The TANGO Trial:
A phase II below-the-knee study investigating the adventitial micro-infusion of Temsirolimus after PTA or atherectomy

Ian Cawich, MD
Arkansas Heart Hospital
Little Rock, Arkansas, USA
Disclosure

Speaker name: Ian Cawich, MD

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

✓ I do not have any potential conflict of interest
Improving BTK Intervention

• While intimal drug delivery has demonstrated marked improvements in SFA and popliteal intervention, below-the-knee intervention has had mixed results with luminal drug delivery
• A variety of causes for inconsistent results from DCB in BTK have been proposed:
  – Limited dosage from drug-coated balloons
  – Limited ability to drive drug past calcium
  – Transit time leads to wash-off of drug from balloons
• Drug delivery BTK has not all been negative:
  – Stents offer limited solution in focal lesions, and have shown proof-of-concept with -limus drugs
• Learning from successes and failures to treat BTK:
  – LIMBO trials using Bullfrog device to deliver anti-inflammatory drug dexamethasone to adventitia and perivascular tissues have begun
  – Given success with -limus stents, can further examination coupling -limus with Bullfrog show success in BTK?
Randomized Trials for Drug-Eluting Stents BTK

- Dominated by Sirolimus and its analogs
  - Focal lesions (<3.1 cm)
  - Improvements over PTA or BMS

![Bar chart showing 1-Year Patency Rate](chart.png)

Zakir RM. NCVH 2015.
Adventitial and Perivascular Targeting with Micro-Infusion Device

- **The Bullfrog® Device**
  - Injects therapeutic and diagnostic agents into adventitial and perivascular tissue
  - FDA 510(k)-cleared and CE-marked
- **Atraumatic design**
  - Single, 34-gauge microneedle sheathed by folding balloon
  - 2 atmosphere balloon self adjusts to treat a range of vessel diameters
    - Small: 2-4 mm
    - Medium: 3-6 mm
    - Large: 4-8 mm
- **Drug is only delivered once final target location is reached**
  - No drug elution or washout, drug not lost during transit time or rubbed off at off-target locations
  - Contrast/drug mixture allows for visual treatment confirmation
Visualizing Drug Delivery

20% contrast: 80% drug is mixed and co-administered to provide immediate feedback

“Painting” the vessel
DANCE 12-Month Efficacy Endpoint (13-Month K-M Primary Patency)

**DANCE-ATX**
- Kaplan-Meier Survival Estimate (PP)
  - Freedom from TLR
  - Primary Patency
  - Days: 0, 91, 183, 274, 365, 395
  - At Risk: 139, 124, 109, 96, 92, 99, 95
  - 100%, 89.6%, 83.6%, 80.0%

**DANCE-PTA**
- Kaplan-Meier Survival Estimate (PP)
  - Freedom from TLR
  - Primary Patency
  - Days: 0, 91, 183, 274, 365, 395
  - At Risk: 108, 103, 96, 85, 79, 77
  - 100%, 89.1%, 80.2%, 78.2%
Exploring the Alternatives in Targeted Drug Therapy

Trauma ➔ Signaling ➔ Recruitment ➔ Proliferation ➔ Migration ➔ Obstruction

- Dexamethasone
- Temsirolimus

SFA
- DANCE
  - 281 subjects
  - Open-label

Popliteal
- LIMBO-PTA & LIMBO-ATX
  - 240 total subjects
  - 1:1 RCT

Infrapop
- TANGO
  - 60 total subjects
  - Dose-escalation RCT

Cawich, LINC 2017
Temsrolimus

- Commercially available as TORISEL
  - I.V. form
  - Indicated for treatment of renal cell carcinoma
- Analog of sirolimus (similar to everolimus, zotarolimus or biolimus)
- A principal metabolite is sirolimus, which may extend the pharmacokinetic profile of temsirolimus

Retained concentrations of temsirolimus as delivered by Bullfrog are similar to everolimus concentrations found in Xience V preclinical testing from 0 to 28 days*

Bullfrog/temsirolimus therapy leaves no metal behind, for no chronic inflammatory signal

Temsirolimus concentration tested: 0.24 mg/mL

Preclinical Safety and Effectiveness

- Cellular proliferation measured by Ki67+ cells confirms anti-proliferative activity of adventitial Temsirolimus (0.24 mg/mL) from day 3 to 28 in response to balloon injury of porcine femoral arteries.

- Lack of toxicity demonstrated by histopathology at 90 days in GLP porcine study of coronary and peripheral arteries using exaggerated dose (4 mg/mL), nominal dose (0.4 mg/mL) and comparison to saline control.
TANGO Trial Design

- Phase II prospective, multi-center, randomized, double-blind, dose-escalation trial
- FDA IND-regulated
- Principal Investigator: Ian Cawich, MD
  Arkansas Heart Hospital
- Dosing concentrations:
  - Low dose: 0.1 mg/mL
  - High dose: 0.4 mg/mL
  - Control: saline
- Dosing volume:
  - Popliteal (P3): 0.5 mL/cm
  - Infrapopliteal: 0.25 mL/cm
  - Injections as needed to provide diffusion coverage

### Flowchart

1. Screening
2. Baseline angiogram and biomarker blood draw
3. Successful revascularization with atherectomy and/or PTA
4. Final enrollment and randomization (2:1)
5. 20 low dose
6. 20 high dose
7. 20 controls
8. 24-hour blood draw for Δ biomarkers
9. 1-month blood draw for Δ biomarkers
10. 6-month clinical, hemodynamic, angiographic (TVAL) follow-up
11. 12-month clinical, hemodynamic, duplex ultrasound follow-up

Cawich, LINC 2017
TANGO: Selected Eligibility Criteria

• 18-90 years old
• Rutherford 3-5 due to arterial stenosis of at least 70% between the knee joint space and the ankle
• Target vessel 2 to 8 mm diameter
• Target lesion up to 25 cm in length
• Successful revascularization of the TL with <30% residual stenosis, runoff to the foot, and flow to any foot wound
• No planned major target limb amputations
• No recent MI, CVA, or history of intracerebral hemorrhage
• No eGFR<30 unless on chronic hemodialysis
• No WIfI Stage 3 or worse, or non-ischemic heel ulcers
TANGO: Primary Endpoints

- **Safety:**
  Freedom from major adverse limb event (MALE) and post-operative death (POD) at 30 days post procedure

- **Efficacy:**
  Transverse-view vessel area loss percentage (TVAL) of the target lesion at 6 months (or prior, in the case of any TLR) by core lab quantitative vascular angiography

**What Is TVAL?**

\[ \text{TVA} = \text{TVA}_{\text{f/u}} - \frac{\text{TVA}_{\text{baseline}}}{100} \]

<table>
<thead>
<tr>
<th>TVA BASELINE</th>
<th>TVA FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area: 810.23 mm²</td>
<td>Area: 1073.01 mm²</td>
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TVA is the shaded area within TL

\[ \text{TVAL} = 100\% - \left( \frac{\text{TVA}_{\text{f/u}}}{\text{TVA}_{\text{baseline}}} \right) \]
Conclusions

• Targeted adventitial drug therapy for BTK
  – DANCE trial (dexamethasone in fem/pop lesions) has shown results that are promising for BTK therapy
  – Intimal drug delivery has limitations that are overcome by Bullfrog (limited dose on DCB, stenting only applies to focal lesions)
  – Not tied to one drug (LIMBO trials ongoing with dexamethasone, TANGO trial now beginning with temsirolimus)

• TANGO design should generate results allowing the power of a larger, Phase III study with Bullfrog-temsriolimus to improve vascular patency

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