The LIMBO trial: a RCT investigating adventitial dexamethasone infusion to prevent restenosis in BTK arteries utilizing a novel angiographic endpoint

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Disclosure

Speaker name: Ulrich Beschorner

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
The Bullfrog® Micro-Infusion Device
(Mercator MedSystems)

20% contrast
80% dexamethasone

Micro-Needle Infusion

Lumen
Media
Adventitia
Perivascular tissue
Interrupting the Cascade at Inflammation

ATVB 2011;31:1530-1539

Cell recruitment

INJURY

Proliferation
Neointima
Lumen Loss
Background Data from DANCE (Adventitial DEX in SFA/Pop)

**Interim: 73 DANCE Atherectomy Subjects**

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Rutherford 2</td>
<td>23.3%</td>
</tr>
<tr>
<td>Rutherford 3</td>
<td>61.6%</td>
</tr>
<tr>
<td>Rutherford 4</td>
<td>15.1%</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>26.6%</td>
</tr>
<tr>
<td>Popliteal Involvement</td>
<td>20.5%</td>
</tr>
<tr>
<td>TASC II Classification</td>
<td>36% A; 59% B; 6% C</td>
</tr>
<tr>
<td>Restenosis</td>
<td>8.2%</td>
</tr>
<tr>
<td>Lesion Length (cm)</td>
<td>8.8 ± 5.2</td>
</tr>
<tr>
<td>%DS (Pre)</td>
<td>69% ± 17%</td>
</tr>
<tr>
<td>Total Occlusions</td>
<td>15.4%</td>
</tr>
<tr>
<td>Grade B-D Dissection</td>
<td>25.0%</td>
</tr>
<tr>
<td>Stent Utilization</td>
<td>34.2%</td>
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<tr>
<td>%DS (Post)</td>
<td>20% ± 7%</td>
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**Safety (0-360 Days)**

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<thead>
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<tbody>
<tr>
<td>Device-related SAE</td>
<td>0/83 (0%)</td>
</tr>
<tr>
<td>Drug-related SAE</td>
<td>0/83 (0%)</td>
</tr>
<tr>
<td>Major Adverse Limb Events</td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>0/83 (0%)</td>
</tr>
<tr>
<td>Bypass</td>
<td>2/83 (2.4%)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0/83 (0%)</td>
</tr>
<tr>
<td>Death 0-30 Days</td>
<td>0/97 (0%)</td>
</tr>
<tr>
<td>Death 0-360 Days</td>
<td>5/88 (5.7%)</td>
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**Efficacy**

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<tbody>
<tr>
<td>TLR at 360 Days</td>
<td>8.3%</td>
</tr>
<tr>
<td>Patency at 360 Days</td>
<td>85.0%</td>
</tr>
<tr>
<td>TLR at 390 Days</td>
<td>8.8%</td>
</tr>
<tr>
<td>Patency at 390 Days</td>
<td>81.5%</td>
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LIMBO Trial Design

- Below-Knee
- 2 trials: Adventitial Dexamethasone added to PTA (Germany) or atherectomy (U.S.)
- Anticipated start: Q1 2016
- LIMBO-PTA PI: Dierk Scheinert, MD, University Hospital Leipzig, Germany
- LIMBO-ATX coPIs: George Adams, MD, UNC-Rex, Raleigh, NC
  Don Jacobs, MD, St. Louis University, MO

**LIMBO-ATX**
- Baseline angiogram and biomarker blood draw
- 120 ATX (U.S.)
- 60 controls
- 60 DEX
- 24-hour blood draw for Δ biomarkers
- 1-month blood draw for Δ biomarkers
- Clinical, hemodynamic and angiographic follow-up at 6 months

**LIMBO-PTA**
- 120 PTA (Germany)
- 60 controls
- 60 DEX
Gold-Standard Vascular Patency Endpoints in BTK

- Duplex Ultrasound (DUS) vs Digital Subtraction Angiography (DSA)
  - SFA and popliteal
    - Good agreement between DUS and DSA
    - Good technical success of DUS
    - Good technical success of DSA
  - Infrapopliteal
    - Moderate agreement between DUS and DSA
    - Poor technical success of DUS
    - Moderate technical success of DSA

Not All Restenosis is Equal

In long lesions, standard measures of patency do not account for focal vs. diffuse restenosis

FOCAL RESTENOSIS

- Greater late lumen loss
- Greater angiographic restenosis
- Greater PSVR

DIFFUSE RESTENOSIS

- Greater reduction in blood flow to foot

How do we show the difference between this and this numerically with a clinically meaningful endpoint?
What is Patency in BTK Disease?

• Run-off to the foot
• Perfusion of wounds or ischemic tissues
• Improvement in blood flow (reduction of flow resistance)

Flow resistance is proportionate to
- Inverse of diameter (to the 4th power)
- Length (to the 1st power)
- Viscosity (to the 1st power) - unchanging
Opportunity for Improvement in BTK Patency Assessment

• LLL provides a measure of a single cross-section of the vessel (at the minimal lumen diameter)
• %DS (percent diameter stenosis) describes flow constriction, but also only at a single cross-section

• How can we measure blood flow resistance over the entire lesion length?

\[
\int_{\text{proximal}}^{\text{distal}} \% \text{ Diameter Stenosis}
\]
Novel LIMBO Endpoint - TVAL

**TVAL:**
Transverse-view Vessel Area Loss
A measurement of AREA opacified by contrast, rather than the narrowest cross-section, which LLL defines

\[
\text{TVA} = \text{shaded area within TL end constraints (in mm}^2) \\
\text{TVAL} = 100\% - \left( \frac{\text{TVA}_{f/u}}{\text{TVA}_{baseline}} \right)
\]

\[
\text{LLL} = \text{MLD}_{baseline} - \text{MLD}_{follow-up} \text{ (in mm)}
\]

Courtesy of Kirk Seward, PhD, Mercator MedSystems
TVAL Example

TVA = shaded area within TL end constraints (in mm²)

TVAL = 100% - (TVA\text{f/u} / TVA\text{baseline})
TVAL = 100% - (810.23 / 1073.01)
TVAL = 100% - (76%)
TVAL = 24%

LLL = MLD\text{baseline} – MLD\text{follow-up} (in mm)
LLL = 3.89 – 1.49
LLL = 2.40

Possible restenosis, but unclear extent

Recognition of diffuse low-grade stenosis or focal restenosis
Conclusion

• Angiographic follow-up is more informative than duplex ultrasound in BTK lesions
• TVAL provides a new measure that is potentially more informative of the condition of the vessel than LLL
Acknowledgements

• Definition of TVAL:
  – Kirk Seward, PhD, Mercator MedSystems
  – Prof. Dierk Scheinert, MD, Universitaet Leipzig
  – George Adams, MD, University of North Carolina, Rex Hospital

• TVAL measurements:
  – Cardiovascular Research Foundation, New York, NY, USA – Philippe Genereux, MD, Director
  – Bad Krozingen CoreLab, Germany – Ulrich Beschorner, MD, Director
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