Not all DCBs are created equal
Side by side pre-clinical safety evaluation of leading DCBs

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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

Honorarium: 480 Biomedical, Abbott Vascular, Boston Scientific, CeloNova, Claret Medical, Cordis J&J, Lutonix, Medtronic, Merck, ReCor, Terumo Corporation, and W.L. Gore.

## 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>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Lutonix DCB® (Moxy)</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 in USA.

## HOW IS DCB DIFFERENT FROM DES

<table>
<thead>
<tr>
<th>Parameters that distinguish DCB from DES</th>
<th>DES</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug concentration on the device</td>
<td>Low 5-10 μg/mm</td>
<td>Very High 2-3 μg/mm² (≒20-30 μg/mm)</td>
</tr>
<tr>
<td>Drug transfer at the time of deployment</td>
<td>Slow</td>
<td>Rapid, all at once</td>
</tr>
<tr>
<td>Reservoir of drug</td>
<td>Polymer</td>
<td>No (excipient important)</td>
</tr>
<tr>
<td>Drug retention in tissues</td>
<td>Short term</td>
<td>Need a drug which binds to cell membranes and is easily transferable to adjacent cells</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Lipophilic</td>
<td>yes</td>
<td>Even better</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>Not necessary</td>
<td>Should be active immediately</td>
</tr>
</tbody>
</table>

**Zilver PTX**

- **67.6%** Zilver PTX
- **45.5%** Optimal PTA + BMS

![Graph showing primary patency over years](image1)

![Images of DES, PTX Coated, Uncoated, and DCB](image2)
Requirements For DCB

- Must deliver large quantities of the drug within seconds
- Must 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
- Light microscopy must show biologic effects at 28-days at least
Lutonix Coating Durability

LUTONIX 035

IN.PACT

Note: Clinical data referenced is for the Lutonix 035 DCB.
PTX Adherence to Balloon: iopromide versus urea coating

* p=0.002
** through a blood-filled hemostatic valve and guiding catheter and 1min in stirred blood
*** not released during expansion in a coronary artery

Does Drug Coating Matter?

**Data obtained from two data sets. Virmani preclinical animal data on file. Animal test results may not be indicative of clinical performance. Different test methods may yield different results.**
Histologic Parameters for Evaluation of DCB Safety/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>1x dose</th>
<th>28-days</th>
<th>90-days</th>
<th>180-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;E</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>Actin</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>
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<tr>
<td>Movat</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
</tr>
<tr>
<td>Masson</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Vascular, downstream, and pharmacokinetic responses of Lutonix to treatment with a low dose drug-coated balloon in a swine femoral artery model.
Vascular Changes in Downstream Skeletal Muscle

(None of physiological significance observed for Lutonix DCB 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
Rare Changes in Downstream Porcine Skeletal Muscle: None of Physiological Significance

LUTONIX® DCB Catheter Final Formulation

(1x dose) vs (4x dose)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time Point</th>
<th>*Total Vessels with changes in Skeletal Muscle/Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x</td>
<td>28 Days</td>
<td>0.0035</td>
</tr>
<tr>
<td></td>
<td>90 Days</td>
<td>0.0046</td>
</tr>
</tbody>
</table>

*Mean of only sections showing changes
Histologic findings of emboli/vascular changes by coronary band and skeletal muscle territories in swine peripheral artery following Lutonix drug coated balloon X3 (2µg/mm² paclitaxel) dilatation at 90-days

Loss of medial SMCs with 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
Histologic findings of emboli/vascular changes by coronary band and skeletal muscle territories in swine peripheral artery following IN.PACT AMPHIRION DCB x3 (3µg/mm² paclitaxel) dilatation at 90-days

38/78 (48.7%) 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
Safety Profile
All about Balancing Safety, Efficacy and Biologic Response

Not all balloons are created equal

Efficacy
More

Less neointima
Absence of restenosis
No, early or late thrombosis

Safety
Less

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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