Ongoing trials and future concepts for Local drug delivery in BTK arteries

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Disclosure

Speaker name: Dierk Scheinert

I have the following potential conflicts of interest to report:

Consulting: Abbott, Angioslide, Atheromed, Biotronik, Boston Scientific, Cook Medical, Cordis, Covidien, CR Bard, Gardia Medical, Hemoteq, Intact Vascular Inc., Medtronic, Ostial Inc, TriReme Medical, Trivascular, Upstream Peripheral Technologies

Stockholder: IDEV Technologies
POBA for CLI Treatment

• 68 CLI patients due to BTK lesions
• Lesion length: $140 \pm 90 \text{ mm}$
• Restenosis at 3 months: 73%
• Restenosis delays healing

$Iida\ O.\ et\ al.\ EJVES\ 2012;\ 44:425-31.$

Complete ulcer healing rates
DCBs are not all the same

Technology of the In.Pact Deep Balloon: first folded and then coated

With courtesy C. I. Mena
Dry Inflate / Shake Test - SFA

- Test Articles (n=5 each):
  - Medtronic In.Pact Admiral – 6x60mm
  - Lutonix® 035 Drug Coated Balloon – 6x60mm

With courtesy C. I. Mena
Ex Vivo Administration of Fluorescent-Labeled PTX to Excised Porcine Artery

10% Oregon green labeled PTX incorporated into Lutonix DCB coating

Segment-to-segment variability ± 4.0 %
Pharmacokinetics PTX in Arterial Tissue in a Porcine Model
Comparison In.Pact vs. Lutonix

**In.Pact 3 x 3µg/mm²**

- $C_{\text{max}}$ of PTX at 3X Dose = 66.26 ng/mg

**Lutonix 2µg/mm²**

- $C_{\text{max}}$ of PTX at 1X Dose = 58.9 ng/mg
# Lutonix BTK Trial Summary

| PRIMARY ENDPOINTS          | Safety at 30 days  
<table>
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<th>Limb salvage &amp; primary patency at 12 months</th>
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<td>NUMBER OF PATIENTS/SITES</td>
<td>480 patients at 55 global sites</td>
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| FOLLOW-UP                  | **Clinical:** 1, 6, 12, 24, and 36 Months  
|                           | **Duplex Ultrasound (DUS):** 0–30 days, 6, 12, 24, & 36 months |
|                           | **Angiography in subset of patients:** 12 months  
|                           | **Telephone:** 48 and 60 Months             |
| NATIONAL PRINCIPAL         | **Patrick Geraghty:** Washington University, St. Louis, MO |
| INVESTIGATORS              | **Jihad Mustapha:** Metro Health Hospital, Wyoming, MI |
|                           | **Marianne Brodmann:** Medical University Graz, Austria |
| SPONSOR                    | Lutonix Inc., Minneapolis, MN               |

Caution – Investigational Device, Limited by Federal (USA) Law to Investigational Use
Primary Endpoints

SAFETY
Freedom from Major Adverse Limb Events & All-Cause Death at 30 DAYS

★ Amputation (above ankle)
★ Major re-intervention
  • New bypass graft
  • Jump/Interposition graft revision
  • Thrombectomy/Thrombolysis

EFFICACY
Composite of Limb Salvage and Primary Patency at 12 Months

Defined as freedom from the composite of above ankle amputation, target vessel occlusion, and clinically-driven target lesion re-intervention.

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Patient Eligibility

Inclusion Criteria

• Male or non-pregnant female ≥18 years of age
• Rutherford 4-5
• Life expectancy ≥ 1 year;
• Significant stenosis (≥70%)
• A patent inflow artery
• Target vessel(s) diameter between 2 and 4 mm
• Target vessel(s) reconstitute(s) at or above the ankle

Exclusion Criteria

• Pregnant or planning on becoming pregnant
• History of stroke within 3 months
• History of MI, thrombolysis or angina within 30 days of enrollment
• Prior or planned major amputation
• GFR ≤ 30 ml/min per 1.73m²
• Acute limb ischemia
• In-stent restenosis of target lesion
BTK Trial Design

Protocol Features

• Randomized 2:1 versus POBA
• Permits treatment of two tibial arteries (two flow pathways)
• Combined lesion length of up to 32 cm treatable (36 cm balloon length allowed)
• Retrograde wire access permitted, but not retrograde intervention
• Balloon lengths of up to 12 cm
• First U.S. use of tibial patency assessment via duplex ultrasound (VasCore)
• Angiographic assessment of normal-risk subset at one year (Synvacor)
• Broad range of secondary endpoints including QOL instruments
Study Flowchart

Inflow Treatment
If needed

PTA Pre-Dilatation
With Uncoated Balloon

Successful PTA with Outflow
Randomize 2:1

Test Arm:
Dilatation of ALL target lesions with Drug Coated Balloon

Control Arm:
Dilatation of ALL target lesions with Uncoated Balloon

Suboptimal PTA
Absence of above ankle reconstitution
>75% residual stenosis

Treat per standard practice
30 day follow-up for safety
The Bullfrog® Micro-Infusion Device (Mercator MedSystems)
Bullfrog Device Features

- Microneedle is 34 Ga (0.007”) diameter; smaller than most suture needles, so insertion does not injure the vessel.
- Needle is constantly sheathed during manipulation to prevent scratching the vessel.
- 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.
Bullfrog Adventitial Infusion

Pre-Revascularization Post-Revascularization Post-Infusion

20% contrast, 80% drug
Bullfrog Adventitial Infusion

Pre-Revascularization

Post-Revascularization

Post-Infusion

Without Angio  With Angio

20% contrast, 80% drug
Revascularization Injures the Deep Layers of the Artery

- What is seen during vascular intervention
- What is affected during vascular intervention
Restenosis Begins with Inflammation

INJURY

INFLAMMATION, RECRUITMENT

PROLIFERATION, MIGRATION

FIBROSIS, HYPERPLASIA

Timeframe:

- Hours to Days
- Weeks
- Months

Agents:

- Dexamethasone
- Paclitaxel, -limus compounds
Clinical Hypothesis: Adventitial delivery of dexamethasone at the time of peripheral artery endovascular revascularization reduces inflammation and improves long-term patency*

DANCE-Pilot study results

- 20 patients with average lesion length 8.9cm
- 6-month primary patency: 89% (17/19)
- 1-year primary patency: 81% (13/16)

DANCE: Dexamethasone to the Adventitia to eNhance Clinical Efficacy after fem-pop revascularization

PAD Trials Utilizing Bullfrog

**DANCE**  N=300

- Baseline angiogram and biomarker blood draw (1/3 of pts)
- 150 PTA
- 150 atherectomy
- Adventitial DEX treatment
- 24-hour blood draw for Δ biomarkers (1/3 of pts)
- 1-month blood draw for Δ biomarkers (1/3 of pts)
- Clinical, hemodynamic and duplex U/S follow-up at 6, 12, 18, 24 months

**DANCE-R**

- Long lesions
- ISR
- Rutherford 5
- Adventitial DEX treatment
- 24-hour blood draw for Δ biomarkers (1/3 of pts)
- Clinical, hemodynamic and duplex U/S follow-up at 12 months

**LIMBO (2 Trials) Beginning Q1 2015**  N≈1,000

- Baseline angiogram and biomarker blood draw
- 100 PTA and 100 ATX revascularization (2 trials)
- 50 controls (each)
- 50 DEX treatment (each)
- 24-hour blood draw for Δ biomarkers
- 1-month blood draw for Δ biomarkers
- Clinical, hemodynamic and angiographic follow-up at 6 months

**Controls**

- 50 controls (each)
- 50 DEX treatment (each)
- Clinical, hemodynamic and angiographic follow-up at 6 months
Summary

• There is still an unmet need for improved durability in the BTK area
• Drug-delivery via balloon-based solutions may still be the most realistic approach
• Different approaches with DCB and alternative ways of adventitial drug delivery are currently underway.