TANGO
A Randomized Dose-Escalation Trial of Temsirolimus Adventitial Delivery to Improve Below the Knee Outcomes

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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 Vascular, Boston Scientific, Philips, PQ Bypass, Shockwave
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Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

Presented on Behalf of Enrolling Sites

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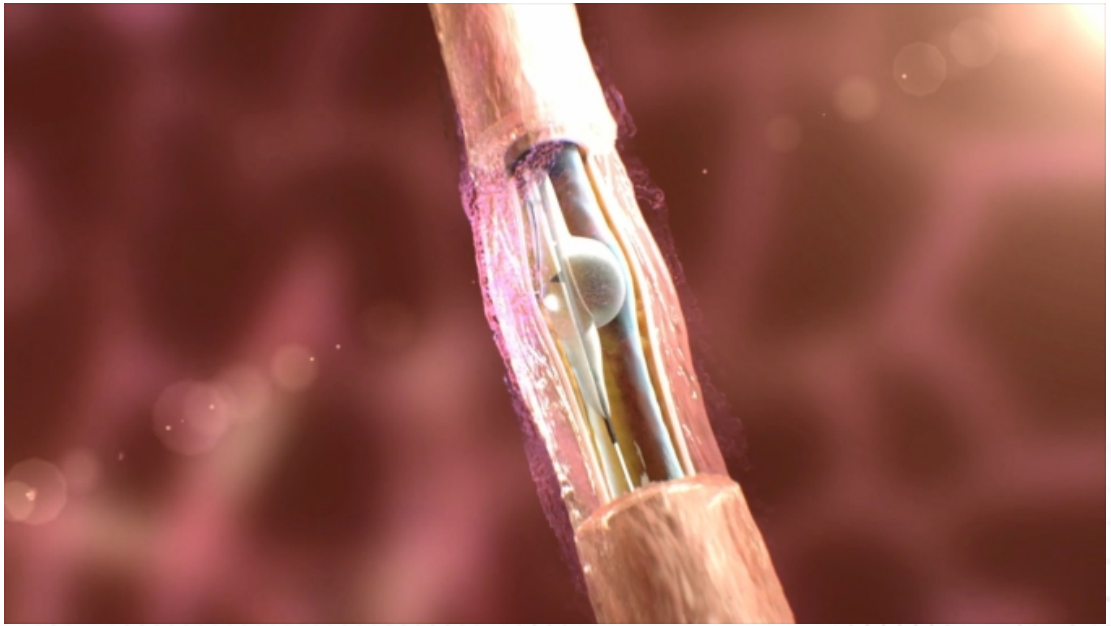
Background

- Current infrapopliteal treatments continue to lack long-term durability
- Drug-coated balloons have not demonstrated consistent benefit in the BTK region
- Failure of DCB in BTK region may be inherent to heavy thrombus, plaque and calcium burden
- Direct adventitial delivery provides a shortcut through the disease
- Temsirolimus is an ideal agent to reduce restenosis

The Bullfrog ® Micro-Infusion Device

- Adventitial delivery confirmed with contrast medium
- Dose control: Inject from separate syringe only after needle is engaged
- Unlimited payload: Not limited to the tiny surface area and thickness of a drug coating
- Multiple injections with one device – no need to swap out balloons for long lesion treatment



Temsirolimus Provides Treatment Advantages over Sirolimus or Paclitaxel in Reducing Restenosis

Improved pharmaceutical profile vs. sirolimus

Temsirolimus functions in a manner similar to rapamycin but with an improved pharmaceutical profile.

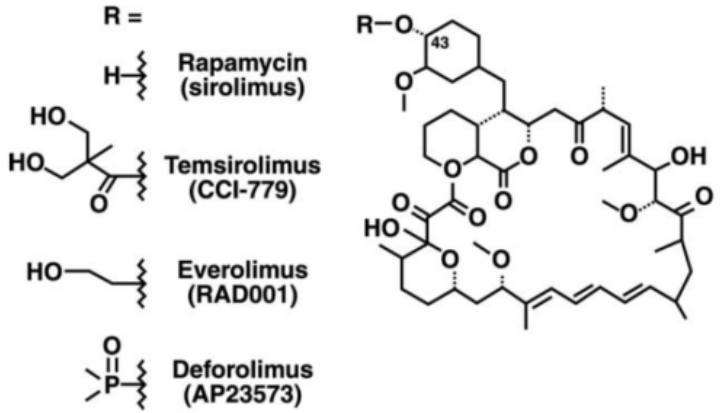


Figure 1. Chemical structures of rapamycin analogs in oncology clinical trials.

Boni, Semin Oncol 2009;35 (Suppl 3):S18-S25

Improved safety vs. paclitaxel

	Temsirolimus	Paclitaxel
Mode of Action	Cytostatic	Cytotoxic, Necrotic
Margin of Safety	10,000 Fold	100 Fold
Therapeutic Range	Wide	Narrow
Anti-Restenotic	Yes	Yes
Anti-inflammatory	Yes	No
Market Acceptance	Accepted	Questioned
Tissue Absorption	Moderate	Fast
Tissue Retention	Moderate	Long

TANGO Trial Design and Enrollment

- TANGO: Temsirolimus adventitial delivery to improve ANGiographic Outcomes below the knee
- Phase II prospective, multi-center, randomized, double-blinded, dose-escalation trial
- FDA IND-regulated
- Randomized 2:1 for treatment vs. control

Temsirolimus 0.1 mg/mL (n=20)
Temsirolimus 0.4 mg/mL (n=21)

vs.

Saline control (n=20)

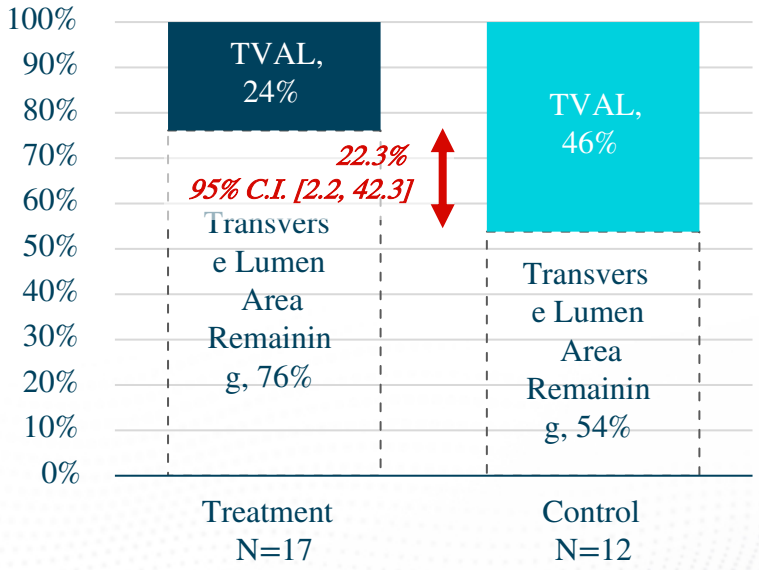
- Primary endpoint (biologic signal)
  - 6-month angiographic TVAL – Transverse View Area Loss
- Key secondary endpoint (primary endpoint for Phase 3)
  - 6-month composite freedom from Clinically Relevant Target Lesion Failure (CR-TLF):
    - CD-TLR
    - Ischemia-related major amputation
    - Clinically relevant target lesion occlusion

Characteristic	Treatment	Control
N	41	20
Age (years)	72.4 ± 9.4	73.2 ± 7.9
Male	63%	60%
Black or African Descent	32%	30%
Caucasian	68%	60%
Obesity (BMI ≥ 30 kg/m ^{2})	34%	25%
CAD	51%	70%
Diabetes Mellitus	59%	70%
Hyperlipidemia	90%	85%
Hypertension	85%	85%
Tobacco Use (Current)	10%	20%
Rutherford 3 | 4 | 5	42% | 17% | 42%	45% | 10% | 45%
ABI	0.8 ± 0.41	0.9 ± 0.36
Lesion Length (cm)	10.9 ± 7.8	12.7 ± 7.8
TASCII A | B | C | D	32% | 17% | 22% | 29%	20% | 25% | 10% | 45%
Severe Calcification	13%	10%
Total Occlusion at Baseline	32%	45%

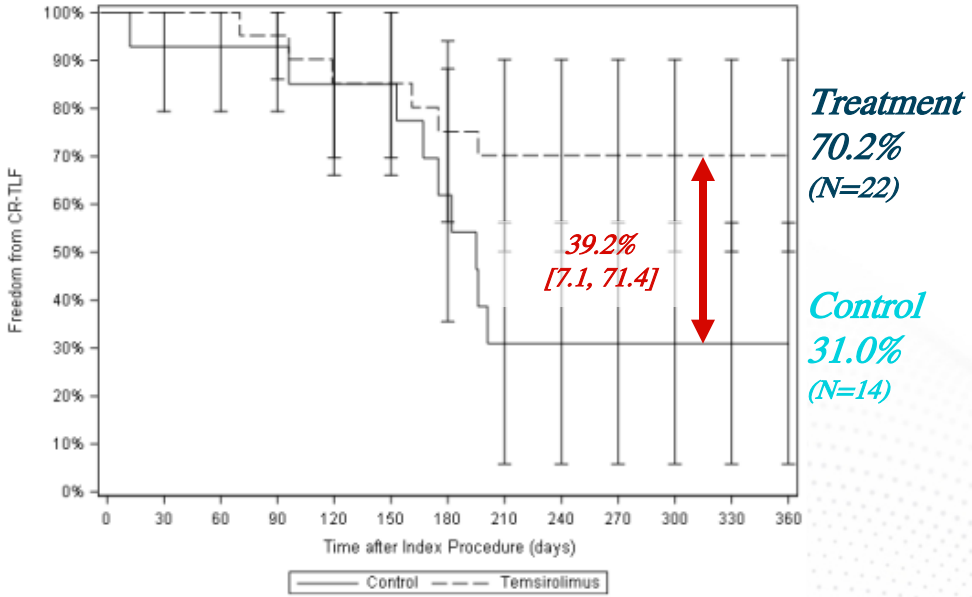
P=NS for each category

TANGO Efficacy Results Excluding TASC A Lesions

Mean 6-month TVAL in PP TASC B -D Group, Relative to Transverse Lumen Area Remaining



Kaplan-Meier Freedom from Clinically Relevant Target Lesion Failure in PP TASC B-D Group



Conclusions

- BTK disease has been more difficult to achieve positive improvement with drug-enhanced therapy than ATK
- BTK drug treatment must pass through excessive tissue barriers
- While new DCB and DES are in development, positive results have been limited to short, focal segments
- Adventitial drug delivery has provided robust outcomes in a multicenter, dual-blinded Phase 2 RCT
- A sizable effect has been seen in more complex lesions with adventitial temsirolimus delivery