Alternative methods of drug delivery in BTK vessels – Initial insights from the TANGO trial

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Disclosure

Speaker name: Ehrin Armstrong

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)

X I do not have any potential conflict of interest
Adventitial Drug Delivery (ADD) with the Bullfrog® Micro-Infusion Device

1.5 mm long "Painting" the vessel with 0.5 mL per cm of lesion:

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

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Restenosis results from the inflammatory cascade:

- Injury
- Endovascular procedure
- Transcription
- Signaling
- Recruitment
- Proliferation
- Migration
- Hyperplasia/narrowing

Sirolimus and its analogs have shown the ability to decrease inflammation and reduce cellular proliferation, targeting multiple aspects of the restenosis cascade.
Temsiriolumus

- 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

Similar PK to Xience V stent

**Comparison of Xience V Everolimus to Bullfrog Temsiroliumus Tissue Concentration**

TANGO Trial Design

- TANGO: Temsirolimus adventitial delivery to improve ANGiographic Outcomes below the knee
- Phase II prospective, multi-center, randomized, double-blind, dose-escalation trial
- FDA IND-regulated
- 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

Today:
- 20 low dose
- 20 high dose
- 20 controls
- 10 controls
- 24-hour blood draw for Δ biomarkers
- 1-month blood draw for Δ biomarkers
- 6-month clinical, hemodynamic, angiographic (TVAL) follow-up
- 12-month clinical, hemodynamic, duplex ultrasound follow-up
Enrolling Sites

- PI: Ian Cawich, MD, Arkansas Heart Hospital, Little Rock, AR, USA
- Jaafer Golzar, MD, Advocate Health Care, Chicago, IL, USA
- Mehdi Shishehbor, DO, MPH, PhD, University Hospital, Cleveland, OH, USA
- Ehrin Armstrong, MD, VA Eastern Colorado Health System, Denver, CO, USA
- Miguel Montero-Baker, MD, Baylor University, Houston, TX, USA
- Mahmood Razavi, MD, St. Joseph’s Vascular Institute, Orange, CA, USA
- Jon George, MD, Einstein Hospital, Philadelphia, PA, USA
Principal Eligibility Criteria

- Age 18-90 years
- Rutherford 3-5
- Lesions up to 25 cm in length in BTK segments
- Artery diameter 2-8 mm
- Successful wire crossing and revascularization
- eGFR must be >30 unless patient is on chronic hemodialysis
- Adherent to contra-indications in temsirolimus labeling
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?
TVA BASELINE
TVA FOLLOW-UP

TVA is the opacified area within the target lesion
TVAL is the area lost from post-procedure to follow-up
## Patient & Lesion Characteristics, TANGO Low-Dose

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Dose</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74.4 ± 9.2</td>
<td>71.4 ± 6.7</td>
</tr>
<tr>
<td>Male</td>
<td>13 (65%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Black of African American</td>
<td>6 (30%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>14 (70%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30 kg/m²)</td>
<td>5 (25%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>CAD</td>
<td>8 (40%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>11 (55%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>19 (95%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (90%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Tobacco Use (Current)</td>
<td>3 (15%)</td>
<td>3 (30%)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Characteristic</th>
<th>Low Dose</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutherford 3</td>
<td>11 (55%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Rutherford 4</td>
<td>1 (5%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Rutherford 5</td>
<td>8 (40%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>ABI or TBI</td>
<td>0.79 ± 0.34</td>
<td>0.74 ± 0.32</td>
</tr>
<tr>
<td>Lesion Length (cm)</td>
<td>11.7 ± 6.7</td>
<td>11.7 ± 8.3</td>
</tr>
<tr>
<td>TASCII A</td>
<td>4 (20%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>TASCII B</td>
<td>4 (20%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>TASCII C</td>
<td>3 (15%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>TASCII D</td>
<td>9 (45%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>1 (5%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Total Occlusion at Baseline</td>
<td>9 (45%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>
Preliminary Outcomes, TANGO Low-Dose

- 30 day Major Adverse Limb Event
  - Treatment: 0
  - Control: 0
- 30 day Post-Operative Death
  - Treatment: 0
  - Control: 0

CD-TLR at 6 months

- Treatment
- Control
Does Baseline Opacified Area Matter?

CASE 1
Pre-revasc

CASE 2
Pre-revasc

CASE 3
Pre-revasc

TVAL=70%, but are these three results different?

Post-revasc

6 mo f/u
Worse than pre-revasc

6 mo f/u
Same as pre-revasc

6 mo f/u
Better than pre-revasc
InLARG, TVAL, and Durable Improvement

- **In-Lesion Area Revascularization Gained (InLARG)**: 70%
- **Transverse View Area Loss (TVAL)**: 40%
- **Durable Improvement from Baseline**: +30%

- Pre-revasc: 30% of the lumen opacified at baseline
- Final revasc result: Normalize the revascularization result to 100%
- Follow-Up: 60% of the post-revasc area remains

Normalize the revascularization result to 100%
Preliminary Angiographic Results from TANGO-Low Dose

Opacified In-Lesion Area, Normalized to Final Revascularization Result in TANGO-LD, Average of All Subjects

- Pre-revasc: 75% (Treatment), 61% (Control)
- Follow-up: 76% (Treatment), 66% (Control)

TVAL in TANGO-LD, Average ± S.D.

- Treatment: 24% (±50%)
- Control: 34% (±50%)

Durable Improvement from Baseline to F/U in TANGO-LD (Average ± SD)

- Treatment: 15% (±10%)
- Control: 10% (±10%)

P < 0.05
TANGO – Low Dose Subject

PRE REVASC

POST REVASC

6 MO FOLLOW UP

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Summary

• The adventitial delivery of Temsirolimus in BTK lesions has been well tolerated at concentrations of 0.1 mg/mL in up to 25 cm lesions

• CD-TLR rates in TANGO Low Dose subjects are promising relative to controls

• A relevant biologic signal has been angiographically detected using TVAL, particularly when normalized to baseline angiographic result
Current Clinical Trials of Adventitial-Perivascular Therapy with Bullfrog Delivery

- **Trauma**
  - **Recoil**
  - **Signaling**
  - **Recruitment**
  - **Proliferation**
  - **Migration**
  - **Obstruction**

### SFA
- **Vonapanitase**
- **Dexamethasone**
- **Temsirolimus**

#### SFA
- **Popliteal**
- **Infrapop**

#### PRT201-115
- 40 subjects
- Dose-escalation RCT
- Enrolling

#### DANCE
- 283 limbs
- (159 ATX, 124 PTA)
- Open-label
- PUBLISHED

#### LIMBO-ATX
- 106 total subjects
- 1:1 RCT
- Enrollment COMPLETE

#### LIMBO-PTA
- 50 total subjects
- 1:1 RCT
- Enrollment COMPLETE

#### TWIST
- 40 total subjects
- Additional arm of TANGO (10 control, 30 combo dose)
- Enrollment to begin 1H2019

#### TANGO
- 60 total subjects
- Dose-escalation RCT (20 control, 20 low, 20 high dose)
- Enrollment near complete

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