DOES PACLITAXEL INTERFERE WITH WOUND HEALING?

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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:

PROPOSED MECHANISM OF ACTION (2009)

PACCOCATH (2009)
Granada JF. Open Heart. 2014

PACLITAXEL COATING MORPHOLOGY DETERMINES PARTICLE ADHESION AND TISSUE PHARMACOKINETICS

STELLAREX (SPECTRANETICS)


15 Min 1 Day 3 Days 7 Days 14 Days
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>

<table>
<thead>
<tr>
<th></th>
<th>LEVANT II Trial¹-²</th>
<th>IN.PACT SFA Trial³-⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutonix 035</td>
<td>73.5%</td>
<td>IN.PACT Admiral</td>
</tr>
<tr>
<td>PTA</td>
<td>56.8%</td>
<td>87.5%</td>
</tr>
<tr>
<td><strong>Δ16.7%</strong></td>
<td><strong>P&lt;0.001</strong></td>
<td><strong>Δ31.7%</strong></td>
</tr>
<tr>
<td>2-Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutonix 035</td>
<td>58.6%</td>
<td>IN.PACT Admiral</td>
</tr>
<tr>
<td>PTA</td>
<td>53.0%</td>
<td>78.9%</td>
</tr>
<tr>
<td><strong>Δ5.6%</strong></td>
<td><strong>P=0.05</strong></td>
<td><strong>Δ28.8%</strong></td>
</tr>
<tr>
<td>3-Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td></td>
<td>IN.PACT Admiral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69.5%</td>
</tr>
<tr>
<td><strong>Δ24.4%</strong></td>
<td><strong>P&lt;0.001</strong></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.

THEORETICAL CONCERNS

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

Biological effect of long-term Paclitaxel tissue residency in wound healing?
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>Subjects</th>
<th>LEVANT II</th>
<th>Global</th>
<th>IN.PACT SFA</th>
<th>Long</th>
<th>IN.PACT Global CTO</th>
<th>IN.PACT Global ISR</th>
<th>Clinical</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>3.7%</td>
<td>1.4%</td>
<td>3.7%</td>
<td>4.3%</td>
<td>0.8%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Revasc. due to Thrombosis</td>
<td>0.7%</td>
<td>0.4%</td>
<td>1.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1/140)</td>
<td>(1/285)</td>
<td>(8/634)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Amputation</td>
<td>0.0%</td>
<td>0.3%</td>
<td>0.5%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>(0/140)</td>
<td>(1/286)</td>
<td>(3/635)</td>
<td>(0/107)</td>
<td>(0/207)</td>
<td>(0/134)</td>
<td>(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 DCB USE IN THE PRESENCE OF DISTAL LIMB WOUNDS

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

Hollander Scoring-Margin Separation

DCB 1x versus PTA

DCB 3x versus PTA

Pictures courtesy of Bob Melder, Medtronic.
WOUND HEALING RESPONSE AND PACLITAXEL TISSUE LEVELS

ATRROWS INDICATE WOUND MARGIN

Re-Epithelialization

Dermal Inflammation

Drug Concentration (mg/ml)

Paclitaxel Concentration in Skin

PTA

DCBx1

DCBx3

Day 0

Day 14

Day 28

Pictures courtesy of Bob Melder, Medtronic
CONCLUSIONS

• Complications following DCB use in the SFA territory are rare and not any different compared to PTA controls
• Paclitaxel particle solubility impacts sustained drug tissue residence and long term anti-proliferative activity
• Downstream paclitaxel particle dislodgment is a real phenomenon and occurs in all DCB technologies
• Experimental data suggests that the use of a DCB in the SFA territory in the early phases of wound healing does not affect healing response
• However, the impact of paclitaxel tissue residence on wound healing in the presence of poor distal vessel run-off is still unknown and deserves further investigation
• The development of DCB displaying lower paclitaxel particle dislodgment rates is worth it, as long as the sustainability of the anti-restenotic effect could be maintained over-time
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