How DCB drug dose effects vessel healing

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Disclosure Statement of Financial Interest

Speaker's name: Aloke, Finn, Gaithersburg

☑️ I have the following potential conflicts of interest to report:

Institutional Receipt of grants / research supports: Abbott, Biosensors, Biotronik, Boston Scientific, Celonova, Edwards Lifesciences, Medtronic, MicroPort, Mitralign, OrbusNeich, Sinomed

Receipt of honoraria or consultation fees: Abbott, Boston Scientific, Celonova, Sinomed, Cook, Bard, Amgen
Biologic changes secondary to DCB (paclitaxel) and Healing in Porcine Peripheral arteries.

• Biologic changes induced by Paclitaxel (in the first few weeks):
  – Loss of endothelial cells and fibrin deposition: intima and media
  – Smooth muscle cell death in the media - transmural and circumferential

• Healing following use of DCB (paclitaxel) (weeks to months)
  – Endothelialization, smooth muscle cell proliferation and intimal thickening with proteoglycan deposition, persistent fibrin, with time will resolve
  – Proteoglycan deposition in the medial wall and adventitia – transmural and circumferential, followed by collagen deposition in media and adventitia
  – Duration of healing is dependent on the persistence of paclitaxel within the arterial wall (loading and efficiency of drug transfer) - pk related
# 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**

**In.Pact™**

- **Distal Tip**
- **Medial**
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 Pharmacokinetic Responses to Treatment with a Lutonix 035 in a Swine Femoral Artery

## Vascular Changes Following Lutonix DCB Treatment in Porcine Iliac Arteries

<table>
<thead>
<tr>
<th>28 DAYS</th>
<th>90 DAYS</th>
<th>180 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x DCB</td>
<td>1x DCB</td>
<td>1x DCB</td>
</tr>
<tr>
<td>4x DCB</td>
<td>4x DCB</td>
<td>4x DCB</td>
</tr>
</tbody>
</table>

![Images of vascular changes following Lutonix DCB treatment](image-url)
Beyond Drug Dose: Drug-Bioavailability

- Paclitaxel is a lipophilic, poorly water soluble compound.
- The activity of the drug is dependent upon solubilization by plasma matrix components and transport into the tissue.
- Both urea and sorbitol are hydrophilic substances but there may be differences in their ability to facilitate dissolution of paclitaxel.
# 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 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).

**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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SMC loss score (Depth)</th>
<th>SMC loss score (Circumference)</th>
<th>Medial proteoglycan score</th>
<th>Fibrin/thrombus score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix 035</td>
<td><img src="chart1" alt="" /></td>
<td><img src="chart2" alt="" /></td>
<td><img src="chart3" alt="" /></td>
<td><img src="chart4" alt="" /></td>
</tr>
<tr>
<td>IN.PACT DCB</td>
<td><img src="chart5" alt="" /></td>
<td><img src="chart6" alt="" /></td>
<td><img src="chart7" alt="" /></td>
<td><img src="chart8" alt="" /></td>
</tr>
<tr>
<td>POBA</td>
<td><img src="chart9" alt="" /></td>
<td><img src="chart10" alt="" /></td>
<td><img src="chart11" alt="" /></td>
<td><img src="chart12" alt="" /></td>
</tr>
</tbody>
</table>

Lutonix 035: n=5, IN.PACT DCB: n=5, POBA: n=4

P-values:
P=0.21
P=0.22
P=0.14
P=0.41
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)

SMC loss score (Circumference)

Medial proteoglycan score

Fibrin/thrombus score

P=0.004

P=0.02

P=0.01

P=0.02

P=0.01

P=0.007

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).
### Distal Embolization (%)

#### 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
  - P=0.04

- **Overlapping Balloons (3x)**
  - Lutonix 035: 7.7% (0-15.4) n=5
  - IN.PACT: 38.5% (15.4-42.3) n=5
  - P=0.07

**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><strong>Number of micro-vessels with paclitaxel-associated findings</strong></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><strong>Paclitaxel concentration in downstream tissues (ng/g)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>60.8 (32.6-118.1)</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>170.9 (19.7-221.5)</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>16.1 (12.8-319.2)</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
Acknowledgments

Funding
CVPath Institute Inc.

CVPath Institute
Hiroyuki Jinnouchi, MD
Sho Torii, MD
Atsushi Sakamoto, MD
Anne Cornelissen, MD
Maria Romero, MD
Abebe Atiso, HT
Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Liang Guo, PhD
Renu Virmani, MD

Washington DC
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

(None observed for 1x dose at 180 days)
Histological Findings of Emboli / Vascular Changes, Skeletal Muscle Arteries

Lutonix 035 x3 (2µg/mm² paclitaxel) at 90-days

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

<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><strong>38</strong></td>
<td><strong>9</strong></td>
<td><strong>4</strong></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
Histologic Vascular Changes following Lutonix vs. In.Pact DCB Treatment (3x)

Luminal Stenosis, %
P=0.02  P=.044

Neointimal Area, mm²
P=0.02  P=.030
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

Inflammmatory cells

In.Pact (3x)

Fibrinoid necrosis

Lutonix (3x)

Fibrinoid necrosis

Inflammmatory cells

POBA (3x)
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, mm^2**
P = .042
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 anti-platelet therapy
- Biologic effects at 28-days at least
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.

* 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.
**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.*
How DCB drug dose effects vessel healing

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