The LIMBO Trial
Alternative Methods of Drug Delivery for BTK

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Disclosure

Speaker name: George Adams

I have the following potential conflicts of interest to report:

- [x] 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
The Continuing Need in BTK

- More than 1 million lower extremity endovascular interventions per year in U.S. and Europe, nearly one-third are below-the-knee
- Local luminal drug delivery with DCB and DES have improved patency rates above the knee, but BTK intervention has had mixed results
- A variety of causes for inconsistent results from DCB in BTK have been proposed:
  - Limited dosage from smaller drug-coated balloons
  - Limited ability to drive drug past calcium
  - Transit time with distal treatment leads to wash-off of drug from balloons
- The LIMBO trials are underway in the U.S. and Europe, exploring the use of adventitial drug delivery of dexamethasone (ADD-DEX) to treat the chronic underlying and acute inflammation and improve patency in BTK lesions
Treating Inflammation with a Potent Anti-Inflammatory

Restenosis results from the inflammatory cascade:

- **Hours**
  - INJURY
  - ENDOVASCULAR PROCEDURE
  - DEXAMETHASONE

- **Days**
  - TRANSCRIPTION
  - SIGNALING

- **Weeks**
  - RECRUITMENT

- **Months**
  - MIGRATION
  - PROLIFERATION
  - HYPERPLASIA / NARROWING

Upstream targeting of the early inflammatory process limits or eliminates downstream restenosis, but allows healing and resolution.
Adventitial and Perivascular Targeting with Bullfrog® Micro-Infusion Device

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

“Painting” the vessel

Adams, LINC 2017
DANCE: the Proof-of Concept and Precursor to LIMBO

- Multicenter, open-label trial
- SFA and Popliteal
- Primary atherectomy (ATX) or primary angioplasty (PTA)
- National co-PIs:
  - George Adams, MD
  - Mahmood Razavi, MD

**Baseline angiogram and biomarker blood draw**

157 ATX

ADD-DEX Treatment

124 PTA

Blood draws for change in biomarkers (~1/3 of patients) at 24 hours and 4 weeks

Clinical, hemodynamic and duplex U/S follow-up at 6, 12, 18, 24 months
## DANCE 12-Month Safety Endpoints

<table>
<thead>
<tr>
<th>Safety Outcomes (ITT population)</th>
<th>DANCE-PTA</th>
<th>DANCE-ATX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-related SAE 0-365 Days</td>
<td>0/124 (0.0%)</td>
<td>0/157 (0.0%)</td>
</tr>
<tr>
<td>Drug-related SAE 0-365 Days</td>
<td>0/124 (0.0%)</td>
<td>0/157 (0.0%)</td>
</tr>
<tr>
<td>Major Adverse Limb Events 0-365 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>0/114 (0.0%)</td>
<td>1/126 (0.8%)</td>
</tr>
<tr>
<td>Bypass</td>
<td>1/114 (0.9%)</td>
<td>1/126 (0.8%)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0/114 (0.0%)</td>
<td>0/126 (0.0%)</td>
</tr>
<tr>
<td>Death 0-30 Days</td>
<td></td>
<td>0/244 (0.0%)</td>
</tr>
<tr>
<td>Death 0-365 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Cardiovascular</td>
<td></td>
<td>2/231 (0.9%)</td>
</tr>
<tr>
<td>Cardiovascular or Unknown</td>
<td></td>
<td>7/231 (3.0%)</td>
</tr>
</tbody>
</table>
DANCE 12-Month Efficacy Endpoint (13-Month K-M M Primary Patency)

**DANCE-ATX**
Kaplan-Meier Survival Estimate (PP)
Freedom from TLR
Primary Patency

**DANCE-PTA**
Kaplan-Meier Survival Estimate (PP)
Freedom from TLR
Primary Patency
DANCE Subgroup Analysis
(13-Month Primary Patency)

Distal anatomy results justify examination in BTK

SFA and Popliteal
- **ATX: 80% patency**
  - (N=139, LL_{avg}=8.8cm)
- **PTA: 78% patency**
  - (N=108, LL_{avg}=7.4cm)

Popliteal Involvement
- **ATX: 95% patency**
  - (N=23, LL_{avg}=6.3)
- **PTA: 77% patency**
  - (N=15, LL_{avg}=5.8)

P2-P3 Involvement
- **ATX: 100% patency**
  - (N=10, LL_{avg}=4.7)
- **PTA: 75% patency**
  - (N=4, LL_{avg}=8.8)
LIMBO Trials Underway

- Below-Knee Study in CLI
- 2 trials: Adventitial Dexamethasone added to atherectomy (U.S.) or PTA (Germany, Austria, Switzerland)

- LIMBO-ATX co-PIs: George Adams, MD, UNC-Rex, Raleigh, NC
  Don Jacobs, MD, St. Louis University, MO

- LIMBO-PTA PI: Dierk Scheinert, MD, University Hospital Leipzig, Germany
  (Began January 2016)
LIMBO: Selected Eligibility Criteria

- 18-90 years old
- Rutherford 4-6 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 or CVA
- No eGFR<30 unless on chronic hemodialysis
- No WIfI Stage 3 or worse, or non-ischemic heel ulcers
LIMBO: 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 is the shaded area within TL

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

• The ADD-DEX procedure in DANCE has produced positive results in both primary atherectomy (in a challenging patient population) and primary angioplasty intervention in the SFA and Popliteal
• Micro-Infusion with the Bullfrog device is not limited by surface area contact or transit time issues
• ADD-DEX has demonstrated pilot-scale positive results in P2-P3 segments from DANCE, justifying a push into BTK
• The LIMBO trials are designed to show an effect between randomized treatment and control groups with one trial examining primary atherectomy and one trial examining primary angioplasty
Adventitial Drug Delivery: What the Future Holds for BTK

• LIMBO-ATX
  – ADD-DEX in BTK with Atherectomy (N=120)
  – U.S. Trial, enrolling (PIs: George Adams, Don Jacobs)
• LIMBO-PTA
  – ADD-DEX in BTK with PTA (N=120)
  – European Trial, enrolling (PI: Dierk Scheinert)
• PRT-201-115 (Proteon)
  – ADD-Vonapanitase in BTK (N=40)
  – Phase 1 Dose Escalation U.S. Trial, enrolling (PI: Jihad Mustapha)
• TANGO
  – ADD-LIMUS in BTK (N=60)
  – U.S. Trial planned for Q1 2017 start (PI: Ian Cawich)
• TWIST
  – ADD-COMBO
  – In planning stages

~35% enrolled
Goal to complete enrollment mid-2017

~15% enrolled
Goal to complete enrollment by end of 2017
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