SELUTION SLR – a Sirolimus DEB: Use of preclinical studies in predicting device safety

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Employment in industry: No

Honorarium:
Amgen; Abbott Vascular; Biosensors; Boston Scientific; Celonova; Cook Medical; CSI; Lutonix Bard; Sinomed; Terumo Corporation.

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Owner of a healthcare company: No

Stockholder of a healthcare company: No
Common anti-restenotic drug for DCB is **Paclitaxel**

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Drug</th>
<th>Drug dose (µg/mm²)</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN. PACT Admiral</td>
<td>Medtronic, Minneapolis, MN, USA</td>
<td>Paclitaxel</td>
<td>3.5</td>
<td>Urea</td>
</tr>
<tr>
<td>Lutonix</td>
<td>C.R. BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Polysorbate/Sorbitol</td>
</tr>
<tr>
<td>Ranger</td>
<td>Boston Scientific, Marlborough, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Citrate ester</td>
</tr>
<tr>
<td>Stellarex</td>
<td>Philips, Amsterdam, The Netherlands</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>SeQuent Please</td>
<td>B. Braun, Melsungen, Germany</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Resveratrol</td>
</tr>
<tr>
<td>Passeo-18 Lux</td>
<td>Biotronik, Buelach, Switzerland</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Butyryl-tri-hexyl citrate</td>
</tr>
<tr>
<td>LEGFLOW</td>
<td>Cardionovum GmbH, Bonn, Germany</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Shelloic acid</td>
</tr>
<tr>
<td>SurVeil</td>
<td>SurModics, Eden Prairie, MN, USA</td>
<td>Paclitaxel</td>
<td>3.2</td>
<td>Proprietary photolink</td>
</tr>
<tr>
<td>Lumior</td>
<td>iVascular, Barcelona, Spain</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Water reduce ester</td>
</tr>
<tr>
<td><strong>SELUTION</strong></td>
<td><strong>Med Alliance, Irvine, CA, USA</strong></td>
<td><strong>Sirolimus</strong></td>
<td><strong>1.0</strong></td>
<td><strong>Cell adherent technology</strong></td>
</tr>
<tr>
<td>Magic Touch PTA</td>
<td>Concept Medical, Surat, India</td>
<td>Sirolimus</td>
<td>1.27</td>
<td>Nanolute technology</td>
</tr>
</tbody>
</table>
Sirolimus Coated Balloon benefits

Arterial Drug Concentration (ug/g)

(Presentation Granada at CRT 20140)
Sirolimus Drug Coated Balloons

Sirolimus offers potential benefits over Paclitaxel

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Sirolimus (or Analogs)</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Cytostatic</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Margin of safety</td>
<td>10’000 fold</td>
<td>100 fold</td>
</tr>
<tr>
<td>Therapeutic range</td>
<td>Wide</td>
<td>Narrow</td>
</tr>
<tr>
<td>Anti-restenotic</td>
<td>Yes – lower late lumen loss</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tissue absorption</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Tissue retention</td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>

Sirolimus is *drug of choice* for coronary DES supported by solid clinical based evidence.

Absorption and Retention

<table>
<thead>
<tr>
<th>Paclitaxel</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tends to localize in sub-intimal space and <strong>partitions</strong> significantly in adventitia.</td>
<td>Diffuses <strong>slowly</strong> and spreads throughout entire artery where it <strong>dilutes down</strong> to sub-therapeutic levels.</td>
</tr>
</tbody>
</table>

(Tissue Binding Capacity (TBC) of labeled Dextran, Paclitaxel and Sirolimus in 0.040-mm-thick bovine internal carotid tissue segments. Source: PNAS 2004)
Sirolimus DEB SELUTION: MedAlliance

- Micro-reservoirs made out of biodegradable polymer intermixed with Sirolimus:
  - Controlled and sustained drug release mechanism
  - Maintains therapeutic effect in tissue over long period of time

- Novel Cell Adherent Technology – CAT:
  - CAT transfer membrane houses and protects micro-reservoirs during balloon insertion, lesion crossing and expansion.
  - CAT transfer membrane with embedded micro-reservoirs releases from balloon delivery system and adheres to vessel lumen with short balloon inflation.
Preclinical Study in Rabbit Iliac Artery Model

1 hour post PTA

24 hours post PTA
Preclinical Study in Rabbit Iliac Artery Model

Foamy macrophage

112 day

180 day

Morphometry analysis

p = NS

Neointimal thickness (mm)

Neointimal area (mm²)

Inflammatory score

Medial SMC loss score

112 day (n=3) 180 day (n=3)
Preclinical Study in Porcine Peripheral Artery Model

Peripheral – 28 days histopathology

SELUTION
DCB

CONTROL
POBA

Histological Comparison – Scoring

- Medial Injury: SELUTION DCB 2.6, CONTROL POBA 1.9
- Medial SMC Loss: SELUTION DCB 2.8, CONTROL POBA 0.3
- Medial Fibrin: SELUTION DCB 1.5, CONTROL POBA 0.4

P≤0.05 Statistically Significant

Source: Med Alliance – Histo Study (MEA 439-14).
Preclinical Study (Porcine Coronary Model)

Morphometry analysis

Excipient coated balloon
Non coated balloon
SELUTION 1×
SELUTION 3×

SMC loss (circuit) score

Fibrin score

Injury score

p < 0.05

p = NS

Excipient coated balloon (n=6) Non coated balloon (n=6) SELUTION 1× (n=6) SELUTION 3× (n=6)
Summary

• Sirolimus has wider therapeutic range and thus higher index as compared to paclitaxel.

• Paclitaxel has faster absorption and longer retention of tissue than sirolimus. On the other hand, sirolimus is absorbed slowly and spreads throughout entire artery.

• Medial SMC loss and fibrin scores were relatively higher in SELUTION groups, suggesting the existence of sirolimus drug effect on the vessels wall healing process and not injury alone.

• Sirolimus is drug of choice and maybe a better choice than paclitaxel for peripheral artery and coronary DCBs.
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