Drug Coated Balloons for PAD

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Department of Vascular and Endovascular Surgery
- Introduction
- PAD Burden
- Anatomy of a Drug Coated Balloon
- LUTONIX® 035 Device Overview
- Product Offering Procedure Steps

- LUTONIX® 035 Treatment Algorithm
- LUTONIX® 035 Pre-Clinical Evidence
- LEVANT2ClinicalTrial
- LEVANT2ClinicalCase Studies
- Resources
### DCB available:

- **LUTONIX® 035 Drug Coated Balloon** is the first and ONLY of its kind technology in the U.S. that can advance our treatment algorithm for SFA/Popliteal disease.

- Others are in the process of obtaining FDA approval.
Peripheral Artery Disease affects an estimated 202 million people worldwide. This represents an increase of 23.5% in the last decade alone.

23.5% INCREASE IN THE LAST DECADE

360,000+ SFA CASES PER YEAR IN THE US

PAD IS THE LEADING CAUSE OF AMPUTATION IN PEOPLE AGE 50+ AND ACCOUNTS FOR UP TO 90% OF AMPUTATIONS OVERALL
How Does Paclitaxel Work?

Paclitaxel is an anti-proliferative agent and an ideal drug for DCBs

- Highly lipophilic and readily diffuses across cell membranes

- Preclinical testing* has shown paclitaxel inhibits neointimal proliferation in turn aiding in long-term patency in treated vessels

- LUTONIX® 035’s drug coating is designed to inhibit restenosis in the arterial wall while allowing the lumen to restore and reendothelialize
What’s an Effective DCB Formulation?

The ideal formulation needs to do the following:

- **Retain drug** during transit
- Ensure **rapid drug transfer** upon contact
- Have **uniform, durable, transfer-efficient coating**
Extensive Development
LUTONIX® 035 Formulation

The LUTONIX® 035 formulation was the result of extensive development and rigorous testing, which included:

- 50,000 balloons
- >11,400 histology samples
- >250 formulations
- 45 preclinical studies

Resulted in an optimized formulation with a therapeutic dose of 2 μg/mm²
Drug + Carrier = Coating

**Drug**
LUTONIX® 035 drug dose of Paclitaxel is 2μg/mm²

**Carrier**
Polysorbate and Sorbitol

**Coating**
Facilitates therapeutic drug retention and release of drug at the treatment site
LUTONIX® 035 Formulation - Carriers

LUTONIX® 035 proprietary formulation is designed to:

- Deliver an optimal, therapeutic drug dose to the target vessel wall after a minimum 30 second inflation time
- Minimize downstream and systemic exposure of unnecessary drug

Ideal DCB design: highly efficient carrier that facilitates transfer of therapeutic tissue dose with minimal downstream loss
LUTONIX® 035 Design: Coating Integrity
Sheath/Tuohy Passage Test

Limit drug flaking during balloon preparation and handling*

Potentially minimizing unnecessary drug exposure to staff and patients*

LUTONIX® 035 has a durable coating, with ≤0.08% drug dose lost within the introducer sheath during insertion.*

Drug on Hemostatic Adapter* after Balloon Passage

Durability of coating preserved through sheath value or tuohy insertion

0.08% 0.03%
6F Sheath N=10 6F Tuohy N=10
**LUTONIX® 035 Design: Coating Integrity**

Prep Simulation Shake Test

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LUTONIX® 035 has a durable coating, with <0.1% drug loss after dry inflate “shake” test.*

<table>
<thead>
<tr>
<th></th>
<th>Residual Drug on DCB Balloon After Inflation/Shake</th>
<th>Drug Loss After DCB Inflation/Shake</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LUTONIX® 035</strong></td>
<td>98.9% ± 1.1%</td>
<td>&lt;0.1%*</td>
</tr>
</tbody>
</table>
Coating Uniformity
Coating Variability Analysis

LUTONIX® 035 is uniformly coated while inflated allowing for 360° paclitaxel coverage to the target vessel.*
Consistent Uniformity
In vivo Delivery

Scientifically designed to:

- Deliver an optimal therapeutic drug dose at the treatment site following a minimum 30-second inflation time*
- LUTONIX® 035 has a consistent coating, resulting in 360° paclitaxel treatment at the target vessel *

Uniform Delivery in vivo at 1 hour
(Animal vessel cross section after 30 sec. inflation*)
LUTONIX® 035 Mechanism of Action

1. After pre-dilatation of the stenosis, the DCB is centered across the entire treated area.
2. 30 second minimum inflation transfers an optimal therapeutic dose of the drug to the endoluminal surface.
3. Paclitaxel diffuses into the arterial wall from the endoluminal surface after drug delivery.
4. Therapeutic drug levels are sustained in the artery through 30 days post treatment.*
5. Drug continues to inhibit restenosis in the arterial wall while allowing the lumen to restore and re-endothelialize.
6. Evidence of pharmacological effects peaks at 90 days.*
Dr. Renu Virmani Pre-Clinical Safety Data

• Evaluate the safety of variable doses paclitaxel, polysorbate and sorbitol in a swine femoral artery model

• Study arms:
  • 1x Dose (2 μg/mm² Paclitaxel)
  • 4x the Dose (8 μg/mm²)
  • Control POBA Uncoated PTA
- Sustained presence of paclitaxel, in the arterial wall though 30 days
- Demonstrated pharmacological effects up to 90 days
- Evidence of drug effect peaks at 90 days
- **No physiologically significant distal embolic or downstream drug effects from the LUTONIX® 035 formulation even at 4X the dose**

LUTONIX® 035 coating was designed with an optimal therapeutic dose to achieve a maximum balance between safety and efficacy.
LEVANT 2 Randomized Study Design

PTA Pre-Dilatation
with 1 mm undersized uncoated balloon
N=487

Successful Pre-Dilation
N=476

Suboptimal PTA:
Major flow limiting dissection or >70% residual stenosis
N=11

Randomization 2:1

Test Arm
DCB
N=316

Control Arm
PTA (POBA)
N=160

 Treat Per Standard Practice
30 day follow-up for safety
LEVANT 2 Study Primary Endpoints

**Safety**

Composite of freedom from all-cause peri-operative death & freedom at 1 YEAR in the index limb from:

- Amputation (ATK or BTK)
- Re-intervention
- Index-limb-related death

**Efficacy**

Primary patency of the target lesion at 1 YEAR:

- Absence of restenosis defined by DUS PSVR ≥2.5 & freedom from target lesion revascularization (TLR)
## LEVANT 2 Unique Study Design

<table>
<thead>
<tr>
<th>Study Effect of Drug</th>
<th>Strive to Exclude Stenting</th>
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<tbody>
<tr>
<td>Controlled pre-dilation prior to randomization limited the number of bailout stents placed.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Remove Bias During Re-intervention</th>
<th>Blinding and Clinically-Driven Follow-Up</th>
</tr>
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<tbody>
<tr>
<td>Patients, follow-up physicians and Core Labs were blinded to treatment modality. Reintervention decisions were based on patient’s symptoms alone.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Assess Durability of Treatment vs. Acute Results</th>
<th>Bailout Stenting Not Counted as a Failure</th>
</tr>
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<tbody>
<tr>
<td>This ensured that the study assessed and compared the performance of the treatment modalities alone.</td>
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</table>
**Studied in a Challenging Femoropopliteal Cohort**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>DCB (n=316)</th>
<th>PTA (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>43% (137)</td>
<td>42% (67)</td>
</tr>
<tr>
<td>Rutherford Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29% (93)</td>
<td>34% (55)</td>
</tr>
<tr>
<td>3</td>
<td>63% (198)</td>
<td>58% (92)</td>
</tr>
<tr>
<td>4</td>
<td>8% (25)</td>
<td>8% (13)</td>
</tr>
<tr>
<td>Treated Length (mm)</td>
<td>107.9 ± 47.0</td>
<td>107.9 ± 49.4</td>
</tr>
<tr>
<td>Calcification – Total</td>
<td>59% (187)</td>
<td>58% (93)</td>
</tr>
<tr>
<td>Calcification – Severe</td>
<td>18% (33/187)</td>
<td>14% (13/93)</td>
</tr>
<tr>
<td>Total Occlusion</td>
<td>21% (65)</td>
<td>22% (35)</td>
</tr>
<tr>
<td>Restenotic Lesions</td>
<td>16% (51)</td>
<td>13% (20)</td>
</tr>
</tbody>
</table>
Proven Safety Comparable to Standard PTA
Demonstrated in LEVANT 2

Freedom from Primary Safety Event* at 365 Days

<table>
<thead>
<tr>
<th>Event Summary</th>
<th>DCB n (%)</th>
<th>PTA n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal embolization with study treatment</td>
<td>1/316 (0.3%)</td>
<td>1/160 (0.6%)</td>
</tr>
<tr>
<td>Distal embolization with post-treatment</td>
<td>0/316 (0.0%)</td>
<td>1/160 (0.6%)</td>
</tr>
<tr>
<td>Reintervention for thrombosis</td>
<td>1/285 (0.4%)</td>
<td>1/140 (0.0%)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>1/286 (0.3%)</td>
<td>0/140 (0.0%)</td>
</tr>
</tbody>
</table>
Proven Superior Primary Patency to PTA
29.4% Better Primary Patency than PTA
LEVANT 2 at 12 Months*

Bailout stenting was NOT considered a TLR or loss of Primary Patency
- DCB Bail-out stent rate: 2.5%
- PTA Bail-out stent rate: 6.9%
Proven Outcomes
In LEVANT 2, 9/10 patients treated with LUTONIX® 035 did not require reintervention within a year

**LUTONIX® 035 Freedom from TLR Rate**

- **6 Months**: 96.0%
- **12 Months**: 89.7%
LUTONIX® 035 – Stent-Like TLR
In LEVANT 2, LUTONIX® 035 demonstrated a TLR rate consistent with reported SFA stent TLRs*
Sustained Quality of Life Improvement

Improvement in Walking Distance scores

- Patients treated with DCB reported less pain and the ability to walk further at 12 months compared to patients treated with PTA alone.*

Improvement in Rutherford Scores

- Patients demonstrated clinical benefits of sustained improvement in Rutherford categories at 12 months.*
IFU and Intended Use

The LUTONIX® 035 Drug Coated Balloon PTA catheter is indicated for percutaneous transluminal angioplasty, after pre-dilatation, of de novo or restenotic lesions up to 150mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-6mm.

- Electronic IFU can be found at bardpv.com/lutonix-IFU.pdf
- Hard copy can be obtained through our MS&S department: (800) 562-0027
- LUTONIX® 035 and packaging is LATEX FREE
Product Offering

- 035 Guidewire Compatible, Nylon, Semi-compliant Balloon
- Over the wire, Co-axial shaft
- 2 Radiopaque platinum: 1mm markers delineate balloon length
- Balloon protector sleeve and stylet in place
- Catheter Lengths: 75, 130cm

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Balloon Lengths (mm)</th>
<th>Nominal (atm)</th>
<th>RBP (atm)</th>
<th>Sheath Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
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Procedure Treatment Considerations

- Handle the DCB with dry sterile gloves: Keep the balloon dry whenever possible and minimize wet contact

- Avoid dipping the balloon in a bowl full of saline, wet wipe downs, wet 4x4s or fluid puddles

- If flushing is desired, point balloon tip down to prevent backflow on balloon/coating

- The balloon guard and wire lumen stylet should stay in place during procedure prep, and should not be removed until just prior to placing the guidewire.

- Negative pressure should be maintained while inserting the DCB through the introducer sheath
LUTONIX® 035 Balloon Guard Removal

Carefully adhere to the following instructions to properly remove the balloon guard from the LUTONIX® 035

**Step 1:**
With wire lumen stylet in place, prepare balloon under negative pressure to aid in balloon guard removal.

**Step 2:**
Flex the balloon guard slightly upward approximately 15° and run thumb and forefinger upward from proximal end to distal tip of the balloon guard.

**Step 3:**
Flex the balloon guard downward approximately 15° and repeat thumb and forefinger movement downward.

**Step 4:**
Grasp the balloon guard at midpoint and slide the guard off while also removing the stylet.
Pre-Dilatation

- Adequately **pre-dilate to at least 1 mm of the reference vessel diameter**
  - After pre-dilation, LUTONIX® 035 should extend approximately 5 mm proximally and distally beyond the pre-dilatation injury segment
  - Use of a radiopaque ruler or vascular tape is recommended to ensure appropriate placement of the LUTONIX® 035
Procedure Summary

Key Procedure Goals
1. **Complete** dilation of the diseased segment to reference vessel diameter
2. **Complete** coverage of treatment area with drug (DCB)
Post-Dilatation and Antiplatelet Regimen

- **Post-dilatation** (if preferred) with POBA or re-inflated LUTONIX® 035
- Dual antiplatelet therapy should be administered according to current medical standards pre-procedure and for a minimum of 4 weeks after the intervention.
- Prolonged antiplatelet therapy can be given at the discretion of the physician.
Proven effective with pre-dilatation alone in LEVANT 2

- 29.4% better primary patency than PTA alone at 12 months*
- 89.7% Freedom from TLR at 12 months

LUTONIX® 035 is a first-line treatment option that can be used in conjunction with bare metal stenting in femoropopliteal lesions
**Case 1: Calcification**

**Patient Demographics**
- 91 year old male
- Med hx: Previous Smoker, HTN, Dyslipidemia, CAD w/ CABG, RBS-3
- Prior peripheral revascularization of target vessel (PTA/Stent distal SFA 8/2010)

**Lesion Details**
- Site reported: Left mid SFA
  - Baseline: RVD 6mm, 70% stenosis, 90mm
  - Post pre-dilatation: 40% residual, Grade A dissection
  - Post DCB treatment: 10% residual, Grade A dissection
- Core lab reported: Left mid SFA
  - Baseline: RVD 4.86mm, 70% stenosis, 87.52mm, calcified
  - Post pre-dilatation: 33% residual, Grade A dissection
  - Post DCB treatment: 14% residual, Grade A dissection
Case 2: Calcification & CTO

Patient Demographics
- 63 year old male
- Med hx: Smoker, DM, HTN, CAD w/ MI, Dyslipidemia, RBS-3
- Prior peripheral revascularization to target vessel (proximal SFA 2009)

Lesion Details
Site reported: Left distal SFA
- Baseline: RVD 5mm, 100% stenosis, 80mm
- Post pre-dilatation: 60% residual, no dissection
- Post DCB treatment: 0% residual, no dissection

Core lab reported: Left mid SFA
- Baseline: RVD 4.39mm, 100% stenosis, 90mm, calcified
- Post pre-dilatation: 72% residual, no dissection
- Post DCB treatment: 2% residual, no dissection
Case 3: Calcification & CTO

Patient Demographics
- 60 year old male
- Prior peripheral revascularization to non-target limb

Lesion Details
- Site reported: Right mid SFA
- Baseline: RVD 5.6mm, 99% stenosis, 56mm
- Post pre-dilatation: 30% residual, no dissection
- Post DCB treatment: 0% residual, no dissection

Core lab reported: Right mid SFA
- Baseline: RVD 5.48mm, 90% stenosis, 67.74mm, calcified
- Post pre-dilatation: 52% residual, Grade A dissection
- Post DCB treatment: 28% residual, Grade A dissection
Case 4: Post-Treatment Grade B Dissection

**Patient Demographics**
- 78 year old female
- Med hx: Smoker, HTN, PVD, CAD w/ PCI, RBS-2
- Prior peripheral revascularization in both legs
- Revascularization of target vessel, unknown if this involved target lesion

**Lesion Details**
- Site reported: Left mid SFA
- Baseline: RVD 4mm, 90% stenosis, 80mm
- Post pre-dilatation: 20% residual, no dissection
- Post DCB treatment: 5% residual, Grade B dissection
- After post-dilatation for dissection: 5%, no flow limiting dissection

Core lab reported: Left mid SFA
- Baseline: RVD 2.98mm, 85% stenosis, 74.63mm, calcified
- Post pre-dilatation: 23% residual, Grade A dissection
- Post DCB treatment: 19% residual, Grade B dissection
- After post-dilatation: 19% residual, Grade B dissection
Case 5: No Stent Zones

**Patient Demographics**
- 74 year old male
- Med hx: Previous smoker, HTN, Dyslipidemia, CVA (stroke), RBS-3

**Lesion Details**
- Site reported: Right mid popliteal
- Baseline: RVD 5mm, 100% stenosis, 50mm
- Post pre-dilatation: 50% residual, no dissection
- Post DCB treatment: 0% residual, no dissection

Core lab reported: Right mid popliteal
- Baseline: RVD 4.51mm, 100% stenosis, 52.1mm, calcified
- Post pre-dilatation: 50% residual, Grade B dissection
- Post DCB treatment: 3% residual, Grade B dissection
Case 6: No Stent Zones

Patient Demographics
- 57 year old male
- Med hx: Smoker, Dyslipidemia, RBS-3
- Prior peripheral intervention on target lesion (PTA 2009)

Lesion Details
Site reported: Right mid popliteal
- Baseline: RVD 4.8mm, 99% stenosis, 39mm
- Post pre-dilatation: 30% residual, no dissection
- Post DCB treatment: 10% residual, no dissection

Core lab reported: Right mid popliteal
- Baseline: RVD 4.87mm, 94% stenosis, 57.88mm, calcified
- Post pre-dilatation: 44% residual, no dissection
- Post DCB treatment: 19% residual, no dissection
• ?