Requirements For DCB

- 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>Eurostar</td>
<td>Biotronik, Bülach, Switzerland</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
</tr>
<tr>
<td>In.Pact™</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel–butyryl-tri-hexyl-citrate</td>
<td>3.0</td>
<td>No → 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–polysorbate/sorbitol</td>
<td>2.0</td>
<td>No</td>
</tr>
<tr>
<td>Stellarex®</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>No</td>
</tr>
</tbody>
</table>

Lutonix® 035 vs. In.Pact™ Differences

- **Lutonix® 035**
  - Drug Coated Balloon
  - Drug dose: 2 µg/mm²
  - Carrier: Polysorbate & Sorbitol
  - Systemic Downstream Effects: None
  - Systemic Product Line: FDA Approved/ BTK Ongoing Trial

- **In.Pact™**
  - Drug Coated Balloon
  - Drug dose: 3.5 µg/mm²
  - Carrier: Polysorbate & Sorbitol
  - Systemic Downstream Effects: FDA Approved/ BTK Product Recall 2014
  - Systemic Product Line: FDA Approved/ BTK Ongoing Trial

PACLITAXEL IS A WELL UNDERSTOOD ANTI-PROLIFERATIVE

- Paclitaxel identified as an inhibitor of mitosis by promoting and stabilizing microtubules within the cell
- Benefits in oncology applications established in ovarian cancer
- Coronary drug-eluting stent trials demonstrate paclitaxel exerts an anti-restenotic effect on atherosclerotic coronary arteries
- To maintain long-term therapeutic effect, paclitaxel must remain in tissue to offset restenosis

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

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PRE-CLINICAL METHODS USED TO INVESTIGATE DIFFERENCES IN CLINICAL OUTCOMES

How does coating formulation, including paclitaxel dose and excipient, influence these differing outcomes?

Hypothesis: Balance between solid and soluble phase paclitaxel moderates prolonged tissue response

Methods:

1. Characterize the transition of paclitaxel from solid to soluble phases:
   - IN.PACT Admiral™ DCB and Lutonix™ DCB
   - Assess 28-day tissue response in terms of cell proliferation and neointima formation
   - Compare the tissue response to different coating formulations

DRUG PHASE DETERMINES DURATION OF BIOLOGIC ACTIVITY

- Not all drug concentrations are equal
- Solid phase drug presence achieves sustained effect through slow release of solid-phase paclitaxel reservoirs
- Burst release of soluble paclitaxel leads to higher short-term SMC loss, but acute toxic injury, signified by fibrin deposition and extended SMC loss
- Prolonged anti-proliferative effect resulting in less neointima formation
- Solid-phase paclitaxel dissolution determines prolonged biologic activity

INFLUENCE OF EXCIPIENT ON DRUG DISSOLUTION

- Coating formulations (drug dose + excipient) affect availability of solid phase drug
- IN.PACT™ Admiral™ DCB formulation exhibits prolonged solid phase drug presence relative to burst release of Lutonix™ DCB
- IN.PACT Admiral™ DCB excipient does not impact rate of paclitaxel dissolution, while Lutonix™ DCB polysorbate/sorbitol-based acts as an emulsifier and accelerates drug dissolution

TISSUE RESPONSE AT 28 DAYS

1. SMC Loss: Burst release of soluble paclitaxel leads to higher short-term SMC loss, but acute toxic injury, signified by fibrin deposition and extended SMC loss
2. Fibrin Deposition: Paclitaxel dissolution determines prolonged tissue response
3. Resulting Neointima: Burst release of soluble paclitaxel leads to higher short-term SMC loss, but acute toxic injury, signified by fibrin deposition and extended SMC loss
4. Rebound Proliferation: Moderate release of soluble paclitaxel via solid phase drug deposits yields prolonged anti-proliferative effect resulting in less neointima formation

Note: Data on file with Medtronic
**SEM IN.PACT™ DEB in Swine Iliofemoral Model**

- **1-Day**
  - Uniform drug effect
  - Endothelial recovery

- **28-Days**

**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>Skeleton muscles, Gastronemious Muscle, Gluteus Maximus Muscle, Gracilis Muscle, Biceps Femoris Muscle, Semimembranosus Muscle, and Semitendinosus Muscle and coronary band</td>
<td>Same</td>
</tr>
<tr>
<td>28 d treated SFA N</td>
<td>3x ±5; 3x ±5</td>
<td>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>

**Histologic Vascular Changes following Lutonix 035 vs. IN.PACT DCB Treatment (3x) at 28 and 90 days**

- **SMC loss score (Depth)**
  - Lutonix 035: n=5, In.Pact DCB: n=5, POBA: n=4
  - Medial proteoglycan score
  - Fibrin/thrombus score

- **Luminal stenosis, %**
  - Lutonix 035: n=5, In.Pact DCB: n=5, POBA: n=4

**Vascular Changes in Skeletal Muscle (at 28-Day)**

- **In.Pact (1x)**
- **In.Pact (3x)**
- **Lutonix (1x)**
- **Lutonix (3x)**

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 arrows), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).

**Embobilization Incidence(%)**

- **Lutonix DCB(3x)**
- **In.Pact (3x)**
- **POBA(3x)**
- **Lutonix DCB(3x)**
- **In.Pact (3x)**
- **POBA(3x)**
Safety Profile: All about Balancing Safety, Efficacy and Biologic Response
Not all Balloons are Created Equal

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

Efficacy
- Less neointima
- Absence of restenosis
- No, early or late thrombosis

- Rapid Vascular Healing
- Good Re-Endothelialization
- No distal Embol

Rapid Vascular Healing
- Good Re-Endothelialization
- No distal Embol

Rapid Vascular Healing
- Good Re-Endothelialization
- No distal Embol

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VEITH SYMPOSIUM
Connecting the Vascular Community