A study of downstream events of the two leading DCBs on the market

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Consultant: 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore.

Employment in industry: No


Owner of a healthcare company: No

Stockholder of a healthcare company: No
Disclaimer

• The physician has been compensated by C.R. Bard, Inc. to participate in this presentation. The presenter is a consultant of Lutonix, Inc. and Bard Peripheral Vascular, Inc.

• The opinions and data presented herein are for information purposes only, for the sole purpose of engaging in legitimate, scientific exchange regarding the LUTONIX ® Drug Coated Balloon Catheter.

• Pre-clinical data are on file at CV Path and Lutonix, Inc.; results may vary depending on a variety of experimental parameters and may not necessarily be indicative of clinical performance.

• Please note: Certain of the devices discussed in this presentation are classified as investigational in the United States, and are limited by federal law to investigational use only.
Elements of an Effective DCB Formulation

• Must deliver large quantities of the drug within seconds
• Distribute within the media in the first few days
• Therapeutic drug levels must be maintained for more than 4 weeks
• Must allow rapid healing as compared to DES
• No need for long-term anti-platelet therapy
• Biologic effects must be observed by histology at 28-days
• Effective drug delivery to target tissue while avoiding non-target effect (i.e. minimize emboli)
## Drug Coated Balloon Devices (Peripheral artery)

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Coating</th>
<th>Drug dose (µg/mm²)</th>
<th>CE mark*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advance 18 PTX™</td>
<td>Cook Medical, Bloomington, IN, USA</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Cotavance®</td>
<td>Bayer Schering Pharma AG, Berlin, Germany</td>
<td>Paclitaxel–iopromide</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Freeway™</td>
<td>Eurocor, Bonn, Germany</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>In.Pact™ Admiral,</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Lutonix® 035 DCB</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Ranger</td>
<td>Boston Scientific</td>
<td>Paclitaxel–Acetyl Tributyl Citrate 2</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Passeo-18 Lux®</td>
<td>Biotronik, Bülach, Switzerland</td>
<td>Paclitaxel–butyryl-tri-hexyl citrate</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Stellarex®</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel–polyethylene glycol</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>SurVeil™ DCB</td>
<td>SurModics, MN, USA</td>
<td>Paclitaxel–proprietary photolink®</td>
<td>2.0</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- **FDA approval**
- **First in man in USA**
- **Clinical trial under FDA**

# Lutonix® 035 vs. In.Pact™ Differences

<table>
<thead>
<tr>
<th></th>
<th>Lutonix® 035</th>
<th>In.Pact™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel Dose</td>
<td>2 μg/mm²</td>
<td>3.5 μg/mm²</td>
</tr>
<tr>
<td>Carrier</td>
<td>Polysorbate &amp; Sorbitol</td>
<td>Urea</td>
</tr>
<tr>
<td>Systemic Downstream Effects in a Pre-Clinical Model</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>SFA/BTK Product Line</td>
<td>SFA= 1st with FDA Approval / BTK Ongoing Trial</td>
<td>SFA FDA Approval / BTK Product Recall 2014</td>
</tr>
</tbody>
</table>

- **Lutonix® 035**
  - Distal Tip: Medial
  - Systemic: Present
  - FDA Approval: Ongoing

- **In.Pact™**
  - Distal Tip: Medial
  - Systemic: Present
  - FDA Approval: Recall 2014
Coating Integrity is Variable

Crystalline Paclitaxel

Paclitaxel in coating after aqueous exposure

Lutonix® 035

MDT/Invatec (Admiral)
Paclitaxel Adherence to the Balloon
Polysorbate & Sorbitol vs. Urea

- **Significantly less drug loss than In.Pact™** during simulated shake test
- Balance of 2.0 μg/mm² paclitaxel and carriers polysorbate and sorbitol, *minimizes unwanted drug loss in the lab*

Drug Lost During Shake Test
Lutonix® 035 vs. In.Pact™

* Bench test data on file. Bench results may not be indicative of clinical performance. Different test methods may yield different results. 
Paclitaxel Uptake in the Animal Arterial Wall

- Lutonix® 035 offers similar to In.Pact concentration levels at 24 hours and 60 days.
- In.Pact has 75% more Paclitaxel per dose per balloon.

Similar efficacy concentration levels with significantly less drug

* Data obtained from two data sets. Lutonix data from Virmani Pre-clinical animal data GLP study. Medtronic data from Medtronic own reported data, Dr. Melder, LINC presentation 2012.
Histologic Parameters for Evaluation of DCB Efficacy

- Key target parameters:
  - Endothelial loss
  - Fibrin / Platelets
  - Inflammation
  - Injury
  - Medial smooth muscle cell loss
  - Matrix replacement
    - Proteoglycan
    - Collagen
  - Adventitial fibrosis
- Evaluated skeletal muscle and coronary band for potential embolic changes
  - Distal drug concentration
  - Histology
    - Distal embolization
    - Vascular changes
Vascular Pharmacokinetic Responses with a Lutonix 035 in a Swine Femoral Artery-Dose Dependency

Histological Findings of Emboli / Vascular Changes, Skeletal Muscle Arteries

Lutonix 035, 3x (2µg/mm² paclitaxel) at 90-days

Loss of medial SMCs with fibrinoid necrosis and replacement by proteoglycan/collagen

5 /56 = 8.9 % from DCB treatment showed findings of vascular change associated with paclitaxel and/or excipient (drug carrier).

Skeletal Muscle: Gastrocnemius Muscle, Gluteus Maximus Muscle, Gracilis Muscle, Rectus Femoris Muscle, Semimembranosus Muscle, and Semitendinosus Muscle
Histological Findings of Emboli / Vascular Changes, Skeletal Muscle Arteries

In.Pact DCB x3 (3.5µg/mm² paclitaxel) at 90-days

<table>
<thead>
<tr>
<th>No.</th>
<th>No. of sections (Downstream muscle/coronary band)</th>
<th>Vascular Changes</th>
<th>Skeletal Muscle Necrosis/Fibrosis</th>
<th>Crystalline material</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 (12/1)</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>13 (12/1)</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>13 (12/1)</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>13 (12/1)</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>13 (12/1)</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>13 (12/1)</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>38</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

38/78 = 48.7% from DCB treatment showed findings of **vascular changes**

9/78 = 11.5% from DCB showed findings of **skeletal muscle fibrinoid necrosis**

Skeletal Muscle: Gastrocnemius Muscle, Gluteus Maximus Muscle, Gracilis Muscle, Rectus Femoris Muscle, Semimembranosus Muscle, and Semitendinosus Muscle
Pre-clinical Comparative Study
In.Pact™ Admiral vs. LUTONIX® 035 in Swine

- Blinded study – Side-by-side
  - Kolodgie et al, JVIR. November, 2016
- 1x and 3x dose
- Evaluated skeletal muscle and coronary band at 28 and 90 days
  - Distal drug concentration
  - Histology
    - Distal embolization
    - Vascular changes

Different test methods may yield different results.
Pre-clinical test data on file. Pre-clinical results may not be indicative of clinical performance.
Downstream Sampling for Paclitaxel Analysis and Histopathology Assessment
## Lutonix DCB vs. In.Pact DCB Comparison Study

<table>
<thead>
<tr>
<th>Study device</th>
<th>LUTONIX DCB</th>
<th>IN.PACT DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device size</td>
<td>4.0 / 5.0 / 6.0 x 80 mm</td>
<td>4.0 / 5.0 / 6.0 x 80 mm</td>
</tr>
<tr>
<td>Coating dose</td>
<td>2 μg/mm²</td>
<td>3.5 μg/mm²</td>
</tr>
<tr>
<td>Treated sites</td>
<td>SFA, 1x (single); 3x (3 DCB OL)</td>
<td>SFA, 1x (single); 3x (3 DCB OL)</td>
</tr>
<tr>
<td>Organ / Tissues assessed for histopathology and PK</td>
<td>Skeletal muscles, Gastrocnemius Muscle, Gluteus Maximus Muscle, Gracilis Muscle, Rectus Femoris Muscle, Semimembranosus Muscle, and Semitendinosus Muscle and coronary band</td>
<td>Same</td>
</tr>
<tr>
<td>28 d treated SFA N</td>
<td>1x =5; 3x=5,</td>
<td>1 x =5; 3x =5</td>
</tr>
<tr>
<td>90 d treated SFA N</td>
<td>3x=5</td>
<td>3x =5</td>
</tr>
<tr>
<td>Plasma PK</td>
<td>Plasma ptx level tested in selected pigs in which only one kind of DCB used</td>
<td></td>
</tr>
</tbody>
</table>
Left or Right  SFA Randomly Treated by LUTONIX, In.Pact or POBA

**Histo only Treatment Scheme:** A total of 2 DCB treated sites (1/vessel) in the external femoral arteries of one leg (left or right).

**PK and histo Treatment Scheme:** A total of 2 treated sites in the external femoral arteries of one leg (left or right).
Histologic Vascular Changes following Lutonix 035 vs. IN.PACT DCB Treatment (1x) at 28 days

Lutonix 035: n=5, In.Pact DCB: n=5, POBA: n=4

- SMC loss score (Depth): Lutonix 035 vs. IN.PACT vs. POBA, P=0.21
- SMC loss score (Circumference): Lutonix 035 vs. IN.PACT vs. POBA, P=0.22
- Medial proteoglycan score: Lutonix 035 vs. IN.PACT vs. POBA, P=0.14
- Fibrin/thrombus score: Lutonix 035 vs. IN.PACT vs. POBA, P=0.41
Histologic Vascular Changes following Lutonix vs. In.Pact DCB Treatment (1x)
Pre-clinical results demonstrate no significant difference in neointimal hyperplasia.

<table>
<thead>
<tr>
<th>Lutonix 1x-28d</th>
<th>In.Pact 1x-28d</th>
<th>POBA-28d</th>
</tr>
</thead>
</table>

Luminal Stenosis, %
P = .049

Neointimal Area, mm$^2$
P = .042
Histologic Vascular Changes following Lutonix 035 vs. IN.PACT DCB Treatment (3x) at 28 and 90 days

Lutonix 035: n=5, In.Pact DCB: n=5, POBA: n=4

SMC loss score (Depth)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>28 days</th>
<th>90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix 035</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>IN.PACT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>POBA</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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</table>

P=0.004
P=0.02

SMC loss score (Circumference)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>28 days</th>
<th>90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix 035</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>IN.PACT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>POBA</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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</table>

P=0.01
P=0.02

Medial proteoglycan score

<table>
<thead>
<tr>
<th>Treatment</th>
<th>28 days</th>
<th>90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix 035</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>IN.PACT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>POBA</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

P=0.01
P=0.007

Fibrin/thrombus score

<table>
<thead>
<tr>
<th>Treatment</th>
<th>28 days</th>
<th>90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix 035</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>IN.PACT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>POBA</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

P=0.41
P=1.00
Vascular Changes in Porcine Skeletal Muscle (at 28-Day)

High (20x and 40x) power images of vascular changes in skeletal muscle at 28 days.

Vascular changes include pyknotic nuclei embedded in homogenous pink material (yellow arrow), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).
Crystalline Material in Porcine Skeletal Muscle at 28 Days: In.Pact (1x / 3x)

High (40x) power images of crystalline material (red arrows) at 28d
**Downstream Incidence of Distal Embolization (%)**

### A

**28-Day Survival**

- **Single Balloon (1x)**
  - Lutonix 035: 7.7% (0-11.5), n=5
  - IN.PACT: 15.4% (11.5-30.8), n=5

- **Overlapping Balloons (3x)**
  - Lutonix 035: 7.7% (0-15.4), n=5
  - IN.PACT: 38.5% (15.4-42.3), n=5

**P=0.04**

**90-Day Survival**

- **Overlapping Balloons (3x)**
  - Lutonix 035: 0% (0-11.5), N=5
  - IN.PACT: 46.2% (19.2-57.7), N=5

**P=0.01**

### B

<table>
<thead>
<tr>
<th>Survival Treatment &amp; Arteries</th>
<th>Lutonix 035</th>
<th>IN.PACT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of micro-vessels with paclitaxel-associated findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day (1x, n=5)</td>
<td>1 (0-2)</td>
<td>4 (2-12)</td>
<td>0.03</td>
</tr>
<tr>
<td>28-day (3x, n=5)</td>
<td>1 (0-12)</td>
<td>26 (11-34)</td>
<td>0.07</td>
</tr>
<tr>
<td>90-day (3x, n=4)</td>
<td>0 (0-3)</td>
<td>11 (5-15)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### C

<table>
<thead>
<tr>
<th>Survival Treatment &amp; Arteries</th>
<th>Lutonix 035</th>
<th>IN.PACT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel concentration in downstream tissues (ng/g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day (1x, n=5)</td>
<td><strong>1.3 (0.6-2.3)</strong></td>
<td><strong>1.5 (1.1-6.5)</strong></td>
<td>60.8 (32.6-118.1)</td>
</tr>
<tr>
<td>28-day (3x, n=5)</td>
<td><strong>3.7 (1.3-10.9)</strong></td>
<td><strong>31.5 (5.9-54.1)</strong></td>
<td>170.9 (19.7-221.5)</td>
</tr>
<tr>
<td>90-day (3x, n=4)</td>
<td><strong>0.6 (0.5-6.4)</strong></td>
<td><strong>2.7 (0.0-25.5)</strong></td>
<td>16.1 (12.8-319.2)</td>
</tr>
</tbody>
</table>
Clinical Relevance

• In the absence of randomized clinical data, preclinical studies can provide excellent information about the relative performance of different technologies
  • Randomized studies generally exclude high risk patients who probably would be affected most by downstream adverse events

• DCBs which obtain effective drug transfer into the arterial wall while minimizing downstream embolic effects are the goal
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A study of downstream events of the two leading DCBs on the market

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