THE EVOLUTION OF DCB TECHNOLOGY

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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:

Early Skepticism
Drug Eluting Balloon Misnomer
Does It Really Elutes or Even Works?

1st Generation Drug Coated Balloons:
• Passive coating:
  • Drug (lipophilic)
  • Carrier (contrast, lipids, others)
• Mechanically transfers drugs
• No intrinsic delivery system
• Drug elution occurs as a passive and uncontrolled phenomenon
• Variable tissue retention rates

What We Want to Achieve:
• Replace stent-based drug elution
• Reduce restenosis
• Shorten vascular healing time
• Broaden the applicability of local drug delivery (diffuse disease).

...that type technology is a huge leap of faith!

Granada JF. The PACCOCATH Technology. TCT2009
BIOLOGICAL PROOF OF PRINCIPLE

DEB in SFA Evidence: FIH Trials
7 Trials / 6 DEB Technologies; 6-month LLL (Primary Endpoint)

<table>
<thead>
<tr>
<th>Technology</th>
<th>PTX Concentration</th>
<th>Excipient</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACCOCATH</td>
<td>PTX 3µgr/mm²</td>
<td>+ Ultravist</td>
<td>7 Trials / 6 DEB Technologies; 6-month LLL (Primary Endpoint)</td>
</tr>
<tr>
<td>LUTONIX</td>
<td>PTX 2µgr/mm²</td>
<td>+ Sorbitol</td>
<td></td>
</tr>
<tr>
<td>INVATEC-MDE</td>
<td>PTX 3µgr/mm²</td>
<td>+ Urea</td>
<td></td>
</tr>
<tr>
<td>PASSEO 18 LUX</td>
<td>PTX 3µgr/mm²</td>
<td>+ BTHC</td>
<td></td>
</tr>
<tr>
<td>ADVANCE PTX</td>
<td>PTX 3µgr/mm²</td>
<td>NO Excipient</td>
<td></td>
</tr>
<tr>
<td>STELLAREX</td>
<td>PTX 2µgr/mm²</td>
<td>Polymer-Based</td>
<td></td>
</tr>
</tbody>
</table>

7 Trials / 6 DEB Technologies; 6-month LLL (Primary Endpoint)

Early Skepticism

Mechanistic Speculations
PROPOSED MECHANISM OF ACTION (2009)

PACCOCATH (2009)
Granada JF. Open Heart. 2014

IN.PACT

STELLAREX

PACLITAXEL COATING MORPHOLOGY DETERMINES PARTICLE ADHESION AND TISSUE PHARMACOKINETICS

STELLAREX (SPECTRANETICS)

RANGER (BOSTON SCIENTIFIC)

PACLITAXEL PARTICLE SOLUBILITY DETERMINES LONG TERM PACLITAXEL TISSUE LEVELS

**NEXT GENERATION DCB FEATURES**
- Controlled crystallinity
- Reproducible drug content
- Predictable tissue levels
- Long residency time
- Low particulate content

Figure courtesy of Medtronic

Gongora CA. JACC Cardiovasc Interv. 2015

Granada JF. Interventional Cardiology. 2016
Early Skepticism

Mechanistic Speculations

Panic Phase
THEORETICAL CONCERNS

Biological effect of long-term Paclitaxel tissue residency in wound healing?

IN VITRO STUDIES
Gongora CA. JACC Cardiovasc Interv. 2015 Jul;8(8):1115-23
IMPACT OF PACLITAXEL COATING TYPE ON DOWNSTREAM PARTICLE EMBOLIZATION

MAJOR ADVERSE CLINICAL EVENTS IN RCT OF DCB USE IN THE SFA TERRITORY

12-Month Key Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>LEVANT II&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Global&lt;sup&gt;2&lt;/sup&gt;</th>
<th>IN.PACT SFA&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Long&lt;sup&gt;4&lt;/sup&gt;</th>
<th>IN.PACT Global CTO&lt;sup&gt;5&lt;/sup&gt;</th>
<th>ISR&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Clinical&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTA</td>
<td>Lutonix 035</td>
<td>PTA</td>
<td>IN.PACT Admiral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>160</td>
<td>316</td>
<td>691</td>
<td>111</td>
<td>220</td>
<td>157</td>
<td>126</td>
</tr>
<tr>
<td>All Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.7% (4/107)</td>
<td>1.4% (3/207)</td>
<td>3.7% (5/134)</td>
</tr>
<tr>
<td>Revasc. due to Thrombosis</td>
<td>0.7% (1/140)</td>
<td>0.4% (1/285)</td>
<td>1.3% (8/634)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Amputation</td>
<td>0.0% (0/140)</td>
<td>0.3% (1/286)</td>
<td>0.5% (3/635)</td>
<td>0.0% (0/107)</td>
<td>0.0% (0/207)</td>
<td>0.0% (0/134)</td>
<td>0.0% (0/115)</td>
</tr>
</tbody>
</table>

7. Presented by Jaff M, VIVA Las Vegas 2016; includes subjects of imaging cohorts: Long Lesion, CTO, and ISR.

DOES DISTAL DOWNSTREAM PARTICLE EMBOLIZATION IMPACT WOUND HEALING AND COULD IT AFFECT CLINICAL OUTCOMES?
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)

Paclitaxel Concentration in Skin

Hollander Scoring-Margin Separation

Pictures courtesy of Bob Melder, Medtronic
Early Skepticism

Mechanistic Speculations

Panic Phase

Data-Driven Field
1-YEAR DCB EFFICACY IN PIVOTAL RCT

12-Month Primary Patency

<table>
<thead>
<tr>
<th>Patients</th>
<th>DCB (ptx 2 µg/mm²)</th>
<th>PTA (ptx 3.5 µg/mm²)</th>
<th>DCB (ptx 2 µg/mm²)</th>
<th>PTA (ptx 2 µg/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>82.3%</td>
<td>70.9%</td>
<td>89.0%</td>
<td>65.0%</td>
</tr>
<tr>
<td>295</td>
<td>82.2%</td>
<td>52.4%</td>
<td>89.0%</td>
<td>52.4%</td>
</tr>
<tr>
<td>331</td>
<td>73.5%</td>
<td>56.8%</td>
<td>82.2%</td>
<td>52.4%</td>
</tr>
<tr>
<td>476</td>
<td>70.9%</td>
<td>56.8%</td>
<td>73.5%</td>
<td>56.8%</td>
</tr>
</tbody>
</table>

Core-lab adjudicated Duplex derived Primary Patency based on PSVR ≤2.4 (*) or ≤2.5 (†) KM survival estimates at 360 (†) or 365 (‡) days.

1. S.Lyden - ILLUMENATE Pivotal Stellarex DCB IDE Study 12-month Results - oral presentation, TCT 2016
2. M.Brodmann - ILLUMENATE European Randomized Clinical Trial: 12-month Final Results from the Stellarex DCB – oral presentation, AMP 2016
**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>Primary Patency</th>
<th>Δ (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lutonix 035</td>
<td>73.5%</td>
<td>16.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>56.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Lutonix 035</td>
<td>58.6%</td>
<td>5.6%</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>53.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Not available</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IN.PACT SFA Trial³-⁵

<table>
<thead>
<tr>
<th>Year</th>
<th>DCB</th>
<th>Primary Patency</th>
<th>Δ (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IN.PACT Admiral</td>
<td>87.5%</td>
<td>31.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>55.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>IN.PACT Admiral</td>
<td>78.9%</td>
<td>28.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>50.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>IN.PACT Admiral</td>
<td>69.5%</td>
<td>24.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>PTA</td>
<td>45.1%</td>
<td></td>
<td></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.

Early Skepticism

Mechanistic Speculations

Panic Phase

Technology Adoption Competitive Landscape

Data-Driven Field
EXPANSION OF CLINICAL EVIDENCE
- Long lesions, ISR
- High calcium burden
- Use with ancillary devices

NEW CLINICAL APPLICATIONS
- Below the Knee
- AVG/AVF
- Others (i.e., venous)

ADOPTION AND EXPANSION

DCB TECHNOLOGIES 2017
(FUTURE OPPORTUNITIES)

TECHNOLOGY EVOLUTION

TECHNOLOGY ITERATION
- Longer tissue retention
- Lower concentration
- Liquid-based drug delivery

TECHNOLOGY DISRUPTION
- Alternative drugs
- Local delivery of biologics
- Alternative delivery methods
IMPACT OF LOWER DOSE PACLITAXEL CONCENTRATION ON NEOINTIMAL PROLIFERATION

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


PRESSANA™ PRECISION DELIVERY SYSTEM

Walker CM. NCVH 2016

CRYSTALLINE SIROLIMUS DCB


ENCAPSULATED SIROLIMUS DCB (MEDALLIANCE)

MICROPOROUS BALLOON PTA SYSTEM (CALIBER)


ULTRASOUND FACILITATED DRUG DELIVERY
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; specific coating features clearly impact clinical outcomes
• One-year efficacy data is promising for all DCB; however, sustainability of the clinical effect will drive clinical adoption
• Downstream paclitaxel particle embolization is a real phenomenon; however, the impact of paclitaxel tissue residence on wound healing in the presence of appropriate distal vessel run-off may not be of clinical significance
• The local drug delivery field continues to evolve and future investments in DCB iterations are worth it, as long as sustainability of favorable clinical outcomes can be maintained over time
THE EVOLUTION OF DCB TECHNOLOGY

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