DESIGN GOALS AND PRE-CLINICAL EVIDENCE OF NEXT GENERATION DCB

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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:

SUSTAINABILITY OF BIOLOGICAL EFFICACY OVER TIME: A NEED FOR HEAD TO HEAD RCT

<table>
<thead>
<tr>
<th>DCB</th>
<th>Dose (µg/mm²)</th>
<th>Excipient</th>
<th>RCT Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutonix 035 (Bard)</td>
<td>2.0</td>
<td>Polysorbate &amp; Sorbitol</td>
<td>1- and 2-year</td>
</tr>
<tr>
<td>IN.PACT (Medtronic)</td>
<td>3.5</td>
<td>Urea</td>
<td>1-, 2-, and 3-year</td>
</tr>
</tbody>
</table>

### LEVANT II Trial¹-²

<table>
<thead>
<tr>
<th>Year</th>
<th>DCB</th>
<th>Blinded Core Lab-adjudicated primary patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year</td>
<td>Lutonix 035</td>
<td>73.5%</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>56.8%</td>
</tr>
<tr>
<td>2-Year</td>
<td>Lutonix 035</td>
<td>58.6%</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>53.0%</td>
</tr>
<tr>
<td>3-Year</td>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

### IN.PACT SFA Trial³-⁵

<table>
<thead>
<tr>
<th>Year</th>
<th>DCB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year</td>
<td>IN.PACT Admiral</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>55.8%</td>
</tr>
<tr>
<td>2-Year</td>
<td>IN.PACT Admiral</td>
<td>78.9%</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>50.1%</td>
</tr>
<tr>
<td>3-Year</td>
<td>IN.PACT Admiral</td>
<td>69.5%</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>45.1%</td>
</tr>
</tbody>
</table>

Primary patency definitions:
- LEVANT II defined primary patency as PSVR ≤ 2.5 and freedom from TLR¹-²;
- IN.PACT SFA defined primary patency as PSVR ≤ 2.4 and freedom from CD-TLR³-⁵.

DCB: PROPOSED MECHANISM OF ACTION

(1) Paclitaxel Particle Adhesion

(2) Paclitaxel Particle Surface Retention

(3) Paclitaxel Particle Solubility

(4) Paclitaxel Tissue PK

Granada JF. TCT2009

Picture courtesy of BSCI

Picture courtesy of Medtronic

Picture courtesy of Spectranetics
IMPACT OF PACLITAXEL COATING TYPE ON DOWNSTREAM PARTICLE EMBOLIZATION

EXPERIMENTAL EVALUATION OF DCB USE IN THE SFA TERRITORY IN PRESENCE OF DISTAL WOUNDS

Wound Creation; Bilateral Treatment
PTA or DCB x1 vs. DCB x3 (5-6 mm x 80 mm)

Pictures courtesy of Bob Melder, Medtronic
PACLITAXEL PARTICLE SOLUBILITY DETERMINES LONG TERM PACLITAXEL TISSUE LEVELS

Gongora CA. JACC Cardiovasc Interv. 2015;8:1115-23

NEXT GENERATION DCB FEATURES

- Controlled crystallinity
- Reproducible drug content
- Predictable tissue levels
- Long residency time
- Low particulate content

Granada JF. Interventional Cardiology (2E). Chapter 32
Acute Drug Transfer

Particulate Formation

Coating Stability

Acute Drug Transfer

IN VITRO PARTICULATE FORMATION

Gongora CA. JACC Cardiovasc Interv. 2015 Jul;8(8):1115-23

COATING TYPE IMPACTS PARTICULATE FORMATION, ACUTE DRUG TRANSFER AND TISSUE RESIDENCY

1ST GENERATION DCB COATING

Highly Crystalline Drug Content Variability
Inconsistent Tissue Levels
High Residency Time
High Particulate Content

NEWER GENERATION DCB COATINGS

Decreased Paclitaxel Particle Solubility
Controlling Paclitaxel Particle Crystallinity
Encapsulating Paclitaxel Particles

REDUCTION IN BALLOON PACLITAXEL CONTENT
IMPACT OF PACLITAXEL BALLOON DOSE IN NEOINTIMAL PROLIFERATION (RESTENOSIS)

Granada JF. JACC Cardiovasc Interv, Oct 2012

Cotavance DCB Reduction in %AS

- SFA, ISR-Model
- High-cholesterol swine
- 1-µg/mm²: 13.2% (p=0.5) VS. PTA
- 3-µg/mm²: 26% (p<0.04) VS. PTA
**IMPACT OF LOWER DOSE PACLITAXEL CONCENTRATION ON NEOINTIMAL PROLIFERATION**

QVA % DIAMETER STENOSIS AT 42 DAYS IN THE FAMILIAL HYPERCHOLESTEROLEMIA MODEL OF SFA RESTENOSIS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Termination</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 Days</td>
<td>42 Days</td>
<td>2-mcg/mm²</td>
</tr>
<tr>
<td>QVA</td>
<td>QVA</td>
<td>3.5-mcg/mm²</td>
</tr>
<tr>
<td>PTA</td>
<td>OCT</td>
<td>In.Pact Admiral</td>
</tr>
<tr>
<td>Stellarex</td>
<td></td>
<td>In.Pact Admiral</td>
</tr>
<tr>
<td>Lutonix</td>
<td></td>
<td>PTA</td>
</tr>
</tbody>
</table>

Data on File, Skirball Center for Innovation
CONCLUSIONS

• A strong clinical foundation support the use of DCB technologies in the SFA territory (when clinically indicated)
• The mechanism of action of DCB appears to be clearer; particle coating solubility clearly impact clinical outcomes
• One-year efficacy data is promising for all DCB; however, sustainability of the clinical effect will drive clinical adoption
• In the SFA territory, the safety profile of DCB has been proven; then, new generation DCB technologies must focus in matching or exceeding current clinical DCB performance
• Lower-dose DCB have the potential to reduce downstream particle embolization without compromising biological efficacy allowing the potential use in other vascular applications
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