Future Concepts for Drug Delivery

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Conflicts of Interest

- **Consultant**
  - Abbott Vascular (non-compensated)
  - AOPA
  - Boston Scientific (non-compensated)
  - Cardinal Health
  - Cordis Corporation (non-compensated)
  - Janacare, Inc
  - Medtronic (non-compensated)
  - Micell, Inc
  - Novella (DSMB)
  - Primacea
  - Valiant
  - Volcano

- **Equity**
  - Access Closure, Inc
  - Embolitech
  - I.C. Sciences, Inc
  - Janacare, Inc
  - MC10
  - Northwind Medical, Inc.
  - PQ Bypass, Inc
  - Primacea
  - Sano V, Inc.
  - Vascular Therapies, Inc

- **Board Member**
  - VIVA Physicians (Not For Profit 501(c) 3 Organization)
    - www.vivapvd.com
    - Intersocietal Accreditation Commission
    - CBSET

January 2016
Attributes of an Ideal DCB Coating

- Facilitate drug retention on balloon during transit
- Effectively release drug from the balloon to the target lesion site
- Provide adhesion of the drug to the vessel wall
- Drug retention upon restoration blood-flow; formation of depot for long-term release
- Facilitate drug uptake by tissue

Excipients can play a critical role in achieving these attributes
DCB Paclitaxel Content
Clinical Efficacy and Safety
### Peripheral Drug-Coated Balloons

<table>
<thead>
<tr>
<th>Company</th>
<th>Device</th>
<th>Drug Coating</th>
<th>Dose (μg/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aachen-Resonance</td>
<td>Elutax</td>
<td>PTx (no carrier)</td>
<td>2</td>
</tr>
<tr>
<td>B. Braun</td>
<td>SeQuent Please</td>
<td>PTx – Iopromide</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paccocath Technology</td>
<td></td>
</tr>
<tr>
<td>Bard-Lutonix</td>
<td>MOXY</td>
<td>PTx – Polysorbate/Sorbitol</td>
<td>2</td>
</tr>
<tr>
<td>Biotronik</td>
<td>Passeo-18 Lux</td>
<td>PTx – BTHC Butyryl-tri-hexyl-Citrate</td>
<td>3</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Ranger</td>
<td>PTx – Acetyl Tributyl Citrate Transpax Technology</td>
<td>2</td>
</tr>
<tr>
<td>Cook Medical</td>
<td>Advance 18 PTx</td>
<td>PTx (no carrier)</td>
<td>3</td>
</tr>
<tr>
<td>Eurocor</td>
<td>Freeway Series</td>
<td>PTx – Shellac</td>
<td>3</td>
</tr>
<tr>
<td>Medtronic</td>
<td>Cotavance</td>
<td>PTx – Iopromide</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paccocath Technology</td>
<td></td>
</tr>
<tr>
<td>Medtronic</td>
<td>IN.PACT Series</td>
<td>PTx – Urea (FreePac)</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>(Admiral, Pacific)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spectranetics</td>
<td>Stellarex</td>
<td>PTx - ?</td>
<td>2</td>
</tr>
</tbody>
</table>
Clinical Differences in Vessel Patency

Effect of Dosing on Safety and Efficacy

<table>
<thead>
<tr>
<th>Dosing Level</th>
<th>LEVANT 1</th>
<th>LEVANT 2</th>
<th>Italian Registry</th>
<th>IN.PACT SFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-mcg/mm²</td>
<td>67,0%</td>
<td>73,5%</td>
<td>83,7%</td>
<td>89,9%</td>
</tr>
<tr>
<td>3.5-mcg/mm²</td>
<td>55%</td>
<td>53,7%</td>
<td>72,4%</td>
<td></td>
</tr>
</tbody>
</table>

Impact of Dosing on Neointimal Proliferation and Restenosis

Paclitaxel inhibits restenosis in peripheral arteries
- SFA, ISR-Model
- High-cholesterol swine
- 28 day follow-up

% Area Stenosis

Paclitaxel DCB Content vs. Surface Particle Adhesion and Tissue Uptake and Distribution
Paclitaxel Coated Balloon Evolution

- Macro-Crystalline
- Amorphous Coating
- Hybrid Coating
- Crystalline Aggregate
- Micro-Crystalline
- Nano-Encapsulation
Effect of DCB Coating Morphology Amorphous vs Crystalline Transpax™

Crystalline Coating Morphology
- Lower PTx solubility
- Slower dissolution rate
- Lower PTx solubility
- Slower dissolution rate
Coating Morphology Determines Particle Adhesion and Tissue Pharmacokinetics

Coating crystallinity producing highly adhesive low-soluble particles may be key to maintain paclitaxel tissue levels overtime.

Picture courtesy of Boston Scientific

Pictures courtesy of Spectranetics
Comparative PK Profile of Several Clinically Available DCB

Gongora CA. JACC Cardiovasc Interv. 2015 Jul;8(8):1115-23
Coating Integrity and Particulate Formation
Coating Integrity and Particulate Implications for DCB Safety

Adherent* Coating During Hydration

Coating Cracking During Hydration

Ranger™ 6X40 (2μg/mm²)
Lutonix Moxy™ 6X40 (2μg/mm²)
In.Pact Pacific™ 6X40 (3μg/mm²)

Gongora CA. JACC Cardiovasc Interv. 2015 Jul;8(8):1115-23
The SurVeil DCB is a combination product intended to improve luminal diameter for the treatment of obstructive *de novo* lesions in femoral and popliteal arteries above the knee.
SurVeil DCB vs. Competitive DCBs

SurModics SurVeil DCB (dry-expanded)

DCB #1 (From EU Market, dry-expanded)

DCB #2 (From US Market, dry expanded)
SurVeil™ DCB Preclinical Performance  
(Swine model, through 90 days)

• **Safe**
  – Treatment with up to 3x DCBs (100% overlap) is well tolerated
  – No downstream emboli, ischemia, necrosis, or scarring
  – No evidence of systemic toxicity

• **Efficient**
  – More drug transferred to target tissues than comparators (3-6 fold)

• ** Desired Biological Effect**
  – Consistent and uniform markers of drug effect
    • Smooth muscle cell loss
    • Proteoglycan deposition
    • Delayed arterial healing
  – Endothelialization nearly complete at 28 days
Robust Biological Drug Effect at 28 days

Results in the swine model. All data from SurModics-sponsored studies.
SurModics Delivers More Drug than Leading DCB

2 µg/mm²

3.5 µg/mm²

Study UTE038: 40mm Balloons

SurModics SurVeil

Comparator DCB

SurModics DCB Drug Delivery:

5 – 6x higher than DCB #2

5x higher than DCB #3

3 – 4x higher than DCB #1
Early Feasibility Study (EFS)

Study Title:
A Prospective, Multi-Center, Single-Arm Trial to Assess the Safety and Feasibility of the SurModics Drug Coated Balloon in the Treatment of Subjects with De Novo Lesions of the Femoropopliteal Artery.

Study Objective:
To assess the safety and functionality of the SurModics drug coated balloon (SurVeil™ DCB) in the treatment of subjects with symptomatic peripheral artery disease (PAD) due to de novo stenoses of the femoral and popliteal arteries.
Study Design

- Prospective, multi-center, single-arm clinical trial
- Trial will enroll up to 15 subjects with symptomatic PAD due to de novo stenoses of the femoral and popliteal arteries.
- All enrolled subjects will be treated with the SurVeil™ DCB
- Up to 3 clinical sites in the United States (US)
Use in Complex Lesions
Dissection Potential and Crossover
to the Use of Stents
## Vessel Dissection in the DCB Era

### Femoro-Popliteal Dissections

<table>
<thead>
<tr>
<th>Location</th>
<th>Study</th>
<th>Dissection Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFA</td>
<td>PACIFIER</td>
<td>73.5%</td>
</tr>
<tr>
<td>SFA-pop</td>
<td>THUNDER</td>
<td>56%</td>
</tr>
<tr>
<td>SFA</td>
<td>LEVANT 2</td>
<td>63.7%</td>
</tr>
</tbody>
</table>

### THUNDER Trial Reported Rates

<table>
<thead>
<tr>
<th>Dissection Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/B</td>
<td>64%</td>
</tr>
<tr>
<td>C/D/E</td>
<td>36%</td>
</tr>
</tbody>
</table>

### Comparison of 6 Month THUNDER Study Angiographic Data

<table>
<thead>
<tr>
<th></th>
<th>PTA w/o Dissections</th>
<th>Dissection Grade A/B</th>
<th>Dissection Grade C/D/E</th>
<th>All Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binary Restenosis</td>
<td>43%</td>
<td>50%</td>
<td>62%</td>
<td>55%</td>
</tr>
<tr>
<td>Patency (Extrapolated)</td>
<td>71%-91%</td>
<td>50%</td>
<td>38%</td>
<td>45%</td>
</tr>
</tbody>
</table>

| TLR Rates                     | 10.5%                | 33%                   | 44%                     | 37%            |

### 24 Month Clinical Results of THUNDER Study

<table>
<thead>
<tr>
<th></th>
<th>Dissection Grade A/B</th>
<th>Dissection Grade C/D/E</th>
<th>All Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR Rates</td>
<td>43%</td>
<td>78%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Sealing Dissections But Decreasing Metal Burden (Tack-It)

130 Patients, 12 Month Patency = 76.4%

- **Tacks in TOBA**
- **Stents**

<table>
<thead>
<tr>
<th>Metal Surface Area (mm$^2$)</th>
<th>130 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stents ≤40mm (n=40)</td>
<td>84.5, 74% Less</td>
</tr>
<tr>
<td>Stents 60-80mm (n=31)</td>
<td>175.9, 78% Less</td>
</tr>
<tr>
<td>Stents ≥100mm (n=24)</td>
<td>276.5, 81% Less</td>
</tr>
</tbody>
</table>

- 81% Less Metal
DCB Use and Adjunctive Therapy

Other PTA Technologies
- Compliant
- Non-Compliant

Rotational Atherectomy
- Rotablator
- CSI Orbital Atherectomy

Scoring Balloons
- Cutting Balloon
- AngioSculpt
- Chocolate Balloon

Other Atherectomy Devices
- Silverhawk/Rockhawk
- JetStream
- Excimer Laser
Pre-Procedure

- DS=100%
- Lesion Length=76.5 mm

Calcification

- Total Length of Calcium=74.8 mm

Lithoplasty Balloon

Post LB/ Final

- Prox. RVD=5.50 mm
- Dist. RVD=6.05 mm
- MLD=4.59 mm
- DS % =21.94%
- 27.5mm OL

Lithoplasty (Shockwave)
Alternative Drugs and Delivery Mechanisms
Sirolimus DCB (SELUTION™)
Cell Adherent Technology (CAT)

Arterial Tissue Drug Concentration
Sirolimus (RAP) versus Paclitaxel (PAX)

Therapeutic Effect ≥ 1 µg/g

28-Day Yucatan Swine High Injury Model

Histological Comparison – Scoring

En Face Scanning Electron Microscope at 24 hours

Virtue (Caliber): Microporous Balloon Angioplasty System

Sirolimus tissue concentrations > 300-fold higher in coronary artery treatment site and target concentration maintained for 28 days

Granada JF, TCT2015
Conclusions

• Drug-eluting technologies are expected to play an expanding role in endovascular treatment of PAD
• DCBs show promising results in the SFA territory in a selected patient population
• New generation DCB technologies have achieved:
  – Optimal transfer rates and tissue retention at low loading doses
  – Lower particulate formation and drug loss in transit
• DCB use may yield relative cost savings in certain clinical situations
• Adjunctive technologies (ie, atherectomy) may be needed to expand the clinical use of DCBs
Future Concepts for Drug Delivery

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