Are all DCBs the same?

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Conflict of Interest - Disclosure

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

Affiliation/Financial Relationship          Company

Employment in industry: No


Owner of a healthcare company: No

Stockholder of a healthcare company: No
<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>IN.PACT™ Admiral, Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Lutonix® 035 DCB, BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Stellarex®, Spectranetics, Colorado Springs, CO USA</td>
<td>Paclitaxel-polyethylene glycol</td>
<td>2.0</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
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
- 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)
Porcine Pharmacokinetics in SFA

Lutonix formulation designed to achieve a constant drug level in tissue
Lutonix® 035 vs. In.Pact™ Admiral
First Comparative Study in Swine

• Blinded study – Side-by-side
• 1x and 3x dose
• Evaluated skeletal muscle and coronary band at 28 and 90 days
  ▪ Distal drug concentration
  ▪ Histology
    • Distal embolization
    • Vascular changes

Comparison of Particulate Embolization after Femoral Artery Treatment with IN.PACT Admiral versus Lutonix 035 Paclitaxel-Coated Balloons in Healthy Swine
Frank D. Kolodgie, PhD, Erica Pacheco, MS, Kazuyuki Yahagi, MD, Hiroyoshi Mori, MD, Elena Ladich, MD, and Renu Virmani, MD

J Vasc Interv Radiol 2016; 27:1676–1685
Downstream Sampling for Paclitaxel Analysis and Histopathology Assessment

- Evaluated skeletal muscle and coronary band for potential embolic changes
  - Distal paclitaxel concentration
  - Histology
    - Distal embolization
    - Vascular changes
### Downstream Incidence of Distal Embolization (%)

#### Distal Embolization (%)

- **Lutonix 035**: 7.7% (0-11.5) n=5
- **IN.PACT**: 15.4% (11.5-30.8) n=5

#### 28-Day Survival

**Single Balloon (1x)**

- **Lutonix 035**: 7.7% (0-15.4) n=5
- **IN.PACT**: 38.5% (15.4-42.3) n=5

**P=0.04**

**Overlapping Balloons (3x)**

- **Lutonix 035**: 0% (0-11.5) N=5
- **IN.PACT**: 46.2% (19.2-57.7) N=5

**P=0.01**

#### 90-Day Survival

**Single Balloon (1x)**

- **Lutonix 035**: 7.7% (0-11.5) n=5
- **IN.PACT**: 0% (0-11.5) N=5

#### 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>0.009</td>
</tr>
<tr>
<td></td>
<td>60.8 (32.6-118.1)</td>
<td>189.0 (134.0-700.0)</td>
<td>0.02</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></td>
<td>170.9 (19.7-221.5)</td>
<td>871.0 (567.5-1315.0)</td>
<td>0.009</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>
<tr>
<td></td>
<td>16.1 (12.8-319.2)</td>
<td>158.0 (6.3-1178.0)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Downstream Findings in Porcine Skeletal Muscle (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).

High (40x) power images of crystalline material (red arrows) at 28d
In. Pact DCB vs. Stellarex vs. Ranger
The Second Comparative Study

- Same swine model - 28 day study
- 3x dose, same size DCB
- DCB inflated for 60 secs
- Blinded-device ID
- Same sampling method and evaluation endpoints as the first Lutonix vs. IN.PACT comparative study

Treatment Scheme: A total of 2 treated sites in the external femoral arteries (left or right) in each pig.
**Downstream Incidence of Distal Embolization (%)**

**Overlapping Balloons (3x), 28-Day Survival**

### Survival Treatment

<table>
<thead>
<tr>
<th></th>
<th>Second Comparative Study</th>
<th>First Comparative Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IN.PACT (n=12)</td>
<td>Stellarex (n=6)</td>
</tr>
<tr>
<td><strong>Percentage of sections with vascular changes in downstream nontarget tissues (%)</strong></td>
<td>42.9</td>
<td>30</td>
</tr>
<tr>
<td><strong>28-day (3x)</strong></td>
<td></td>
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### Paclitaxel concentration in downstream tissues (ng/g)

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<td>IN.PACT</td>
<td>Stellarex</td>
</tr>
<tr>
<td><strong>28-day (3x)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skeletal muscle</strong></td>
<td>216.5 (326.1-146.2)</td>
<td>911.3 (691.3-1773.8)</td>
</tr>
<tr>
<td><strong>Coronary band</strong></td>
<td>101.9 (44.6-163.8)</td>
<td>962.3 (149.9-1160)</td>
</tr>
</tbody>
</table>

Histologic sections showing Distal Embolization
Downstream changes following IN.PACT vs. Stellarex, dose 3X, at 28 days

IN.PACT

CV38010 R GASTRO1_20x

CV38007 Right Gracilis

Stellarex

CV38012 L SEMM2_20x

CV38010 Left Gastrocnemius
Downstream skeletal muscle fibrosis following IN.PACT vs. Stellarex, dose 3X, at 28 days

IN.PACT

Masson Trichrome

3/168 sections

Stellarex

0/84 sections
Clinical Relevance

- DCBs which obtain effective drug transfer into the arterial wall while minimizing downstream embolic effects are the goal.

Different test methods may yield different results. Pre-clinical test data on file. Pre-clinical test results may not be indicative of clinical performance and different test methods may yield different results.
Acknowledgments

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Liang Guo, PhD
Renu Virmani, MD

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Lutonix DCB in swine AV-shunt model

Distal Femoral Vein

Balloons 6.0 cm

Anastomosis

Proximal Femoral Artery

Distal Femoral Artery

DCB

POBA

Anastomosis

60-day result

Distal vein
Lutonix DCB in swine AV-shunt model

- Lutonix DCB: n=5 in 28-day, n=7 in 60-day
- POBA: n=4 in 28-day, n=7 in 60-day

**%stenosis**
- 28-day: p=NS
- 60-day: p=0.03

**medial injury**
- 28-day: p=NS
- 60-day: p=NS

**EC loss**
- 28-day: p=NS
- 60-day: p=NS

**PG/Collagen deposition**
- 28-day: p=NS
- 60-day: p=0.03

**medial SMC loss (depth)**
- 28-day: p=NS
- 60-day: p=0.01

**medial SMC loss (circ)**
- 28-day: p=NS
- 60-day: p=NS
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