Combo - A Combination Sirolimus Eluting Anti-CD34 Antibody Coated Stent: Technology, Development & Clinical Data

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Vice President, R & D
25 April 2012
Conflict of Interest Disclosure

I am an employee of OrbusNeich Medical, Inc.
### Addressing Unmet Needs with Contemporary PCI

<table>
<thead>
<tr>
<th>• Improve efficacy profile – stable outcomes over time</th>
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<td>• Limit neo-intimal proliferation</td>
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<td>• No chronic inflammation</td>
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<td>• Vessel healing</td>
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<td>• Lowers bleeding risk and its complications</td>
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Stent Surface Coverage by SEM in Stented Porcine Coronary Arteries

Abluminal Sirolimus Drug Delivery
from a completely biodegradable polymer matrix

In vivo elution profile of Combo and Cypher (% of total drug eluted over time)

Full and complete polymer matrix degradation within 90 days

Granada et al., Circ Cardiovasc Intervent. 2010; 3:257-266
Endothelial Progenitor Cell (EPC) Capture

Coronary blood flow

EPCs circulate in the bloodstream

Immobilized antibodies on the stent surface

EPCs are captured by antibodies → EPCs differentiate into endothelial cells → A mature, functional endothelium is formed

Genous stent strut
The REMEDEEE Study: A Randomized Comparison of a Combination Sirolimus Eluting EPC Capture Stent with a Paclitaxel Eluting Stent

Michael Haude, MD
On behalf of the REMEDEEE Investigators
TCT 2011 Late Breaking Clinical Trial
November 11, 2011
REMEDEE Study Design

Objective:
• To demonstrate non-inferiority of the Combo Stent compared to the TAXUS Liberté ® stent for the primary endpoint of 9-month angiographic in-stent late lumen loss

Major Inclusion Criteria:
• Single de-novo lesions in native coronary arteries
• Lesion length ≤ 20 mm
• 2.5 mm to 3.5 mm in diameter

Major Exclusion Criteria:
• Acute Myocardial Infarction
• Ostial lesions
• Unprotected left main with > 50% stenosis
REMEDEE Trial Summation

• FIM 2:1 randomized study
  • 124 Combo & 59 Taxus patients enrolled at 17 sites

• Study endpoints
  • Primary – non-inferiority of angiographic 9 month in stent late loss
  • Secondary – stent thrombosis and clinical endpoints out to 5 years; IVUS follow-up subset

• Balanced patient populations with significant co-morbidities

• No significant differences in baseline lesion characteristics
## Angiographic In-Stent Late Lumen Loss

### Statistical Analysis

<table>
<thead>
<tr>
<th></th>
<th>Combo (N=124)</th>
<th>TAXUS (N=59)</th>
<th>Margin of Non-Inf, Δ (mm)</th>
<th>Non-inferiority p-value</th>
<th>Difference [95% CI]</th>
<th>Superiority p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-stent Late Lumen Loss at 9 months (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>109</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td><strong>0.39 ± 0.45</strong></td>
<td><strong>0.44 ± 0.56</strong></td>
<td>0.2</td>
<td>0.0012</td>
<td><strong>-0.05 [-0.21,0.11]</strong></td>
<td>0.5514</td>
</tr>
<tr>
<td>(min, max)</td>
<td>(-0.34, 2.63)</td>
<td>(-0.40, 1.97)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Full analysis set: ITT patients with qualifying 9-month angiographic follow-up included in the analyses.

Late loss estimated by Angiographic Core Lab for patients with available 9-month qualifying angiogram.
# 9-Month Binary Angiographic Restenosis and In-Segment Late Loss

<table>
<thead>
<tr>
<th></th>
<th>Combo (N=124)</th>
<th>TAXUS (N=59)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Restenosis (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>5.5%</td>
<td>9.6%</td>
<td>0.34</td>
</tr>
<tr>
<td>In-segment</td>
<td>8.3%</td>
<td>13.5%</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Minimum Lumen Diameter (MLD) (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent, mean ± SD</td>
<td>2.31 ± 0.58</td>
<td>2.30 ± 0.56</td>
<td>0.86</td>
</tr>
<tr>
<td>In-segment, mean ± SD</td>
<td>2.09 ± 0.56</td>
<td>1.97 ± 0.57</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>In-stent late lumen loss (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>0.39 ± 0.45</td>
<td>0.44 ± 0.56</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>In-segment late lumen loss (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>0.27±0.46</td>
<td>0.41±0.54</td>
<td>0.08</td>
</tr>
<tr>
<td>Proximal In-segment, mean ± SD</td>
<td>0.19 ± 0.44</td>
<td>0.29 ± 0.53</td>
<td>0.24</td>
</tr>
<tr>
<td>Distal In-Segment, mean ± SD</td>
<td>0.09 ± 0.30</td>
<td>0.13 ± 0.30</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Conclusions

In this First-In-Man study, the COMBO Dual Therapy Stent effectively controls neointimal proliferation:

• 0.39 mm average angiographic in-stent late loss at 9 months with the Combo stent is non-inferior to the Taxus Liberté stent

• In-stent and In-segment Late Loss, and Binary Restenosis Rates are accordingly low and comparable to the Taxus Liberté stent

• Overall low rate of clinical events in both groups, including no stent thrombosis

• Combo shown to be effective & safe
REMDEEE Cumulative Distribution of Angiographic In-stent Late Loss at 9 Months

M Haude, ACC 2012, Chicago, USA
LLL distributions show different patterns:

- Combo Stent: slight tail (n= 109)
- Taxus stent: bimodal appearance (n= 52)
REMEDEEE Restenosis Pattern of Recurrence at 9 Months by QCA

- Combo
- Taxus

*P=NS

M Haude, ACC 2012, Chicago, USA
# REMEDEEE IVUS Endpoints at 9 Months

<table>
<thead>
<tr>
<th></th>
<th>Combo (N=35)</th>
<th>TAXUS (N=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neointimal hyperplasia volume (mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>21.53 ± 21.71</td>
<td>25.95 ± 18.65</td>
<td>0.50</td>
</tr>
<tr>
<td>Relative difference of NIH Volume</td>
<td></td>
<td>(17% less NIH volume)</td>
<td></td>
</tr>
<tr>
<td>In-stent volume obstruction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>15.24 ± 14.22</td>
<td>14.59 ± 8.38</td>
<td>0.84</td>
</tr>
</tbody>
</table>

M Haude, ACC 2012, Chicago, USA
REMEDEE IVUS, IVUS-VH, and OCT at 9 Month F/U

**Combo**
- IVUS
- IVUS-VH
- OCT

**TAXUS**
- OCT

**Homogenous tissue coverage of the stent strut**

**Heterogenous stent strut coverage**

M Haude, ACC 2012, Chicago, USA
**Presentation and Morphology of Restenosis**

- A divergence in the cumulative frequency distribution of late loss
- The patterns of late loss
  - Combo relatively tightly distributed with a slight tail
  - Taxus more of a bimodal pattern
- The patterns of restenosis
  - Combo in-stent focal and diffuse
  - Taxus majority stent margin and diffuse
- NI hyperplasia volume by IVUS (17% reduction)
- Difference in morphology by IVUS, VH-IVUS, and OCT
  - Combo = homogeneous
  - Taxus = heterogeneous

These differences in presentation and morphology of restenosis corresponded with marked differences in clinical results . . .
REMEDEE Clinical Results at 9 Months Follow Up

<table>
<thead>
<tr>
<th>Event</th>
<th>COMBO (124)</th>
<th>Taxus (59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>2.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NQWMI</td>
<td>2.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Clin TLR</td>
<td>5.2</td>
<td>45%</td>
</tr>
<tr>
<td>TVR</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>MACE</td>
<td>7</td>
<td>8.7</td>
</tr>
<tr>
<td>TLF</td>
<td>8.7</td>
<td>8.7</td>
</tr>
</tbody>
</table>

*P-values: P=0.49, P=0.75, P=0.75, P=0.35, P=0.65, P=0.69, P=0.69*
**REMEDEE Clinical Trial Program**

**To demonstrate rapid strut coverage:**
- **Combo : Xience V**
  - 30 : 30 patients

**REMEDEE OCT**
- **ACS patients**
  - (STEMI & Non-STEMI)

**Enrolling**
- **de-novo lesions**
- **Primary end point:**
  - strut coverage by OCT @ 60 days
  - superiority design
  - FPI: Oct 2011

**In preparation**
- **EGO Combo:**
  - Serial OCT

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**To demonstrate effectiveness in reduction of late loss:**
- **Combo : Taxus Liberte**
  - 120 : 60 patients

- **stable patients;**
- **de-novo lesions**
- **Primary end point:**
  - late loss @ 9 mo
  - non-inferiority design

- **LPI: Aug 2010**

**9 mo FU reported**

**REMEDEE 9 mo Late Loss**

**REMEDEE OCT 60 d Strut Coverage**

**REMEDEE Pivotal Clinical Endpoints**
## Combo Dual Therapy Stent

- **Improve efficacy profile – stable outcomes over time**
  - Limit neo-intimal proliferation – *sirolimus elution*
  - No chronic inflammation – *completely biodegradable polymer*
  - Vessel healing – *abluminal drug elution & luminal EPC capture*

- **Improve safety profile – eliminate late stent thrombosis**
  - Rapid endothelial coverage and function – *EPC capture*

- **Reduce dependency on DAPT – *vessel healing***
  - Avoids risk associated with DAPT discontinuation
  - Lowers bleeding risk and its complications