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

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USA
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 at least several weeks
- Must allow rapid healing as compared to DES
- No need for long-term anticoagulation
- Biologic effects at 28-days at least
## 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, Amphirion, Pacific</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Lutonix® DCB</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Legflow®</td>
<td>Cardionovum, Warsaw, Poland</td>
<td>Paclitaxel–shellac</td>
<td>3.0</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>No → Yes</td>
</tr>
<tr>
<td>Stellarex*</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>No → Yes</td>
</tr>
</tbody>
</table>

*Lutonix DCB® and In.Pact™ are currently approved by the FDA for clinical use.*

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# 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= 1(^{st}) with FDA Approval / BTK Ongoing Trial</td>
<td>SFA FDA Approval / BTK Product Recall 2014</td>
</tr>
</tbody>
</table>

![Lutonix® 035](image1.png)

![In.Pact™](image2.png)
Coating Integrity is Variable

Paclitaxel

Paclitaxel in coating after aqueous exposure

Lutonix® 035
Ex Vivo Administration of Fluorescent-Labeled PTX to Excised Porcine Artery

10% Oregon green labeled paclitaxel incorporated into Lutonix DCB coating
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 parameters include:

• Endothelial loss
• Fibrin / Platelets
• Inflammation
• Injury
• Medial smooth muscle cell loss
• Matrix replacement
  • Proteoglycan
  • Collagen
• Adventitial fibrosis
Vascular Changes Following Lutonix DCB Treatment in Porcine Iliac Arteries

<table>
<thead>
<tr>
<th></th>
<th>28 DAYS</th>
<th>90 DAYS</th>
<th>180 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x DCB</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>4x DCB</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Vascular Pharmacokinetic Responses to Treatment with a Lutonix 035 in a Swine Femoral Artery


Graphs showing luminal area, smooth muscle cell loss, proteoglycan deposition, and collagen deposition over 28, 90, and 180 days with different treatment regimens.
Vascular Changes in Downstream Porcine Skeletal Muscle

(NONE of physiological significance observed for Lutonix at any time)

1x Dose

28 Days

90 Days

(None observed for 1x dose at 180 days)

4x Dose

28 Days

90 Days

180 Days
Histological Findings of Emboli / Vascular Changes, Skeletal Muscle Arteries

Lutonix 035 x3 (2µg/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>14 (12/2)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>14 (12/2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>14 (12/2)</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>14 (12/2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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
<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 ug/mm²</td>
<td>3.5 ug/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).

- IN.PACT 1x or 3x Tx site
- LUTONIX 1x or 3x Tx site
- REF 1x or 3x OL
- LEF 1x or 3x OL
- RIF
- LIF

PK and histo Treatment Scheme: A total of 2 treated sites in the external femoral arteries of one leg (left or right).

- 1x or 3x LUTONIX or IN.PACT Tx site
- POBA 1x or 3x Tx site
- LEF:1x or 3x POBA
- REF
- RIF
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**: P=0.21
- **IN.PACT**: P=0.21
- **POBA**: P=0.21

**SMC loss score (Circumference)**

- **Lutonix 035**: P=0.22
- **IN.PACT**: P=0.22
- **POBA**: P=0.22

**Medial proteoglycan score**

- **Lutonix 035**: P=0.14
- **IN.PACT**: P=0.14
- **POBA**: P=0.14

**Fibrin/thrombus score**

- **Lutonix 035**: P=0.41
- **IN.PACT**: P=0.41
- **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.

- Lutonix 1x-28d
- In.Pact 1x-28d
- POBA-28d

**Luminal Stenosis, %**
P = .049

**Neointimal Area, mm²**
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></th>
<th>Lutonix 035 28 days</th>
<th>IN.PACT 28 days</th>
<th>POBA 28 days</th>
<th>Lutonix 035 90 days</th>
<th>IN.PACT 90 days</th>
<th>POBA 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.004</td>
<td></td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### SMC loss score (Circumference)

<table>
<thead>
<tr>
<th></th>
<th>Lutonix 035 28 days</th>
<th>IN.PACT 28 days</th>
<th>POBA 28 days</th>
<th>Lutonix 035 90 days</th>
<th>IN.PACT 90 days</th>
<th>POBA 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Circumference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.01</td>
<td></td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Medial proteoglycan score

<table>
<thead>
<tr>
<th></th>
<th>Lutonix 035 28 days</th>
<th>IN.PACT 28 days</th>
<th>POBA 28 days</th>
<th>Lutonix 035 90 days</th>
<th>IN.PACT 90 days</th>
<th>POBA 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.01</td>
<td></td>
<td></td>
<td>0.007</td>
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</tbody>
</table>

#### Fibrin/thrombus score

<table>
<thead>
<tr>
<th></th>
<th>Lutonix 035 28 days</th>
<th>IN.PACT 28 days</th>
<th>POBA 28 days</th>
<th>Lutonix 035 90 days</th>
<th>IN.PACT 90 days</th>
<th>POBA 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.41</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Histologic Vascular Changes following Lutonix vs. In.Pact DCB Treatment (3x)

**Luminal Stenosis, %**
- Lutonix 035 28 days: 0 (P=0.02)
- IN.PACT 28 days: 10 (P=0.044)
- POBA 28 days: 20
- Lutonix 035 90 days: 5 (P=0.02)
- IN.PACT 90 days: 10
- POBA 90 days: 20

**Neointimal Area, mm²**
- Lutonix 035 28 days: 0.5 (P=0.02)
- IN.PACT 28 days: 1
- POBA 28 days: 2
- Lutonix 035 90 days: 1
- IN.PACT 90 days: 2
- POBA 90 days: 3
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
Vascular Changes in Porcine Skeletal Muscle at 90-Day

In.Pact (3x)

Fibrinoid necrosis

Inflammatory cells

In.Pact (3x)

Fibrinoid necrosis

Lutonix (3x)

Fibrinoid necrosis

Inflammatory cells

POBA (3x)
Downstream Incidence of Distal Embolization (%)

**A**

![Graph showing downstream incidence of distal embolization for different treatments and arteries.](image)

**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>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>28-day (1x, n=5)</td>
<td>1.3 (0.6-2.3)</td>
<td>1.5 (1.1-65.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>28-day (3x, n=5)</td>
<td>3.7 (1.3-10.9)</td>
<td>31.5 (5.9-54.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>90-day (3x, n=4)</td>
<td>0.6 (0.5-6.4)</td>
<td>2.7 (0.0-25.5)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
DCB Design: All About Balancing Safety, Efficacy, and Biologic Response

Not all balloons are created equal.

- **Efficacy**
  - Less neointima
  - Absence of restenosis
  - No early or late thrombosis
  - Biologic changes, but no emboli

- **Safety**
  - Rapid vascular healing
  - Good re-endothelialization
  - No distal emboli

- **Drug Load**
  - Use of Carrier / Excipient
  - Drug Retention
  - Repeat Inflations

More

Less
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