primary and secondary endpoints were met
- Very specific patient population tested
  - Upper 2/3 tibial
  - Required 10 cm from the ankle joint space
- General larger scale patient population still requires rigors of assessment and outcomes