Adventitial Drug Delivery With the BullFrog Device (Mercator MedSystems) and the Spur Device (Reflow Medical)

How do They Work and How Will We Know They Improve Results?

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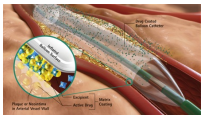
Challenge for Intimal Drug Delivery: Barrier Tissue

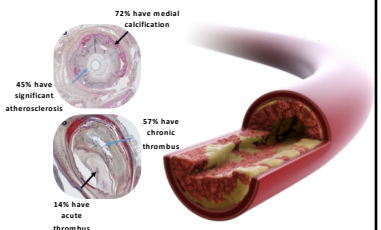
IDEALLY

Idealized cartoon – thin disease and perfect drug transmigration and distribution



Jeger et al. JACC: Cardiovasc Interv 2020;13(12):1391-1402.

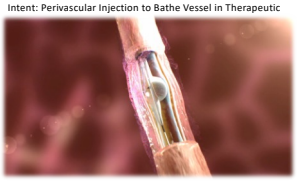
ACTUALLY



Narula, et al. JACC 2018;72:2152-63.

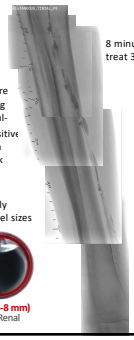
The Bullfrog Device: How It Works

Intent: Perivascular Injection to Bathe Vessel in Therapeutic



Dilute contrast medium admixture with drug gives real-time positive diffusion feedback

8 minutes to treat 30 cm



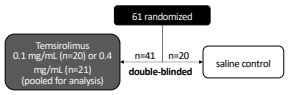
Current product family treats a range of vessel sizes

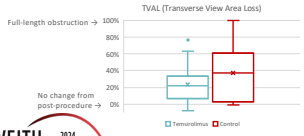
Small (2-4 mm) BTK PAD, Coronary
Medium (3-6 mm) Pop/Distal SFA
Large (4-8 mm) SFA, Renal

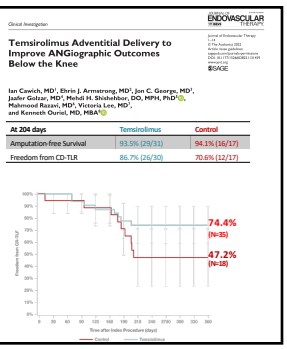
510(k) cleared and CE Marked for therapeutic and diagnostic agent delivery

TANGO study: BTK

Phase 2 prospective, multi-center U.S. trial







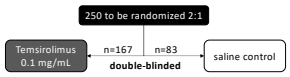
Clinical Investigation

Temsirolimus Adventitial Delivery to Improve ANGiographic Outcomes Below the Knee

Ian Cawich, MD[1], Elvin J. Armstrong, MD[1], Jon C. George, MD[1], Jaafer Golzar, MD[1], Mahdi H. Shishehbor, DO, MPH, PhD[1,2], Mahmood Razavi, MD[1], Victoria Lee, MD[1], and Kenneth Ouriel, MD, MBA[1]

At 204 days	Temsirolimus	Control
Amputation-free Survival	93.5% (29/31)	94.1% (16/17)
Freedom from CD-TLR	86.7% (26/30)	70.6% (12/17)

TANGO-3 BTK: Phase 3 Trial Design



Principal Eligibility Criteria

- Rutherford 3 (up to 20% of enrollment), 4 or 5
- Culprit lesion in distal popliteal (P3), tibial or peroneal artery with:
  - >70% narrowing, or
  - >50% narrowing for >10cm
- Up to 2 distinct lesions
- Up to 30 cm treatment length
- Target lesion may span above knee joint space
- Any contemporary vessel prep
- Other criteria listed on clinicaltrials.gov

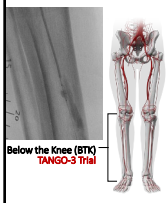
Primary Endpoints

6-month freedom from Clinically Relevant Target Lesion Failure, comprised of:

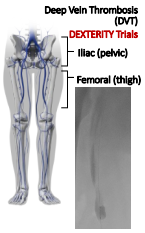
- Ischemia-related major amputation
- Clinically driven target lesion revascularization
- Clinically relevant target lesion occlusion

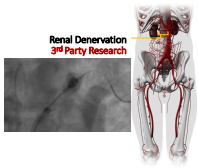
Recruiting sites in U.S. for FPI late 2024/early 2025

Active Bullfrog Therapy Development



Below the Knee (BTK)
TANGO-3 Trial





Retrievable Scaffold Therapy (RST): Spur System Clinical Study Overview

Spur Peripheral Retrievable Scaffold System:

- self-expanding scaffold with radially expandable spikes
- designed for controlled penetration
- an OTW system with integrated dilation balloon catheter
- prior to treatment with a DCB (OUS; IDE underway in US)

DEEPER OUS	DEEPER LIMUS	DEEPER REVEAL
107 patients Europe, New Zealand	26 patients Austria	130 patients USA
Prospective, multi-center, single-arm, performance goal comparator Sub-study: vessel recoil	Prospective, single-center, pilot study, single-arm	Prospective, multi-center, IDE, single-arm, performance goal comparator
Spur + paclitaxel DCB	Spur + sirolimus DCB*	Spur‡
Follow up: 1, 3, 6, 12 and 24 months, and annually phone call for 5 years	Follow up: 1, 3, 6 and 12 months	Enrollment completed April 2024; follow up ongoing 1, 3, 6, and 12 months Spur‡ has FDA Breakthrough Device Designation: De-Novo

* Spur used with MagicTouch™, Concept Medical™ ; ‡ Investigational use only in the US

Spur System Major Endpoint Results to Date

	DEEPER OUS	DEEPER LIMUS
Endpoints/ Results	**Primary Efficacy:** Primary patency at 6 months by DUS • 6-months 85.7% (72/84) • 12-months 74.4% (61/82) **Primary Safety:** Freedom from 30-day perioperative mortality • 100% (102/102)	**Primary Safety:** 6-month composite of All-Cause Mortality, Major Amputation and CD-TLR • 11.5% (3/26) • 1 patient died of COVID-19 • 1 patient had major amputation due to infection • 1 patient with CD-TLR
	Secondary Safety Endpoints: • Freedom from MALE at 12 months • 93/94 (98.9%) • **2 Years:** 79/80 (98.8%) MALE: defined as major amputation above the ankle	**Secondary Safety Evaluations:** • Freedom from MALE and all-cause mortality at 30 days • 96.2% (25/26) • Freedom from MALE at 6 and 12 months • 95.5% (21/22)
	Secondary Efficacy Endpoints: • Freedom from CD-TLR through 6 months post-procedure • **6 Months**: 85/95 (89.5%) • **1 Year:** 84/96 (87.5%) • **2 Years:** 71/85 (83.5%)	**Secondary Efficacy Evaluations:** • LLL at 6 months by QVA: 0.4 ± 0.5 mm • Primary patency at 6 months by QVA: 95.2% (20/21) • Primary patency at 6 and 12 months by DUS • **6 Months:** 91.3% (21/23) • **1 Year:** 89.5% (17/19) • **Change in Rutherford score:** 47.4% of Rutherford category 5 improved to Rutherford 0.
	All-Cause Mortality at 2 Years • **15/107 (14%)**	
Vessel Recoil	**Sub-study: Vessel Recoil* post Spur treatment** 42.5% (17/40) occurrence of vessel recoil Previously published rates with PTA alone 64-97%	**Secondary Efficacy Endpoint: Vessel Recoil* post Spur treatment** 42.9% (3/7) occurrence of vessel recoil
	* Vessel recoil is defined as >10% compromise in lumen diameter immediately po	post Spur treatment and 15 minutes post Spur treatment, prior to use of the DCB

RST: Sirolimus Eluting Spur Stent*

Composition	Function
Sirolimus	Anti-proliferative
Proprietary Blend	Binder
	Antioxidant
	Solvent

*For Investigational Use Only

Global Clinical Trial Development	
Status	**GRANTED FDA BREAKTHROUGH DESIGNATION**
Subjects	Infrapoplíteal arterial disease R4-5
Design	Prospective, multicenter: Drug-Eluting Temporary Spur Stent System vs POBA
Devices	Sirolimus Eluting BTK Spur Stent System (Experimental) vs. POBA (Control)

Summary

- Adventitial therapies appear effective in early testing, suggesting a plausible MOA
  - Either small randomized (dose-finding) or single arm studies
- Additional data from both device approaches will be forthcoming as early as 2025