Direct micropuncture mediated deep adventitial drug delivery – New insights from the DANCE project and future prospects

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Disclosure

Speaker’s name: Dierk Scheinert

I have the following potential conflicts of interest to report:

Advisory Board /Consultant:
  Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, CR Bard, Gardia Medical/Allium, Medtronic, TriReme Medical, Trivascular, Upstream Peripheral Technologies
Targeted Drug Delivery –
The Next Generation for PAD

- Local intimal drug therapy with paclitaxel has shown some limitations
  - DES has shown improvements only in short-segment BTK disease
  - Well-controlled clinical trials of DCB in BTK arteries have been inconsistent or disappointing
  - Flaking of drug from balloons may have negative outflow consequences

- Eliminating the constraint of “what drugs can be coated onto a balloon” allows the exploration of many other medicines to treat the variety of patients we see each day

- Efficient delivery of liquid therapeutics beyond the vessel wall
  - Target the root of the disease: inflammation
  - Bypasses medial calcification regardless of diffusion kinetics
  - Independent of balloon sizing, surface area and full contact to deliver an effective dose
Bullfrog Micro-Infusion Device Features

• Needle (34 Gauge) is constantly sheathed during manipulation to prevent vessel injury
• Balloon self-adjusts to a range of vessel diameters (2-4 mm, 3-6 mm or 4-8 mm)
• Balloon inflation limited to 2 atm to prevent barotrauma

• Contrast co-delivered with drug confirms real-time procedural success

• Each injection starts on one side and then spreads up, down and around the artery
• Diffusion continues over time to fill any visual “gaps”
Visualizing the Therapy

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

“Painting” the vessel

Above the knee

Below the knee
Exploring the Alternatives in Targeted Drug Therapy

- Trauma
- Signaling
- Recruitment
- Proliferation
- Migration
- Obstruction

- Dexamethasone
- Temsirolimus

- SFA
- Popliteal
- Infrapop

- DANCE 281 subjects Open-label
- LIMBO-PTA & LIMBO-ATX 240 total subjects 1:1 RCT
- TANGO 60 total subjects Dose-escalation RCT
Data from the DANCE Trial
(Trial Overview)

- Multicenter, open-label trial in two populations: primary atherectomy (ATX) and primary angioplasty (PTA)

Primary Endpoints

Safety
- Composite of freedom from all cause peri-operative (30 day) death and freedom at 1 year in the index limb from major amputation (ATK or BTK), bypass surgery or thrombolysis

Efficacy
- Primary patency of the target lesion at 1 year: Core lab adjudicated absence of binary restenosis (DUS PSVR > 2.4 or angiographic narrowing >50%) & freedom from clinically-driven target lesion revascularization (CD-TLR)
## DANCE Patient and Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>ATX</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (legs)</td>
<td>124</td>
<td>157</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.9±9.1</td>
<td>68.4±9.6</td>
</tr>
<tr>
<td>Male</td>
<td>65%</td>
<td>57%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>77%</td>
<td>80%</td>
</tr>
<tr>
<td>African American</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>52%</td>
<td>50%</td>
</tr>
<tr>
<td>CAD</td>
<td>55%</td>
<td>67%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>Obesity (BMI≥30 kg/m²)</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.02±0.28</td>
<td>1.10±0.51</td>
</tr>
<tr>
<td>CRP, pre (mg/dL)</td>
<td>5.01±9.37</td>
<td>5.78±7.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>ATX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutherford Category</td>
<td>2: 36.3% 3: 60.5% 4: 3.2%</td>
<td>2: 22.9% 3: 59.9% 4: 17.2%</td>
</tr>
<tr>
<td>TASC II Classification</td>
<td>A: 53% B: 40% C: 6% D: 1%</td>
<td>A: 30% B: 62% C: 6% D: 1%</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>21.3%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Popliteal Involvement</td>
<td>15.3%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Mean Lesion Length (cm)</td>
<td>7.4 ± 4.0</td>
<td>8.8 ± 5.2</td>
</tr>
<tr>
<td>Mean % Diameter Stenosis (Pre)</td>
<td>73% ± 16%</td>
<td>70% ± 17%</td>
</tr>
<tr>
<td>Total Occlusions</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Grade B-D Dissection</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>Stent Utilization</td>
<td>52%</td>
<td>35%</td>
</tr>
<tr>
<td>Mean % Diameter Stenosis (Post)</td>
<td>24%±12%</td>
<td>23%±9%</td>
</tr>
</tbody>
</table>
# DANCE 12-Month Safety

<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>

*The amputation was performed after TLR endpoint was reached*
DANCE 13-Month Efficacy

**DANCE-ATX**

Kaplan-Meier Survival Estimate (PP)

- **Freedom from TLR**
- **Primary Patency**

**DANCE-PTA**

Kaplan-Meier Survival Estimate (PP)

- **Freedom from TLR**
- **Primary Patency**

Days: 0, 91, 183, 274, 365, 395

At Risk: 139, 124, 109, 96, 92, 85, 85

Days: 0, 91, 183, 274, 365, 395

At Risk: 108, 103, 96, 85, 79, 77
Gaining Perspective: DANCE compared to DCB Trials

Efficacy Outcomes: Patency at 390-395 days

- In.Pact PTA
- Stellarex PTA
- Lutonix PTA
- Lutonix DCB
- Stellarex DCB
- In.Pact DCB
- DANCE-PTA Bullfrog
- DANCE-ATX Bullfrog
Gaining Perspective: DANCE and DCB Subgroups

- PTA and DCB results are a weighted average of Levant-2 and In.Pact-SFA results (assumes class effect)
- Is there a gender gap with DCB?
- Anti-inflammatory nature of DANCE
  - Women lack estrogen production post-menopause
  - Women have smaller vessels (less dose with DCB?) (more friable vessels?)
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)
BTK: LIMBO Trials Underway

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

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

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

- Phase 2, Below-Knee Study in CLI
- Adventitial Temsirolimus added to PTA or atherectomy revascularization
- Anticipated FIM 1Q2017 and expansion into European sites 3Q2017
- PI: Ian Cawich, MD, Arkansas Heart Hospital, Little Rock, AR, USA

**TANGO**

- Baseline angiogram and biomarker blood draw
- 60 subjects randomized 2:1 in 2 phases
  - 20 controls
  - 20 low dose
  - 20 high dose
- 24-hour blood draw for Δ biomarkers
- 1-month blood draw for Δ biomarkers
- Clinical, hemodynamic and angiographic follow-up at 6 months
Looking Forward

• Bullfrog delivery of dexamethasone after atherectomy in SFA and popliteal arteries has produced exceptional results compared to other drug delivery platforms in a challenging patient population.

• This represents a paradigm shift in drug delivery to treat lower extremity atherosclerotic disease (an inflammatory process requires an anti-inflammatory remedy).

• DANCE may represent the first outcomes of the ability to target the therapy to the patient (personalized/precision medicine).

• Bullfrog delivery into the BTK area has begun with the LIMBO and TANGO trials, and with an elastase therapy from Proteon Therapeutics.
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