Pre-clinical comparison of drug coated balloons

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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
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><strong>Advance 18 PTX™</strong></td>
<td>Cook Medical, Bloomington, IN, USA</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cotavance</strong></td>
<td>Bayer Schering Pharma AG, Berlin, Germany</td>
<td>Paclitaxel–iopromide</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Freeway™</strong></td>
<td>Eurocor, Bonn, Germany</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>In.Pact™ Admiral</strong></td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Lutonix® 035 DCB</strong></td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Legflow</strong></td>
<td>Cardionovum, Warsaw, Poland</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
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<tr>
<td><strong>Passeo-18 Lux®</strong></td>
<td>Biotronik, Bülach, Switzerland</td>
<td>Paclitaxel–butyryl-tri-hexyl citrate</td>
<td>3.0</td>
<td>Yes</td>
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<tr>
<td><strong>Stellarex®</strong></td>
<td>Spectronetic, Mansfield, MA, USA</td>
<td>Paclitaxel/Polyethylene glycol</td>
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<tr>
<td><strong>SurVeil™ DCB</strong></td>
<td>SurModics, MN, USA</td>
<td>Paclitaxel-proprietary photolink®</td>
<td>2.0</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

Coating Integrity is Variable

SurVeil™ DCB (dry-expanded)

Lutonix® 035 DCB (dry-expanded)

In.Pact™ (dry expanded)
PTX Adherence to Balloon: iopromide versus urea coating

- Split-off during dry inflation
- Loss during passage**
- Remnant on balloon after deflation ***

* 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

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 response following Lutonix® 035 DCB treatment in Porcine Iliac arteries

1x dose

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>H&amp;E</td>
<td><img src="image1" alt="Image" /></td>
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<td>Masson</td>
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<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
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Paclitaxel uptake in the Arterial Wall

Paclitaxel uptake in arterial wall 15-25 minutes Post stent implantation (n= 6 arteries each)

Equal Amounts Drug

Not all drug concentrations are equal

Long-Term Biologic Activity as Solid Phase Paclitaxel Dissolves

Short-Term Biologic Activity as Paclitaxel is Cleared

DRUG PHASE DETERMINES DURATION OF BIOLOGIC ACTIVITY: IN.PACT ADMIRAL DRUG COATED BALLOON
IN.PACT™ ADMIRAL™ MAINTAINS GREATER DRUG IN TISSUE THAN LUTONIX™* DCB

- While there is expected variability across studies, IN.PACT™ Admiral™ consistently provides higher PTX tissue concentration than Lutonix™* DCB through 90 days.
- Paclitaxel available for both IN.PACT™ Admiral™ and Lutonix™* DCB post-24 hours, but IN.PACT™ Admiral™ achieves sustained effect through slow release of solid-phase paclitaxel reservoirs.

Arterial Tissue Concentration

![Graph showing arterial tissue concentration over time for different DCB types.](image)

**Note:** Data on file with Medtronic

Granada, J; JACC INT, 2015

**Note:** Boston Scientific Ranger DCB is not available in the United States.
Burst release of soluble paclitaxel leads to higher short-term SMC loss, but acute toxic injury, signified by fibrin deposition and extended SMC loss.

Note: Data on file with Medtronic
Burst release of soluble paclitaxel leads to higher short-term SMC loss, but acute toxic injury, signified by fibrin deposition and extended SMC loss.

Moderated release of soluble paclitaxel via solid phase drug depots yields prolonged anti-proliferative effect resulting in less neointima formation.

Note: Data on file with Medtronic.
IN.PACT™ Drug Eluting Balloon: Medtronic

Preclinical Response

Histomorphometry of Treated Porcine Arteries*

**Neointimal / Medial Inflammation Score**

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**Neointimal Proteoglycan / Collagen Score**

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**Medial SMC Loss (Depth)**

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**Medial SMC Loss (Circumf)**

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**Paclitaxel action**

- Very mild neointimal / medial inflammation resolved by 180 days
- SMC loss at indicating pharmacological activity of paclitaxel

*Medtronic data on file
PRE-CLINICAL EVALUATION SUPPORTS EFFICACY

Control (POBA)

Therapeutic Dose (1x)
The “optimal” features of DCB response

Safety Margin Dose (3x)
Biological Drug Effect following SurVeil™ DCB treatment at 28-days in Porcine Iliofemoral arteries

Semi-Quantitative Scoring

Markers of Drug Effect at 28-days

- Medial PG/Collagen
- Medial SMC Loss (Depth)
- Medial SMC Loss (Circumf)
- EC Loss
- Medial/Intimal Fibrin
- Medial/Intimal Inflamm

POBA Control
Tissue drug concentration following SurVeil™ DCB treatment

Tissue Concentration (µg/g)

40mm Balloons

0 day 7 day 14 day 21 day 28 day

SurModics SurVeil

- SurVeil treatment reduces tissue drug concentration over time.
High Transfer Efficiency

Arterial Pharmacokinetics

- **Stellarex (2 µg/mm² dose)**
- **Competitor A (2 µg/mm² dose)**
- **Competitor B (3.5 µg/mm² dose)**

- 2µg/mm²
- PEG Excipient (Polyethylene Glycol)
- Open folded CADD* coating technology
  (Controlled Automated Drug Deposition)
Vascular response following Stellarex® DCB treatment in Porcine Iliac arteries

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Neointimal Proteoglycan Collagen Score

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Adventitial Fibrosis Score
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**Therapeutic Dose (1x)**

The “optimal” features of DCB response

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**Safety Margin Dose (3x)**

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Summary

- The effect of drug-coated balloon is characterized by smooth muscle cell loss accompanied with proteoglycan and collagen deposition of media in animal models.
- Endothelial loss and inflammation was minimal.
- The peak effect was observed from 28-day to 90-day.
- Coating excipient is what makes the difference.
- Success will be clinically determined and is dependent on the duration paclitaxel remains within the arterial wall. This must be accompanied by absence of thrombosis, persistent vessel patency, and absence of restenosis. Improvement in Rutherford class must be observed and absence of chronic limb ischemia.
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**
  - More

- **Use of Carrier / Excipient**
  - Less

- **Drug Retention**
  - More

- **Repeat Inflations**
  - Less
Acknowledgments

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