Drug Coated Balloons for Treatment of CLI
Disclosures

- Speaker’s Bureau
  - Abbott Vascular
  - Medtronic

- Honorarium
  - AstraZeneca

- Consultant
  - Bard
  - CSI
  - Terumo Medical
  - Spectranetics
  - Avinger
Critical Limb Ischemia

- Goal of therapy is functional limb preservation
- Revascularization
- Extravascular Care
- Surveillance
BTK Interventions for CLI

- Long, complex, often calcified nature of lesions
- Often associated with multivessel disease, thus success inflow- and outflow-dependent
- Small caliber vessels
- High restenosis rate
- Limb salvage poorly correlated to primary patency
- Literature landscape dominated by small series and case studies

PTA in BTK: CLI Patients

Up to 50% post-PTA TLR rate in real world CLI pts
Occlusion of ATA And ATP  
POBA  
2.5 Months Control-Angiography

Schmidt, CLIC
POBA for CLI Treatment

- 68 CLI patients due to BTK lesions
- Lesion length: 140 ± 90 mm
- Restenosis at 3 months: 73%

- Restenosis delays healing

*Oida O. et al. EJVES 2012; 44:425-31.*
Restenotic Cascade

- Balloon inflation or stent deployment in atherosclerotic vessel
  - Crush plaque
  - Stretch artery
  - De-endothelialization

- Platelets and fibrin deposited at injured site
  - Signaling cascades
  - Inflammatory response

- Neointimal proliferation
  - Smooth muscle cell (SMC) migration
  - Cellular division

- Restenosis
  - Extracellular matrix production
  - Re-endothelialization

Antiproliferative Agents
- Reduce inflammation
- Arrest mitosis
- Inhibit SMC migration

Immediate: days: weeks: months
Drug Coated Balloon

Lutonex® 035 is based upon PTA technology, and is similarly versatile and easy to use.

Drug + Carrier = Coating

Drug
Lutonex® 035 drug dose of Paclitaxel is 2ug/mm²

Carrier
Polysorbate and Sorbitol

Coating
Facilitates therapeutic drug retention and release of drug at the treatment site
Drug Coated Balloon

1. **30-second** minimum inflation **transfers drug** to endoluminal surface delivering a therapeutic dose

2. Paclitaxel **diffuses into the arterial wall** from an endoluminal reservoir

3. Over time, therapeutic **drug levels are sustained in deep cell layers** after endothelial drug levels become sub-therapeutic

4. **Drug continues to inhibit restenosis** in arterial wall while allowing the lumen to restore and re-endothelialize
Femoral- Popliteal

**Primary Patency (KM Day 360)**

- IN.PACT SFA: 89.8%
- LEVANT II: 73.5%
- Zilver PTX: 82.7%

**CD-TLR (12 month)**

- IN.PACT SFA: 2.4%
- LEVANT II*: 12.3%
- Zilver PTX: 9.6%
Debate-BTK

- Single Center, randomized 1 to 1
- 132 Patients, 100% diabetics
- 12.9cm lesion length, 77.5% CTO
- In.Pact Amphiron (DCB) vs POBA

Leipzig Registry

- Single center
- N=104 (73% Diabetics)
  - 17cm mean lesion length, 62% CTO
- 12-mo results
  - 17.3% TLR
- 3-mo results
  - 27.4% Binary Restenosis
  - 8.3% re-occlusion

IN.PACT DEEP
Randomized Trial of IN.PACT Amphirion DEB vs. PTA for Infrapopliteal Revascularization in Critical Limb Ischemia
12-month Results

Thomas Zeller, MD
on behalf of the IN.PACT DEEP Steering Committee:
Iris Baumgartner, Inselspital University of Bern (Bern, Switzerland)
Thomas Zeller, Herz-Zentrum Bad Krozingen (Bad Krozingen, Germany)
Dierk Scheinert, Parkklinikum Leipzig (Leipzig, Germany)
and the IN.PACT DEEP Investigators
ClinicalTrials.gov NCT00941733

- Prospective, Multicenter, Randomized
- Independent Data Safety Monitoring Board (DSMB) [1]
- Independent Clinical Event Committee (CEC) [1]
- Independent Angiographic Corelab [2]
- Independent Wound Corelab [2]
- Wound Measurement through Electronic Reader [3]
- External Monitoring, 100% Source Data Verification [1]

1. Third-party safety monitoring, Clinical Event Committee and external data monitoring services provided by Genae Associates (Antwerp, Belgium)
2. Angiographic and Wound Corelab: SynvaCor (Springfield IL, US)
3. Electronic wound capturing through Sylouette Mobile (Aranz Medical, Auckland, New Zealand)
## Eligibility Criteria

### General (Key) Inclusions
- Rutherford Class 4-5-6
- Age 18-85 years + life expectancy >1 year
- Target vessel: infrapopliteal (incl. Tibio Peroneal Trunk) above the ankle \(^1\)
- RVD 2 - 4 mm
- Single or multiple lesions (≥70%) of any length
- At least one non occluded crural vessel with documented run-off to the foot either direct or through collaterals

### Angio Cohort (Key) Inclusions
- Single or multiple adjacent lesions (≥70%) with cumulative length of 100 mm that can be covered by a single IN.PACT Amphirion

### General (Key) Exclusions
- Planned major index limb amputation
- Inflow impaired or non re-established
- Failure to cross the target lesion with a 0.014” guide wire
- ISR
- Thrombus or aneurysm

### Angio Cohort (Key) Exclusion
- GFR <30 ml/min except for patients with ESRD on chronic haemodialysis
Trial Design

Enrollment = 358 subjects
Randomized 2:1 DEB: PTA
Clinical cohort: All subjects
Angio cohort (subset)
• Single lesion ≤ 10 cm
• GFR ≥ 30 ml/min [1]

1. Except patients with ESRD, on chronic haemodialysis and with life expectancy >1 year
# Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DEB (N 239)</th>
<th>PTA (N 119)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y, mean±SD)</td>
<td>73.3 ± 8.2</td>
<td>71.7 ± 9.9</td>
<td>0.106</td>
</tr>
<tr>
<td>Male gender</td>
<td>76.2%</td>
<td>70.6%</td>
<td>0.304</td>
</tr>
<tr>
<td>Diabetes</td>
<td>75.7%</td>
<td>68.9%</td>
<td>0.204</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89.5%</td>
<td>89.1%</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>73.2%</td>
<td>67.2%</td>
<td>0.265</td>
</tr>
<tr>
<td>History of smoking</td>
<td>51.9%</td>
<td>49.6%</td>
<td>0.737</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15.1%</td>
<td>13.4%</td>
<td>0.752</td>
</tr>
<tr>
<td>BMI (kg/m², mean±SD)</td>
<td>27.4 ± 4.9</td>
<td>27.1 ± 4.9</td>
<td>0.620</td>
</tr>
<tr>
<td>Renal insuff. [1]</td>
<td>8.6%</td>
<td>12.5%</td>
<td>0.254</td>
</tr>
</tbody>
</table>

<table>
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<tr>
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<th>DEB (N 239)</th>
<th>PTA (N 119)</th>
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</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl, mean±SD)</td>
<td>1.4 ± 1.5</td>
<td>1.6 ± 1.8</td>
<td>0.351</td>
</tr>
<tr>
<td>Prev. coronary revasc.</td>
<td>32.6%</td>
<td>27.7%</td>
<td>0.396</td>
</tr>
<tr>
<td>Prev. carotid revasc.</td>
<td>5.0%</td>
<td>2.5%</td>
<td>0.402</td>
</tr>
<tr>
<td>Prev. target limb min. amp.</td>
<td>11.7%</td>
<td>11.8%</td>
<td>1.000</td>
</tr>
<tr>
<td>ABI (mean±SD)</td>
<td>0.75 ± 0.40</td>
<td>0.81 ± 0.44</td>
<td>0.264</td>
</tr>
<tr>
<td>TBI (mean±SD)</td>
<td>0.32 ± 0.20</td>
<td>0.46 ± 0.42</td>
<td>0.178</td>
</tr>
<tr>
<td>TcPO2 (mmHg)</td>
<td>18.6 ± 17.5</td>
<td>15.8 ± 13.6</td>
<td>0.475</td>
</tr>
<tr>
<td>CRP (mg/dl, mean±SD)</td>
<td>12.0 ± 31.1</td>
<td>13.3 ± 35.4</td>
<td>0.750</td>
</tr>
</tbody>
</table>

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1. GFR<30ml/min
## Baseline Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DEB (N 239)</th>
<th>PTA (N 119)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RVD (mm±SD)</strong></td>
<td>2.46 ± 0.69</td>
<td>2.41 ± 0.56</td>
<td>0.304</td>
</tr>
<tr>
<td><strong>Target Lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean length (cm ± SD)</td>
<td>10.2 ± 9.1</td>
<td>12.9 ± 9.5</td>
<td>0.002</td>
</tr>
<tr>
<td>%DS (% ± SD)</td>
<td>83.9 ± 16.9</td>
<td>86.6 ± 15.7</td>
<td>0.078</td>
</tr>
<tr>
<td>Occlusion (%)</td>
<td>38.6%</td>
<td>45.9%</td>
<td>0.114</td>
</tr>
<tr>
<td><strong>MLD (mm ± SD)</strong></td>
<td>0.42 ± 0.49</td>
<td>0.34 ± 0.43</td>
<td>0.075</td>
</tr>
<tr>
<td><strong>Pre-dilatation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90.5% (325/359)</td>
<td>36.0% (68/189)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Infl. time (sec±SD)</strong></td>
<td>166.0 ± 138.4</td>
<td>137.7 ± 111.3</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>(max) Infl. P (atm±SD)</strong></td>
<td>9.5 ± 2.4</td>
<td>10.3 ± 4.6</td>
<td>0.010</td>
</tr>
</tbody>
</table>

### Post-dilation
- DEB (N 239): 10.3% (37/359)
- PTA (N 119): 8.5% (16/189)
- p = 0.488

### Stenting
- DEB (N 239): 3.9%
- PTA (N 119): 2.6%
- p = 0.446

### Procedural complications [2]
- DEB (N 239): 9.7% (23/238)
- PTA (N 119): 3.4% (4/119)
- p = 0.035

### Distal embolization
- DEB (N 239): 2.8% (9/319)
- PTA (N 119): 0.6% (1/169)
- p = 0.176

### Post proc dissections
- DEB (N 239): 12.3% (42/342)
- PTA (N 119): 19.2% (34/177)
- p = 0.046

### Technical Success [3]
- DEB (N 239): 93.2% (331/355)
- PTA (N 119): 88.4% (167/189)
- p = 0.051

### Device Success [4]
- DEB (N 239): 98.0% (348/355)
- PTA (N 119): 96.3% (182/189)
- p = 0.224

### Procedural Success [5]
- DEB (N 239): 98.3% (234/238)
- PTA (N 119): 100.0% (119/119)
- p = 0.155

1. Total Inflation: time of treatment device per device
2. Excluding post-procedure dissections
3. Technical Success: Successful vascular access and completion of the endovascular procedure and immediate morphological success with ≤ 50% residual DS by Angio
4. Device Success: exact deployment of the device according to the IFU as documented with suitable imaging modalities and in case of DSA, in at least 2 different imaging projections
5. Procedural Success: combination of technical success, device success and absence of procedural complications
### Primary IN.PACT DEEP Outcomes

<table>
<thead>
<tr>
<th>Primary Efficacy</th>
<th>DEB</th>
<th>PTA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month LLL (mm)</td>
<td>0.61 ± 0.78</td>
<td>0.62 ± 0.78</td>
<td>0.950</td>
</tr>
<tr>
<td>12-month CD-TLR [2]</td>
<td>9.2% (18/196)</td>
<td>13.1% (14/107)</td>
<td>0.291</td>
</tr>
</tbody>
</table>

### Primary Safety

<table>
<thead>
<tr>
<th>Primary Safety</th>
<th>DEB</th>
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</thead>
<tbody>
<tr>
<td>6-month Death, Major Amputation or CD TLR</td>
<td>17.7% (41/232)</td>
<td>15.8% (18/114)</td>
<td>0.021 (non-inferiority)</td>
</tr>
</tbody>
</table>

1. Angio Cohort, Corelab adjudicated. Angiographic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)
2. Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. “Clinically driven TLR” defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab
# Angio Cohort Outcomes

<table>
<thead>
<tr>
<th>12-month Outcomes [1]</th>
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<tr>
<td>Mean Lesion Length (mm±SD)</td>
<td>59.1 ± 41.7</td>
<td>79.7 ± 74.6</td>
<td>0.060</td>
</tr>
<tr>
<td>Binary (50%) Rest. Rate (%)</td>
<td>41.0% (25/61)</td>
<td>35.5% (11/31)</td>
<td>0.609</td>
</tr>
<tr>
<td>Occlusion Rate (%)</td>
<td>11.5% (7/61)</td>
<td>16.1% (5/31)</td>
<td>0.531</td>
</tr>
<tr>
<td>Longitudinal Restenosis (%) [2]</td>
<td>62.7 ± 56.2</td>
<td>93.2 ± 60.8</td>
<td>0.167</td>
</tr>
</tbody>
</table>

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1. Angio Cohort, Corelab adjudicated. Angiographic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)
2. Mean % of stenosis length vs. treated lesion length± SD (Angiographic Cohort, ITT)
3. As evaluated by additional angiographic core laboratory (Beth Israel Deconess Medical Center, Boston, MA) to confirm earlier analysis
Despite initial small studies demonstrating a benefit, this larger multi-center study did not show efficacy over PTA and raised safety concerns due to a higher amputation rate.

Why
**LLL- Product?**

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No treatment effect  \[\rightarrow\]  Lack of drug effect?

<table>
<thead>
<tr>
<th></th>
<th>Recalled IN.PACT Amphirion</th>
<th>Current IN.PACT Admiral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coating Method</strong></td>
<td>Manually-coated on folded balloon</td>
<td>Automatically-coated on inflated balloon</td>
</tr>
<tr>
<td><strong>Balloon Material</strong></td>
<td>High surface energy</td>
<td>Low surface energy</td>
</tr>
</tbody>
</table>

- Non-uniform coating  
- Lower drug transfer  
- Uniform coating  
- Higher drug transfer
Issues with In.Pact Deep

- Single center vs multicenter results
  - Patient population may not have been representative of everyday patients
  - Complex Endpoints not necessarily dependent on DEB efficacy
  - Small sample size and 2:1 randomization increased the risk of random error
  - Inflow disease may pose a higher risk for BTK index TLR
  - Approximately 50% loss of patients to angiographic follow-up
  - PTA results are not consistent with historical results
  - No standardized wound care across sites for equalization of treatment
  - Insufficient drug delivery

Amphirion IN.PACT DEB in BTK
Study Design and Key Eligibility Criteria

**DEBATE-BTK**
- Investigator initiated
- Single center
- Prospective randomized
- (1:1) DEB vs. PTA
- Self adjudicated
- No external monitoring

*Listro et al, Circulation 2013*

**IN.PACT DEEP**
- Industry sponsored
- Prospective, Multicenter, Randomized (2:1) DEB vs PTA
- Ind. Data Safety Monitoring
- Ind. Clinical Event Committee
- Ind. Angiographic Corelab
- Ind. Wound Corelab
- Wound Measurement through Electronic Reader
- External Monitoring

100% Source Data Verification
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### Amphilirion IN.PACT DEB in BTK

<table>
<thead>
<tr>
<th>DEBATE-BTK</th>
<th>IN.PACT Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC 4-5-6</td>
<td>RC 4-5-6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Age 18-85</td>
</tr>
<tr>
<td><strong>Stenosis / occlusions &gt;40 mm in at least 1 tibial vessel with distal run-off</strong></td>
<td><strong>Stenosis / occlusions of any length in at least one tibial vessel with distal run-off</strong></td>
</tr>
<tr>
<td>GFR&lt;30ml/min and ESRD and dialysis included</td>
<td>GFR&lt;30ml/min (except ESRD and dialysis). <strong>(exclusion criteria in angio cohort)</strong></td>
</tr>
<tr>
<td><strong>Lesions do not reflect those observed in daily practice in angio cohort</strong></td>
<td>Foot arteries can be dilated only with conventional balloon even in DEB cohort</td>
</tr>
</tbody>
</table>
Issues with In.Pact

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Lesion Characteristics Differ by Location

**Above the Knee**
- Calcium: 35%
- CTOs: 20%
- Soft Plaque: 10%
- ISR: 15%
- Fibrotic: 10%
- Thrombus: 10%

**Below the Knee**
- Calcium: 75%
- CTOs: 15%
- Soft Plaque: 10%
- ISR: 15%
- Fibrotic: 3%
- Thrombus: 10%

- Lesions more commonly calcified
- Dense calcium comprises a greater percentage of plaque (27% in tibial vs 12% in popliteal plaque)\(^2\)
- Small vessels (2-3.5 mm)
- Tortuous anatomy

- Multiple plaque types (mixed morphology)
- Large plaque burden\(^2\)
- Medium to large vessels (4-9 mm)

---

1. VIVA 2011 survey – 100 physicians surveyed.
60 patients with SFA stenosis or occlusion treated with DCB

CTA, DSA, and IVUS used to quantify the calcium burden

At 1 year, greater calcification was associated with:
- Lower patency
  - 50% for 270°-360° vs 100% for 0°-90°
- Lower ankle-brachial index
- Greater late lumen loss and TLR rate

IN.PACT DEB in calcified SFA lesions

- 60-patient Registry
- De-novo SFA lesions ~ 6 cm
- Tot Occlusions 31.7%
- pre-dilat with std PTA

Calcium distribution evaluation by CTA (circumf.) and DSA (longitud.)

<table>
<thead>
<tr>
<th>GROUP</th>
<th>DIAMETER</th>
<th>LENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 a</td>
<td>0 – 90°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>1 b</td>
<td>&gt; 3 cm</td>
<td></td>
</tr>
<tr>
<td>2 a</td>
<td>90 – 180°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>2 b</td>
<td>&gt; 3 cm</td>
<td></td>
</tr>
<tr>
<td>3 a</td>
<td>180 – 270°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>3 b</td>
<td>&gt; 3 cm</td>
<td></td>
</tr>
<tr>
<td>4 a</td>
<td>270 – 360°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>4 b</td>
<td>&gt; 3 cm</td>
<td></td>
</tr>
</tbody>
</table>
Atherectomy and Drug-Coated Balloon Efficacy: Clinical Evidence

- DEFINITIVE AR: directional atherectomy + DCB vs DCB alone
  - Third non-randomized arm for directional atherectomy + DCB for severely calcified lesions

- Results suggest that adjunctive atherectomy may improve procedural and clinical outcomes following DCB treatment of the SFA and/or popliteal artery, particularly for longer or severely calcified lesions

**Procedural Results**

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>Atherectomy + DCB</th>
<th>Atherectomy + DCB (Severe Ca$^{2+}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technical Success</strong></td>
<td>64.2%</td>
<td>89.6%</td>
<td>84.2%</td>
</tr>
<tr>
<td><strong>Bail-out Stent</strong></td>
<td>3.7%</td>
<td>0%</td>
<td>5.3%</td>
</tr>
<tr>
<td><strong>Flow-limiting Dissection</strong></td>
<td>19%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**12-Month Results**

- Lesions >10 cm
- All Severe Ca$^{2+}$

<table>
<thead>
<tr>
<th></th>
<th>DUS Patency</th>
<th>Stenosis</th>
<th>DUS Patency</th>
<th>Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherectomy + DCB</td>
<td>97%</td>
<td>86%</td>
<td>70%</td>
<td>63%</td>
</tr>
<tr>
<td>DCB</td>
<td>31%</td>
<td>37%</td>
<td>50%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Legend:
- Atherectomy + DCB
- DCB
Atherectomy and Drug-Coated Balloon Angioplasty in Treatment of Long Infrapopliteal Lesions (ADCAT)

- Target lesion to be treated with atherectomy (TurboHawk, ev3) and paclitaxel-coated balloon
## Lutonix BTK Trial Summary

| PRIMARY ENDPOINTS | Safety at 30 days  
Limb salvage & primary patency at 12 months |
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER OF PATIENTS/SITES</td>
<td>480 patients at 55 global sites</td>
</tr>
</tbody>
</table>
| 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 INVESTIGATORS | Patrick Geraghty: Washington University, St. Louis, MO  
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
Conclusions

- BTK interventions for CLI are challenging and results are hindered with high restenosis rates
- The lack of benefit seen in In.Pact Deep were disappointing but certainly has not closed the door
- We await further studies to define on the role of DCB for CLI