Expert Thoughts on Drug-Eluting Resorbable Scaffolds for Peripheral Interventions: Dreaming or still caution?

William A. Gray MD FACC MSCAI
Professor of Medicine, Thomas Jefferson University
System Chief, Division of Cardiovascular Diseases,
Main Line Health
Phillip D. Robinson Endowed Chair in Cardiovascular Medicine
Co-Director, Lankenau Heart Institute
Wynnewood PA
USA

Challenges for Bioresorbable Technology:
Material Selection and Degradation Properties

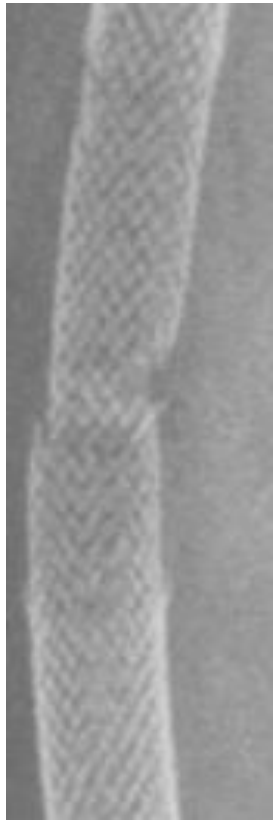
- Material selection
  - Absorbable metals, eg, Mg-based alloys
  - Polymer-based materials susceptible to hydrolytic breakdown
- Mechanical properties and stent design
  - Radial strength and deliverability
  - Provide scaffolding for sufficient duration to allow healing
- Degradation rates and biocompatibility/safety:
  - Must disappear in a time-frame that provides patient benefit without overloading the system with inflammatory by-products as it degrades

It's What's Next

Bioabsorbable Stents

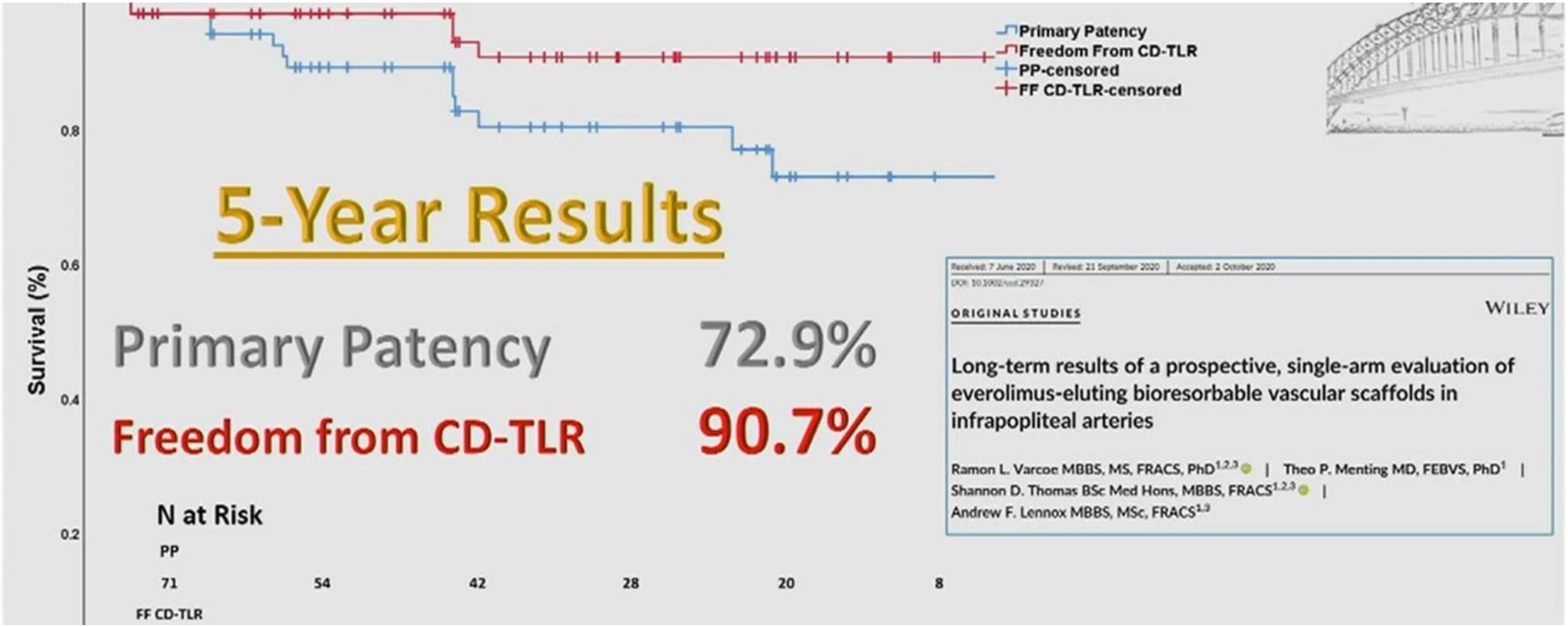
Why Bioabsorbable Stents?

- Advantages
  - No permanent device left behind, no need for stent scaffold later
  - Decrease flow-limiting dissection
  - May allow treatment of areas not suitable for a permanent stent
  - No long-term dual antiplatelet regimen needed
  - Maintain vasomotion of vessel: especially SFA



- Disadvantages
  - Inflammation
  - Embolization of material
  - Unknown time of scaffolding support need

5 Year Results (48 patients) ABSORB BTK Trial: VIVA 2019



5-year results published in *Catheterization and Cardiovascular Interventions* in January 2021 (Volume 97, Issue 1)

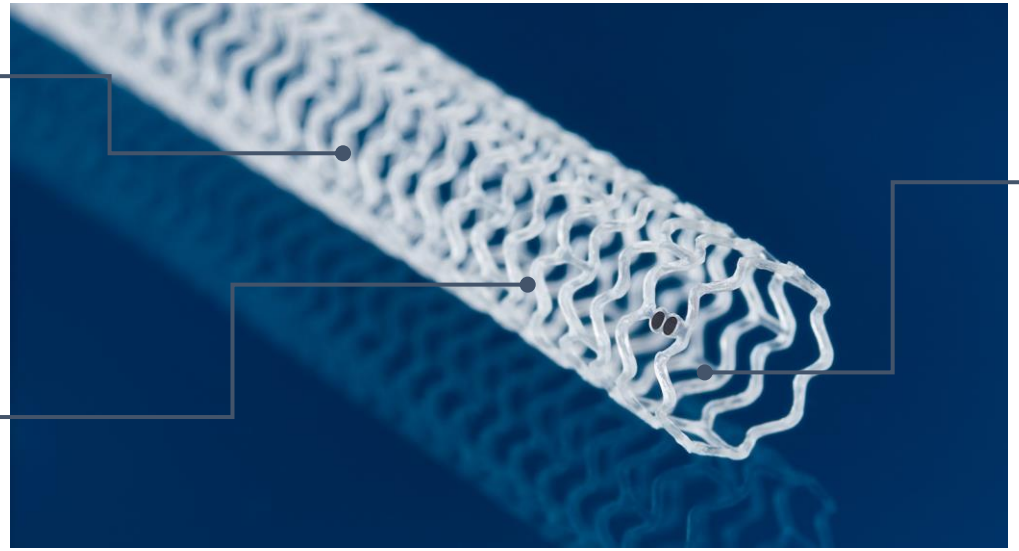
Investigational Device

Design and Components

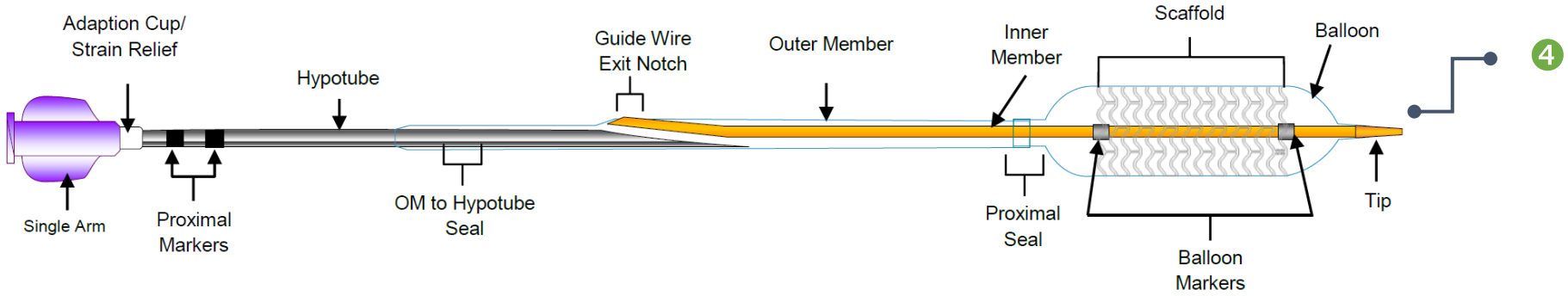
Esprit™ BTK Drug-eluting Resorbable Scaffold (DRS)

❶ Bioresorbable scaffold backbone comprised of 100% poly(L-lactide) (PLLA) and strut thickness of 99 µm**

❷ Coating comprised of the active pharmaceutical ingredient everolimus and bioresorbable poly (D,L-lactide) (PDLLA)



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



*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

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

DATA EVALUATED AT 12 MONTHS

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

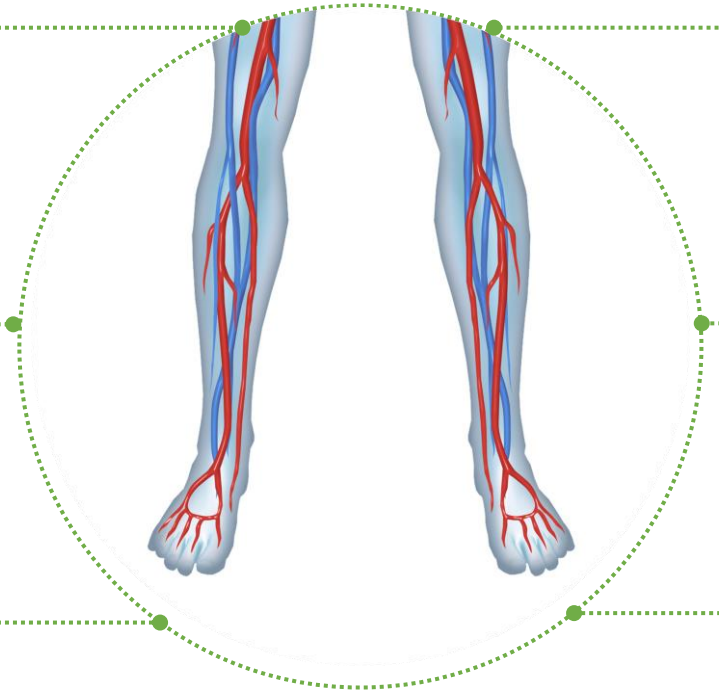
Inclusion Criteria

Study Population LIFE-BTK

Proximal 2/3 of native infrapopliteal arteries

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

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



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

RVD ≥ 2.5 mm and ≤ 4.0 mm

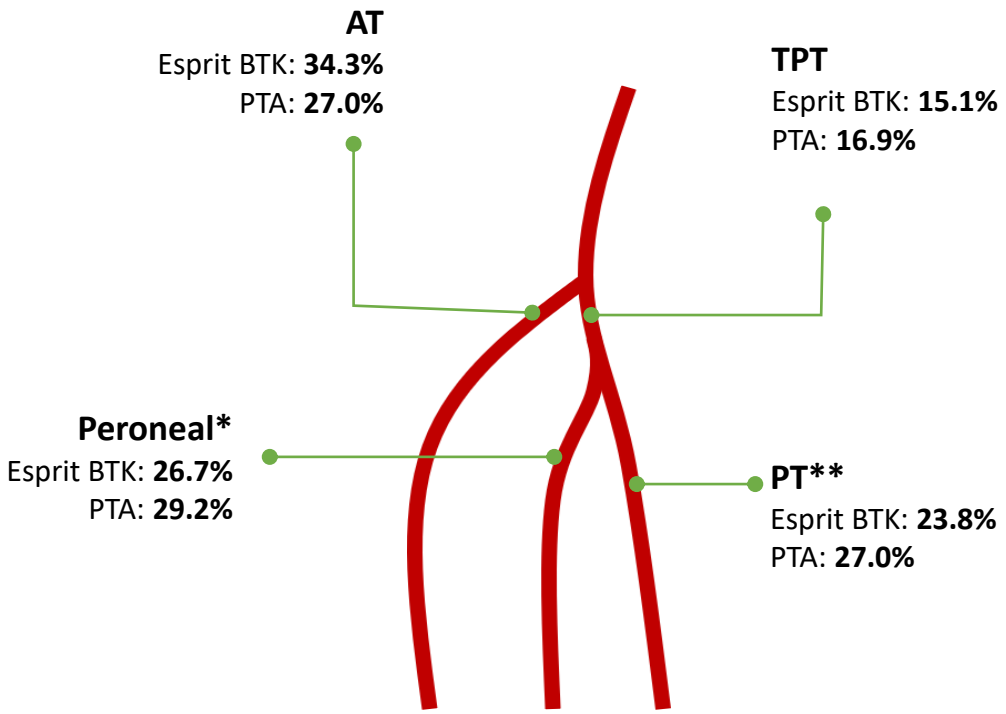
CLTI subjects with RB 4 or 5

*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)



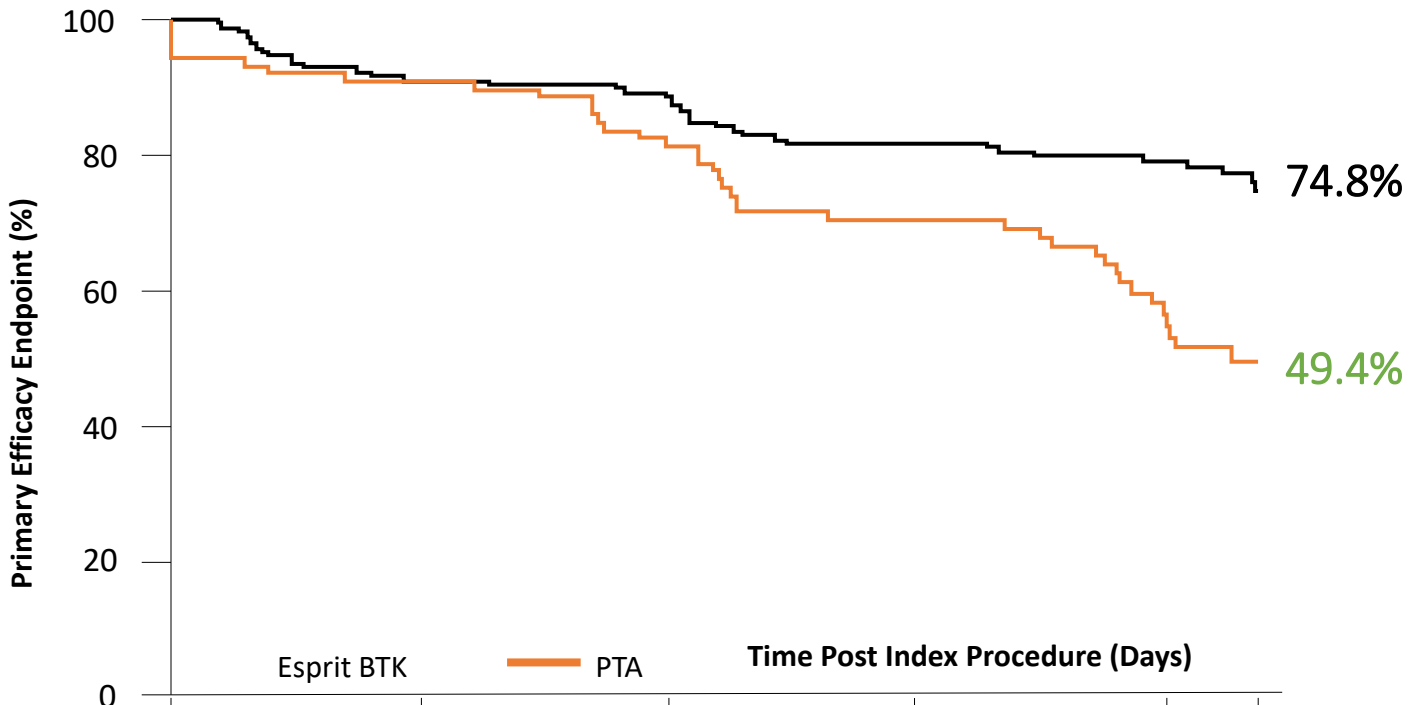
Number of Target Lesions Per Subject
Esprit BTK = 1.0 (1,2)
PTA = 1.0 (1,2)

* 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 (393 Days) – ITT Population

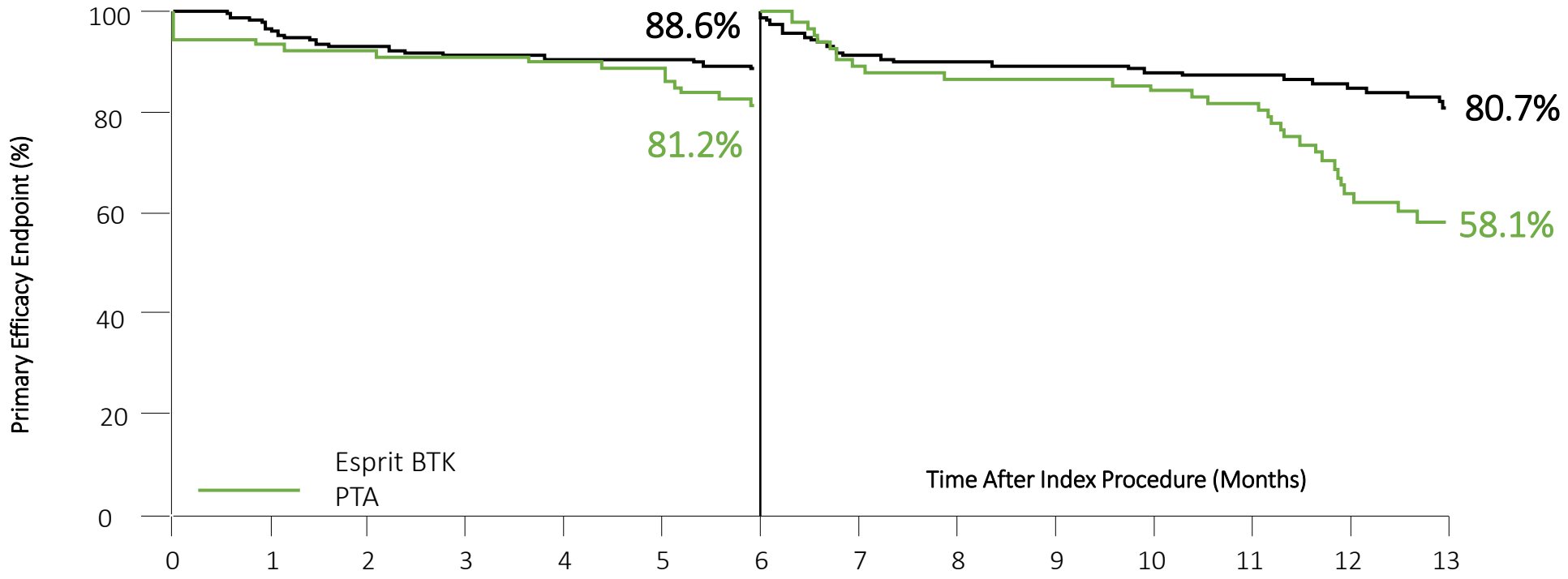
Esprit BTK	PTA	Difference [One-Sided Lower 97.51% CL][2]	P-Value[3]
74.5% (111/149)	43.7% (31/71)	30.8% (17.0%)	<0.0001



No. at Risk	0	90	180	270	360	390
Esprit BTK	173	163	152	142	94	63
PTA	88	82	78	67	31	22

[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

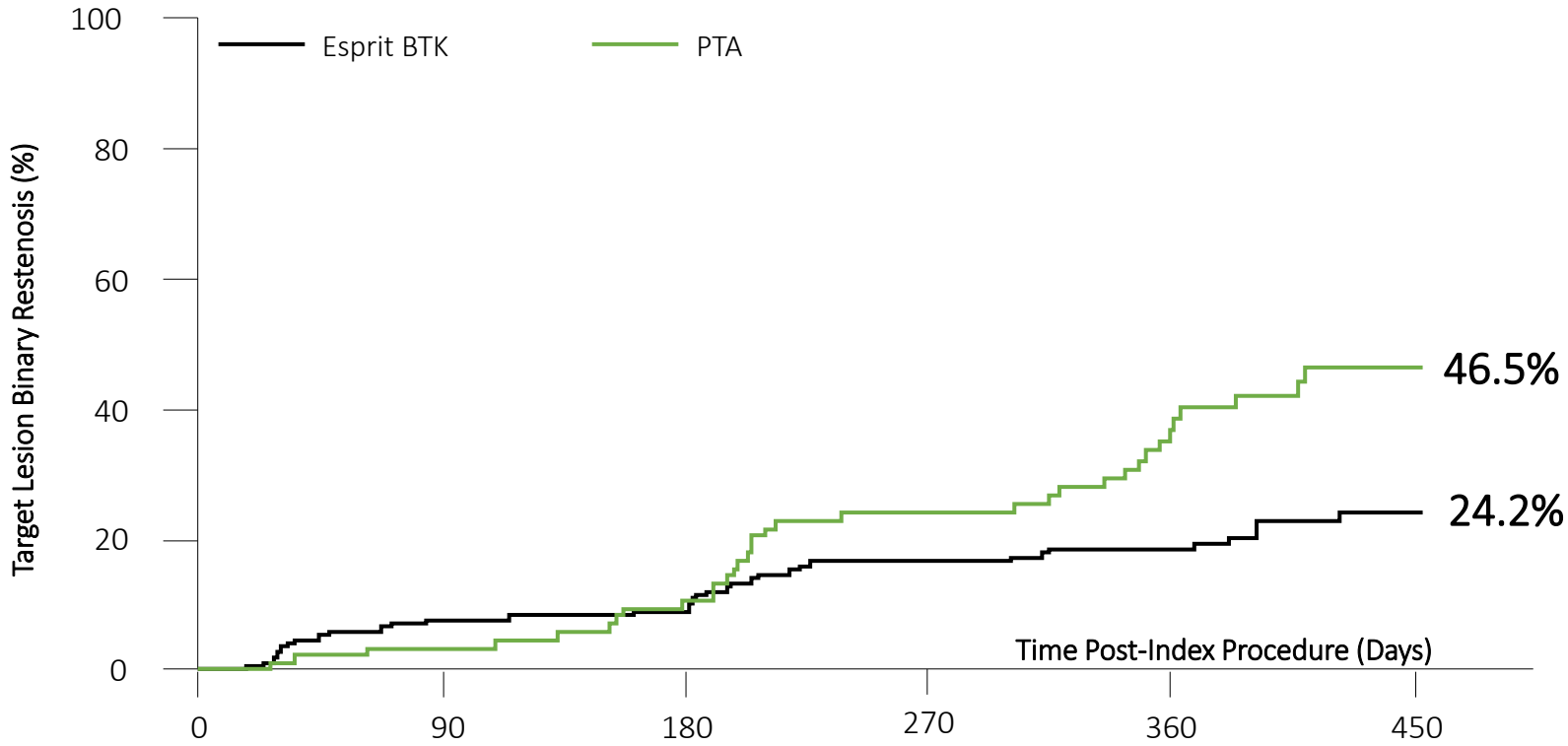


No. at Risk													
Esprit BTK	173					142	157				100	68	
PTA	88					67	82				37	26	

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



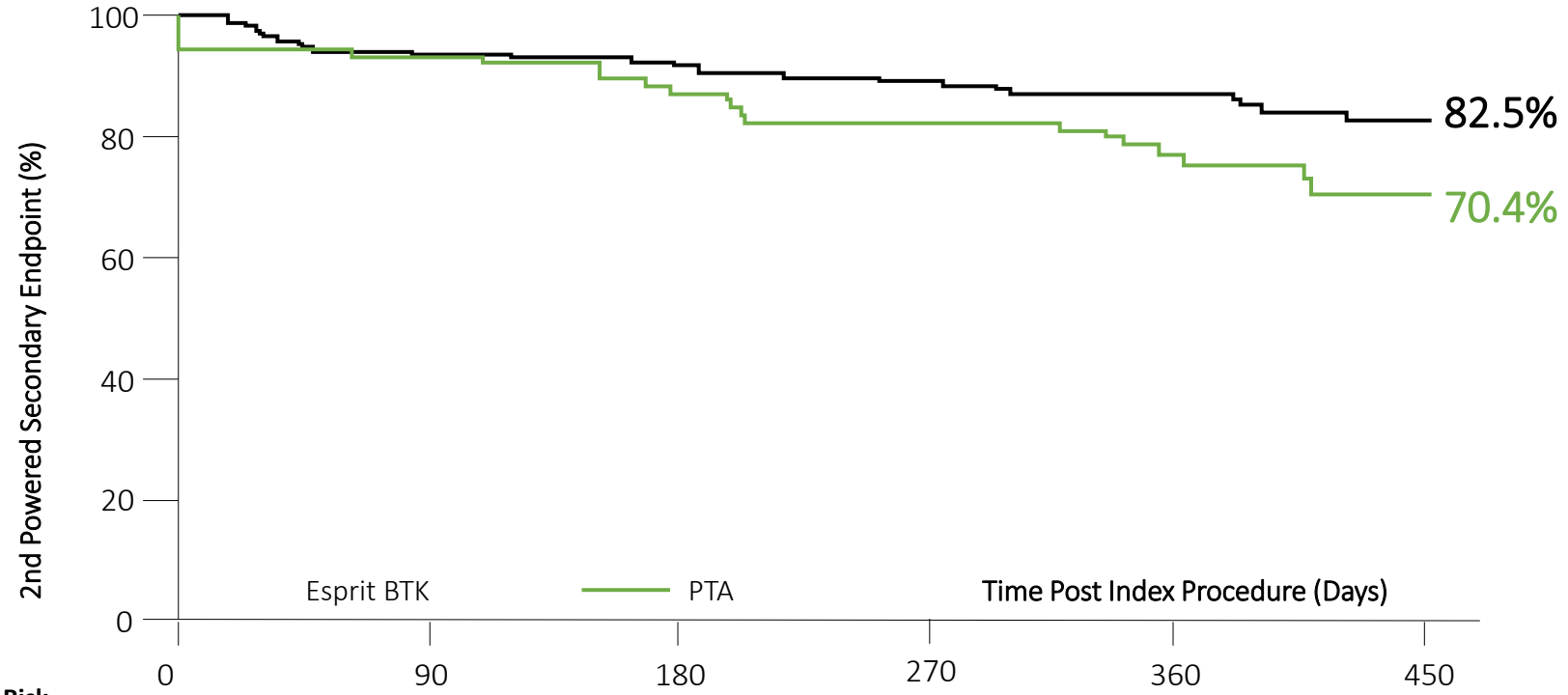
No. at Risk						
Esprit BTK	173	164	153	145	95	72
PTA	88	87	82	73	37	18

[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**

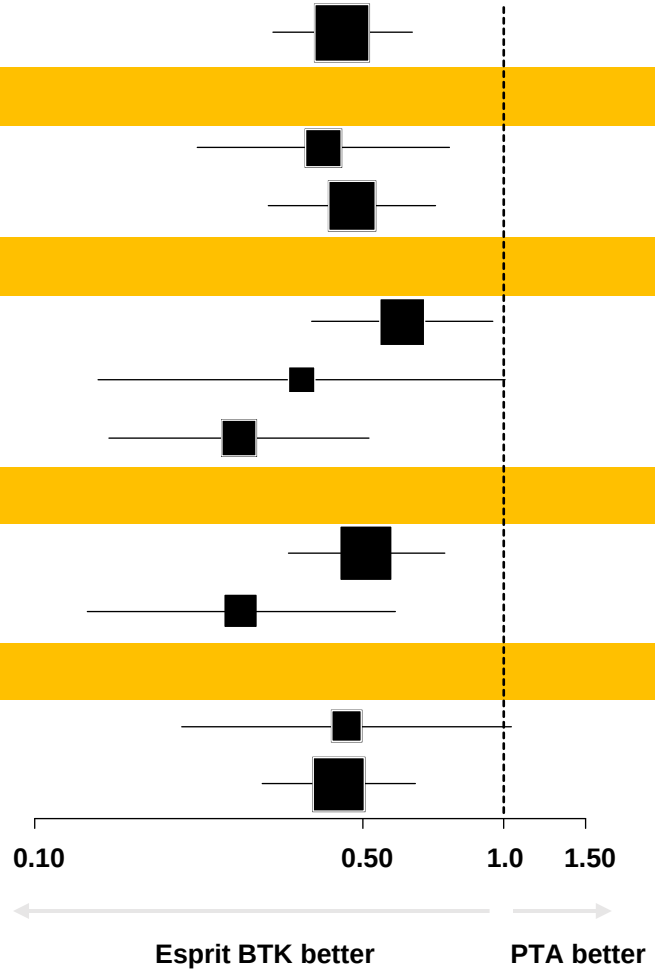


No. at Risk						
Esprit BTK	173	164	156	145	101	47
PTA	88	83	80	72	45	22

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

Subgroup Analyses of Composite Primary Efficacy Endpoint at 1 Year

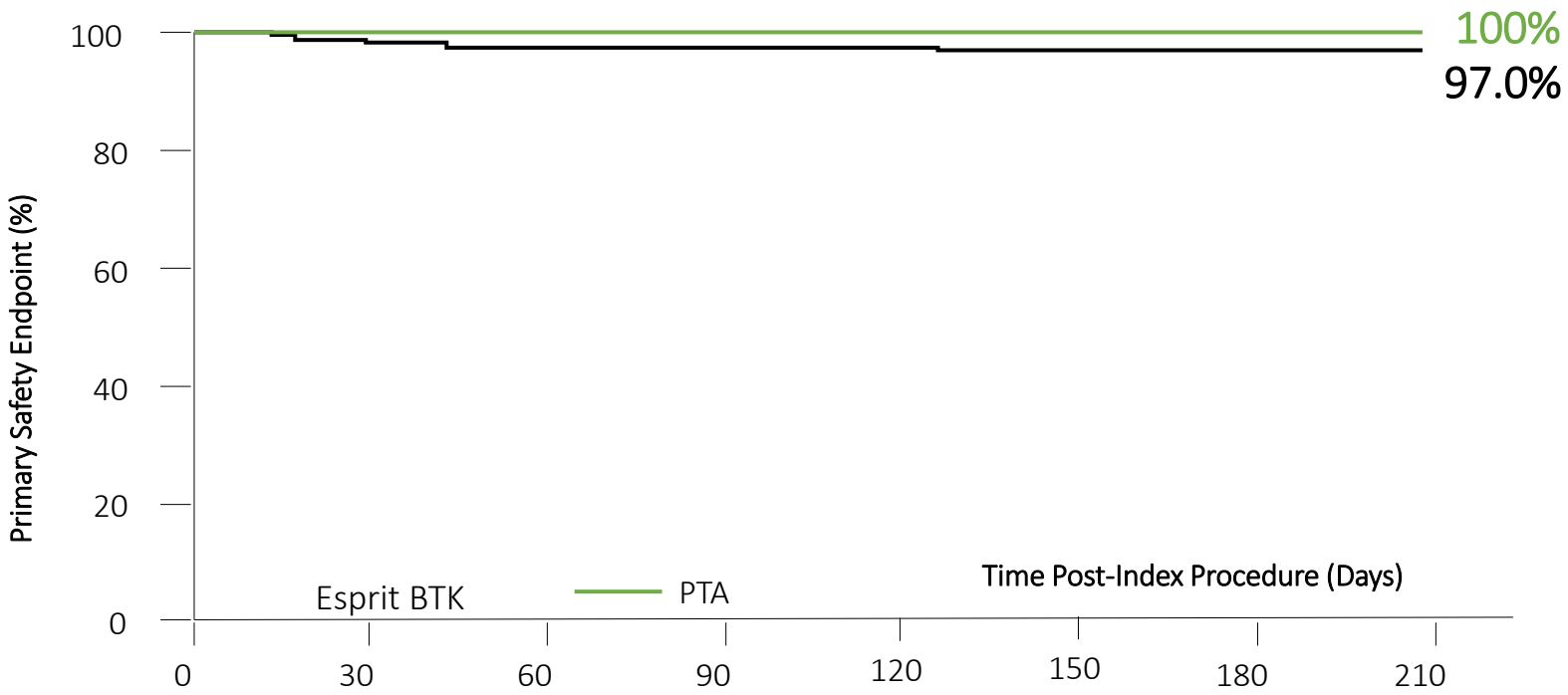
Subgroup	Esprit BTK (%)	PTA (%)	Relative Risk (CI)	Interaction p value
All patients	38/149 (25.5)	40/71 (56.3)	0.45 (0.32-0.64)	
Sex				**0.7709**
Female	12/51 (23.5)	12/21 (57.1)	0.41 (0.22-0.76)	
Male	26/98 (26.5)	28/50 (56.0)	0.47 (0.31-0.71)	
Race				**0.1055**
White	24/79 (30.4)	22/44 (50.0)	0.61 (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)	



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.

REVA Medical: MOTIV BTK Technology

Bioresorbable Peripheral Vascular Scaffold

- **CE Mark** Approved in Europe
  - Excellent 24-month EU Clinical Trial outcomes
- FDA Break-Through Technology Designation
- Made from REVA's proprietary polymer, **Tyrocore**
  - **X-ray visible** for treatment accuracy – No guessing at placement
  - **High Strength** to maintain artery patency during vessel healing
  - **Sustained Sirolimus drug delivery** to maintain long-term vessel patency
  - **Bioresorbable** removes concerns associated with a permanent implant
- Actively Enrolling US IDE Clinical Trial

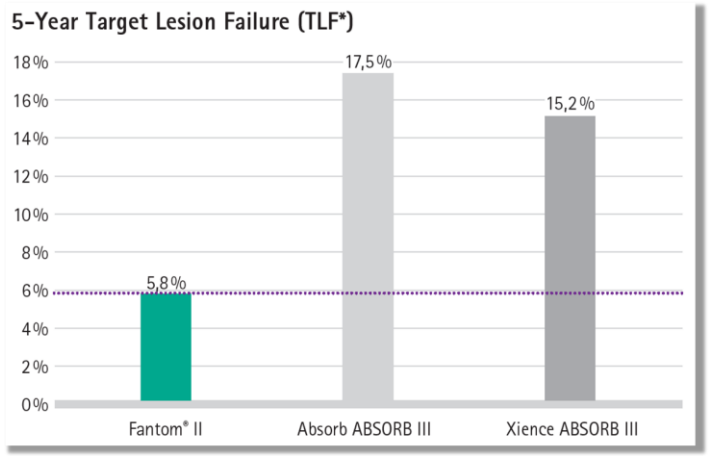
Only BRS CE mark Approved for
Below-the-Knee Revascularization

REVA's MOTIV BTK Technology

Bioresorbable Peripheral Vascular Scaffold

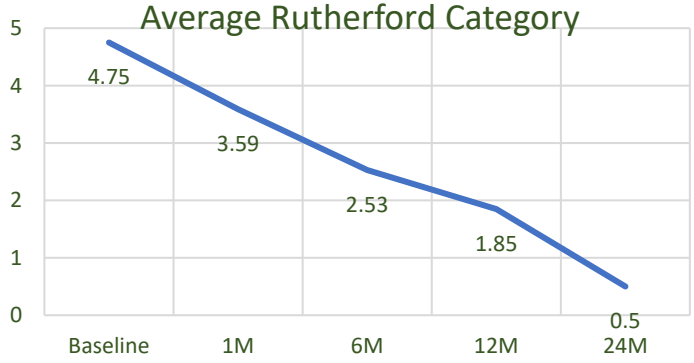
- Demonstrated Safety & Effectiveness
  - Tyrocore based scaffolds implanted in over 500 coronary patients with excellent clinical outcomes through 5 years
  - European Peripheral vascular pilot BTK trial
    - Technical Implant Success 99% in all 58 patients
    - 12 Month Patency 88%, 24 Month Patency 82%

FANTOM II Coronary Trial



- Next Steps/Current Status
  - Global Randomized Clinical Trial for US FDA commercial approval
  - 292 Patients randomized against balloon angioplasty at up to 45 clinical centers
  - Enrollment has been initiated with rapid expansion in-process

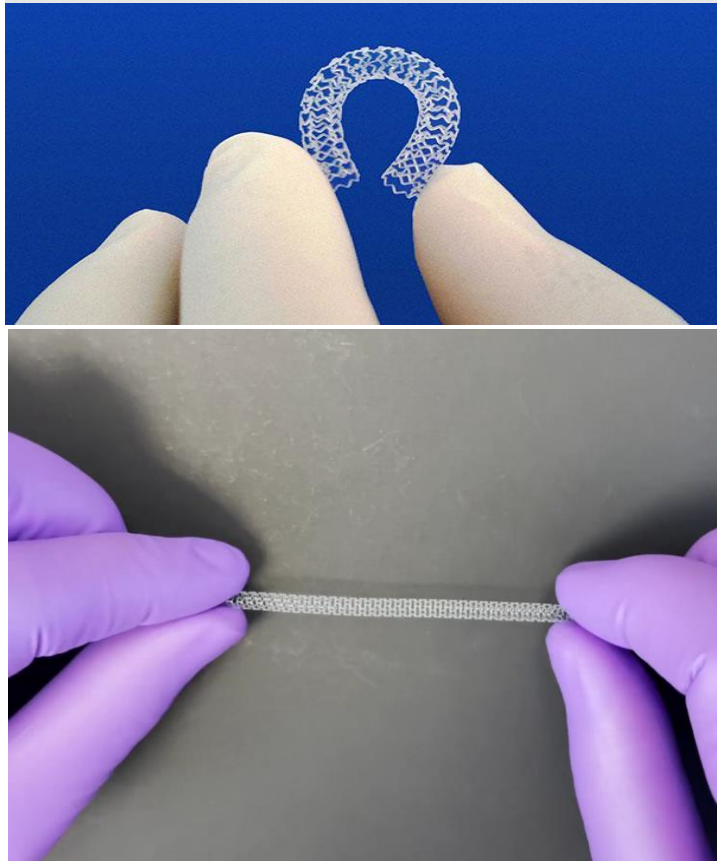
European Peripheral Vascular Trial
Average Rutherford Category



R3 Vascular Program Overview: MAGNITUDE

Bioresorbable Drug-eluting Scaffold and Delivery System

Innovative Scaffold Strength and Flexibility



PLLA Resorbable Scaffold

- 98 um strut thickness
- Balloon expandable
- High radial force
- Resorbs in a benign controlled manner

PDLLA Resorbable Coating

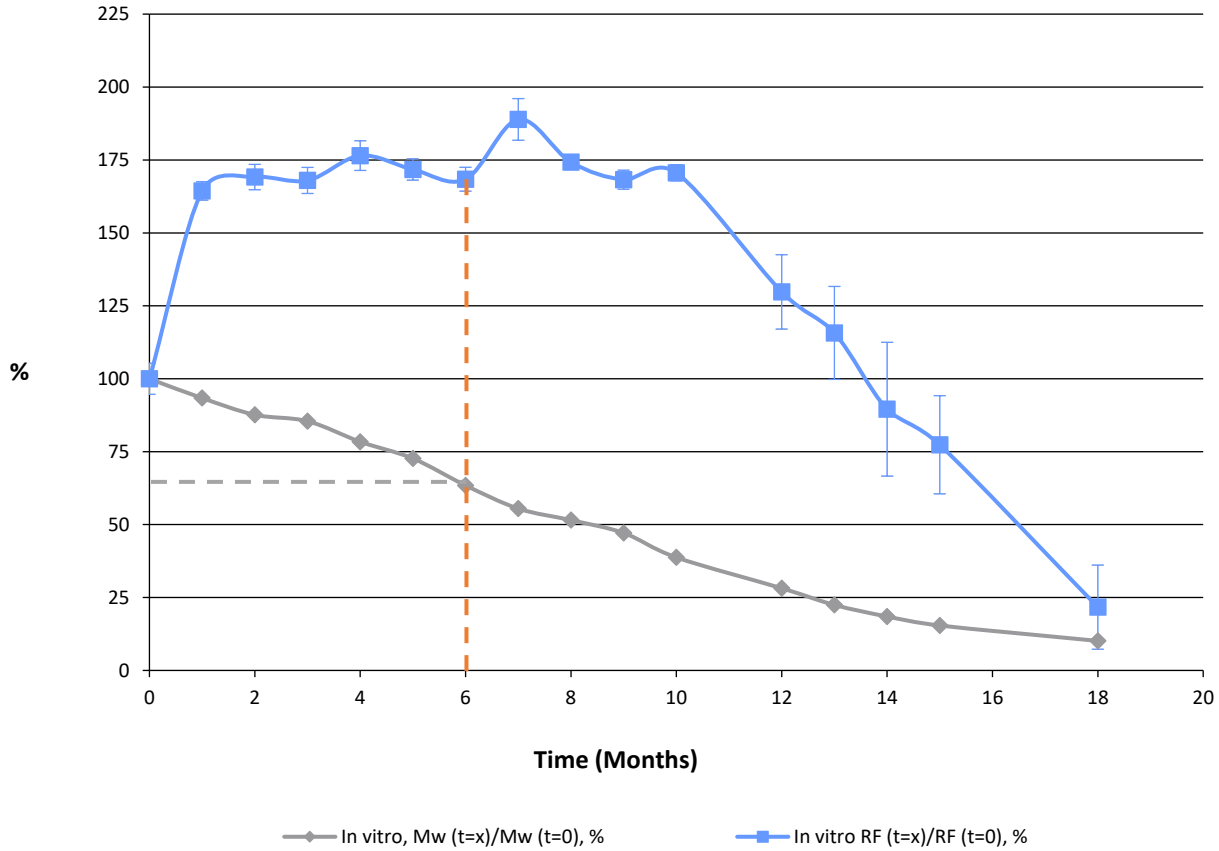
- Provides sustained drug elution to maximize long term patency
- Controlled drug release

Sirolimus

- Anti-proliferative agent with known safety profile
- Minimizes neointimal growth

Resorption Profile of MAGNITUDE Scaffold

1. Gradual rate of resorption
2. Polymer is converted into lactic acid
3. Metabolized and converted into carbon dioxide and water
4. A 95% reduction in molecular weight at 18 months
5. Complete resorption expected by 3.5 years



RESOLV I Study overview

01

Study Design

Prospective, Single arm, Multi-center, First-in-human

02

Enrollment

Up to 50 patients in Austria, Canada, and Italy

03

Patient Type

- Symptomatic
- Infrapop de novo or restenotic lesions
- Rutherford 3-5
- RVD 2.5-3.75
- 51mm max lesion length

04

Follow-up

1, 3, 6, 12 months

Long term FU: 2-5 yrs

05

Primary Safety Endpoint

Freedom from MALE at 6mo + POD

06

Primary Efficacy Endpoint

Angiographic primary patency + freedom from TLR at 6 months

- Major Adverse Limb Event = above ankle amputation in the index limb or major reintervention at 6 months
- Peri-Operative Death = mortality at 30 days

Upcoming IDE Trial: ELITE-BTK

Study Design	Study Population	Follow-up	Primary Safety Endpoint	Primary Efficacy Endpoint
• Prospective • Multi-center • Randomized 1:1 to PTA	• Symptomatic CLTI • Infrapop de novo or restenotic lesions • Rutherford 4-5	1, 3, 6, 12 months Long term FU: 2-5 yrs	Freedom from MALE at 6mo + POD	Angiographic primary patency + freedom from TLR at 6 months

Summary

- Finally! An effective, dedicated FDA and CE mark approved device category.

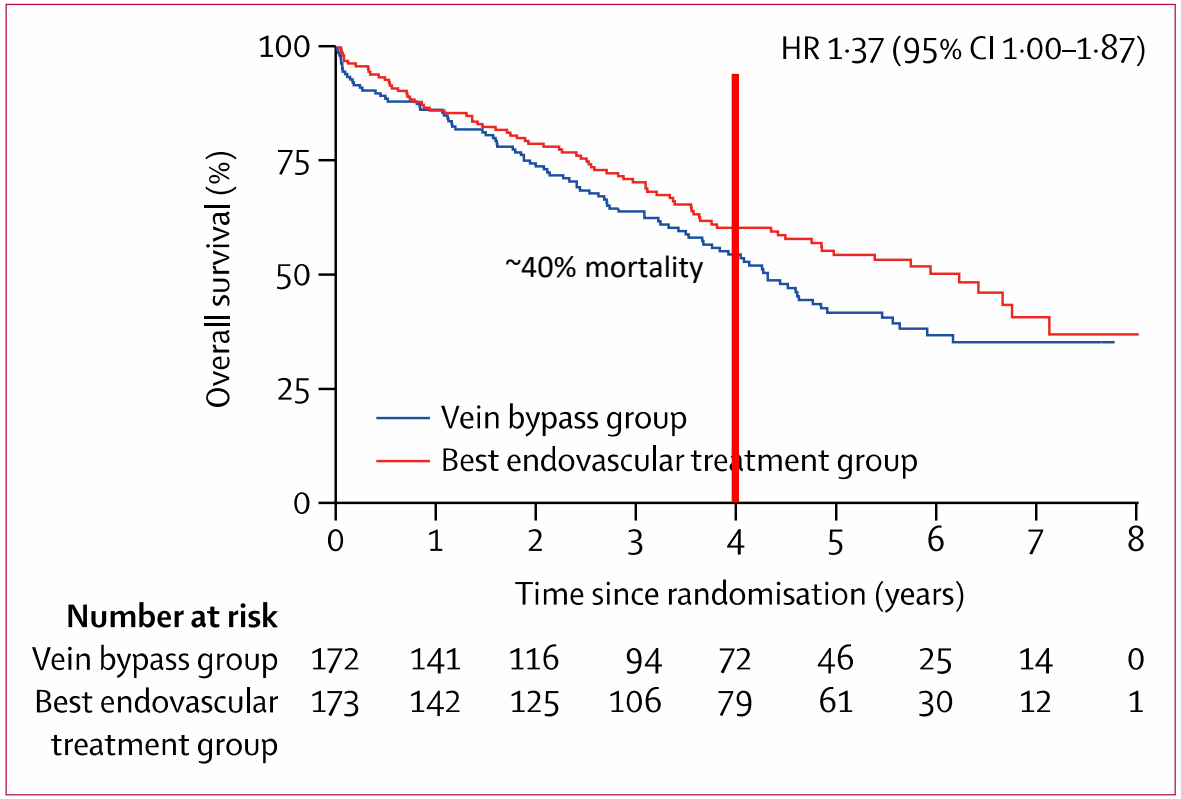
- With 2 more platforms currently in clinical trials, more data and greater options are likely to be forthcoming

But there are other considerations…

- The LIFE-BTK BRS trial lesion length was limited in complexity
  - 40 mm-50 mm
  - Proximal 2/3's of the tibials
  - 80% "simple" lesions by TASC classifications
- How will the scaffold perform in:
  - Longer lesions?
  - More complex lesions?
  - Calcified lesions?
- Cost of BRS device?
  - Coronary DES ~80 Euros
    - Is this a reasonable alternative to treat proximal "short" disease, especially if calcified?

Other considerations…

- BASIL-2 mortality at 4 years:
  - ~40%
- BASIL-3 mortality at 4 years:
  - ~40%
- BEST-CLI mortality at 4 years
  - ~35%



BASIL 2 survival

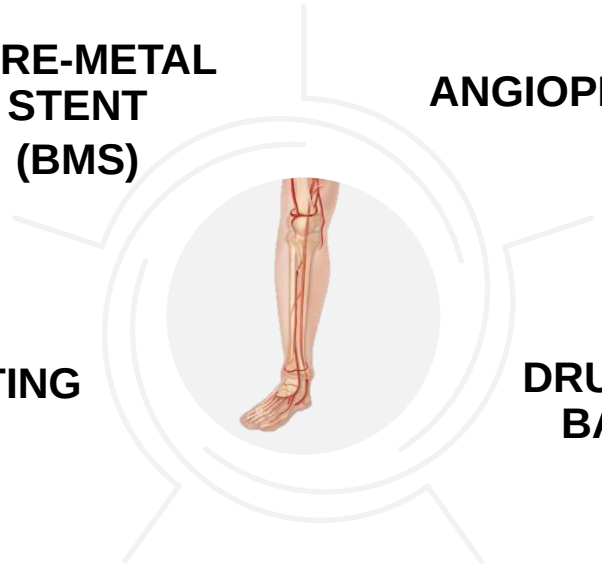
Other considerations…

- Given the acknowledged high mortality rates in the CLTI population, is a resorbable platform a universal solution, or should we be considering a complimentary approach?

- If so, it appears that there is a need to develop a clinical (WiFI ++?) predicative score for mortality in these CLTI patients to better customize---and justify---the device and procedural approaches and associated costs in their care

Multiple options for BTK intervention

Current Treatment Options for Tibial Circulation*



To Effectively Treat BTK Disease

	DRUG (INHIBIT NIH)**	SCAFFOLD (RESIST RECOIL)	LEAVE NOTHING BEHIND
ANGIOPLASTY	✗	✗	✓
ATHERECTOMY/ LITHOTRIPSY	✗	✗	✓
DCB	✓	✗	✓
BMS	✗	✓	✗
DES	✓	✓	✗
UNMET NEED	✓	✓	✓

*Adapted from Varcoe, R., LINC 2020.
**NIH = Neointimal Hyperplasia.
Esprit™ BTK Development and Status of DRS Clinical Trials for Endovascular Applications. Richard J Rapoza, PhD. Released: 17-February-2020.