Evolution of Novel BioMime™ Sirolimus Eluting Stent on a Biodegradable Polymer Platform

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Disclosure Statement of Financial Interest

I, Wojciech Wojakowski DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
DRUG ELUTING STENTS

Significant reduction of in-stent restenosis and TLR vs. BMS, but:

- ISR still present (7-15%)
- Stent thrombosis is a valid safety concern
- Procedure-, patient-, stent-related factors

J Am Coll Cardiol 2010;56:1783–93
J Am Coll Cardiol, 2010; 56:1897-1907
STENT-RELATED FACTORS

- incomplete endothelialization/neointima coverage
- inflammatory reaction
- polymer/drug hypersensitivity reaction
- late incomplete apposition
- chronic drug toxicity
- endothelial dysfunction

J Am Coll Cardiol 2010;56:1783–93
Circulation. 2007;115:1051-1058.
Strut Thickness
Scaffolding
Conformability
Balloon Tapers
Trackability

Stent
- vascular support
- limits recoil

Drug
- modulates vascular responses
- Proliferation inhibitor

Carrier
- elute appropriate drug load
- control kinetic release
MINIMIZING STRUT AND POLYMER THICKNESS TO REDUCE INJURY AND IMPROVE HEALING

1st generation DES

<table>
<thead>
<tr>
<th>CYPHER®</th>
<th>TAXUS® EXPRESS</th>
<th>ENDEAVOR™</th>
<th>XIENCE™ V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strut Thickness:</td>
<td>140 µm</td>
<td>132 µm</td>
<td>91 µm</td>
</tr>
<tr>
<td>Polymer Thickness:</td>
<td>12.6 µm</td>
<td>16 µm</td>
<td>5.3 µm</td>
</tr>
<tr>
<td>PEVA+PBMA</td>
<td>SIBBS</td>
<td>PC</td>
<td>Fluoropolymer</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Paclitaxel</td>
<td>Zotarolimus</td>
<td>Everolimus</td>
</tr>
</tbody>
</table>

2nd generation DES

<table>
<thead>
<tr>
<th>BioMime™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strut Thickness:</td>
</tr>
<tr>
<td>Polymer Thickness:</td>
</tr>
<tr>
<td>PLLA &amp; PLGA Sirolimus</td>
</tr>
</tbody>
</table>

Stent Thickness S1: Turbulent Flow
STENT DESIGN

- BioMime™ stent is built on CE marked NexGen™ – cobalt chromium platform.
- Hybrid cell design

**SEM image of crimped BioMime SES at 50x**

*Closed cell at edges*  *Open cell in mid - segment*
**EDGE DISSECTION IN OCT**

<table>
<thead>
<tr>
<th>Edge dissection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Edge dissection visible, n (%)</td>
<td>20/76 (26.3)</td>
</tr>
<tr>
<td>Length edge dissection flap, mean (SD)</td>
<td>744 (439)</td>
</tr>
</tbody>
</table>

PREVENTION OF EDGE DISSECTION

Staged expansion
PREVENTION OF EDGE DISSECTION

Staged expansion
PREVENTION OF EDGE DISSECTION

Staged expansion
The area of the largest circle circumscribable in the cell of the stent expanded to the nominal diameter: $T_c = 0.71 \text{ mm}^2$

Data on file with Meril Life Sciences.

The expanded BIOMIME 3.0 x 16 mm stent after side branch expansion

Expanded cell perimeter that ensures side branch access: $K_{SBA} = 11.29 \text{ mm}$

Expanded cell area that ensures side branch access: $T_{SBA} = 8.00 \text{ mm}^2$
ADVERSE REACTION TO DRUG ELUTING STENTS

Classical inflammation

Stent implantation → 6-8 months → Neointimal hyperplasia

Drug elution → Polymer hypersensitivity → Thrombus

BMS

CRP (+++) ECP (?) CRP (?) ECP (?) Biomarkers

DES

CRP (+/-) ECP (+) CRP (?) ECP (?) Biomarkers

J Am Coll Cardiol 2010;56:1783–93
Stent
• vascular support
• limits recoil

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• modulates vascular responses
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Carrier
• elute appropriate drug load
• control kinetic release

Polymer-free
Bioabsorbable

Biocompatible durable polymers
BIOABSORBABLE POLYMERS

- Reduced chronic polymer toxicity

- Safety and efficacy of biodegradable polymer DES is not inferior to first generation durable polymer based DES

- Benefits need to be confirmed in larger populations over longer FU to assess the risk of VLST

Windecker, TCT 2010
MECHANICAL INTEGRITY

Displacement of Coating

Webbing Without Metal Exposure

Webbing With Metal Exposure

Peeling of Coating

Fragment of Coating

Basalus et al., EuroIntervention 2009; 5:157-65
ABOUT BIOPOLY™

- Biodegradable co-polymer formulation
- Degradation by hydrolysis to carbon dioxide CO₂ and water (H₂O)
- Degradation time of 40-50 days
- Uniformity in stent coating
- Coating thickness of <2 µm
28-DAY POLYMER RESULTS

28-day results – Biodegradable Polymer coated 3.5 x13 in porcine LCx

Absence of Fibrin, Hemorrhage
Necrosis, Fibrinoid or
Inflammation

No significant differences were found in terms of anatomopathologic features or morphometric measurements, including in-stent endothelialization or neointimal inflammation score versus BMS (all p>0.05)

1. Data on file
Stent
- vascular support
- limits recoil

Drug
- modulates vascular responses
- Proliferation inhibitor

Carrier
- elute appropriate drug load
- control kinetic release

- Therapeutic Window
- Drug Load
- Stability
**PK/PD OF BIOMIME**

**RABBIT ILIAC ARTERY MODEL**

**BioMime In Vivo drug elution**

- 75% in 2 weeks
- >98% in 4 weeks

**Similar tissue concentrations as Cypher**

**BioMime Sirolimus Concentration in Rabbit artery homogenate**

**Cypher Sirolimus concentration in artery homogenate**

*Data on file with Meril Life Sciences. Rabbit iliac model.*
**RABBIT ILIAC ARTERY IMPLANTS (28-DAYS)**

NexgGen BMS

BioMime™

Decreased neointimal thickness

Delayed healing with evidence of uncovered struts
BIOMIME™ LIGHT MICROSCOPY ANALYSIS
28-DAY RABBIT ILIAC

- Neointimal Area
  - BioMime™: 1.5 ± 0.2
  - NexGen BMS: 1.7 ± 0.3
  - P = 0.15

- Stenosis (%)
  - BioMime™: 20 ± 5
  - NexGen BMS: 25 ± 6
  - P = 0.11

- Neointimal Thickness (mm)
  - BioMime™: 0.2 ± 0.05
  - NexGen BMS: 0.3 ± 0.06
  - P = 0.024

- Uncovered Struts (%)
  - BioMime™: 10 ± 2
  - NexGen BMS: 15 ± 3
  - P = 0.064
BIOMIME™ LIGHT MICROSCOPY ANALYSIS
28-DAY RABBIT ILIAC (CONT)

- Struts with fibrin (%): P = 0.14
- Endothelial coverage (%): P = 0.0039
- Intimal Inflammation Score: P = 0.09
- Giant Cells per strut (%): P = 0.87
# meriT-1 Study

**Design:** prospective, single center primary safety and efficacy trial for BioMime™ Sirolimus Eluting Coronary Stent System.

**Principal Investigator – Dr. Sameer Dani, India**

<table>
<thead>
<tr>
<th>Follow-up Time Points</th>
<th>Total Patients Followed up</th>
<th>Death</th>
<th>Myocardial Infarction</th>
<th>Target Lesion / Vessel Revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac</td>
</tr>
<tr>
<td>30-Days</td>
<td>All 30 patients</td>
<td>100%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>6-Months</td>
<td>All 30 patients</td>
<td>100%</td>
<td>0 (0%)</td>
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</tr>
<tr>
<td>8-Months</td>
<td>All 30 patients</td>
<td>100%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1-Year</td>
<td>All 26 patients</td>
<td>87%</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Time Points</th>
<th>Total Patients Followed up</th>
<th>Stent Thrombosis</th>
<th>Any Other Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acute (0D – 1D)</td>
<td>Sub-Acute (&gt;1D – 1M)</td>
</tr>
<tr>
<td>30-Days</td>
<td>All 30 patients</td>
<td>100%</td>
<td>0 (0%)</td>
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<td>100%</td>
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<td>87%</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

*4 patients refused Angiographic follow-up. NA = Not Applicable*
## meriT-1 Study

### QCA Analysis – Follow up

<table>
<thead>
<tr>
<th></th>
<th>Follow-up QCA – 8 months</th>
<th>(N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference Vessel Diameter, mm</strong></td>
<td></td>
<td>2.97 [2.80, 3.28]</td>
</tr>
<tr>
<td><strong>In-Segment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.32 [2.18, 2.62]</td>
<td></td>
</tr>
<tr>
<td>% DS</td>
<td>21.1 [14.9, 26.2]</td>
<td></td>
</tr>
<tr>
<td>Late Lumen Loss, mm</td>
<td>0.18 [0.06, 0.35]</td>
<td></td>
</tr>
<tr>
<td>Binary Restenosis, %</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>In-Stent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.67 [2.32, 2.83]</td>
<td></td>
</tr>
<tr>
<td>% DS</td>
<td>10.9 [8.2, 15.6]</td>
<td></td>
</tr>
<tr>
<td>Late Lumen Loss, mm</td>
<td>0.15 [0.09, 0.33]</td>
<td></td>
</tr>
<tr>
<td>Binary Restenosis, %</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*Preliminary QCA analysis. Median values*
meriT-2 Study Design

Prospective, Non-Randomized, Multi-Centre, Real world study involving 250 patients. Principal Investigator – Dr. Ashok Seth, India

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients enrolled</td>
<td>217</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>57.5 ± 10.2</td>
</tr>
<tr>
<td>Gender, Males</td>
<td>171 (84%)</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>25 ± 3.6</td>
</tr>
<tr>
<td>Previous MI</td>
<td>75 (37%)</td>
</tr>
<tr>
<td>Acute Coronary Syndromes</td>
<td>177 (87%)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>82 (40%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>27 (13%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>116 (57%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>65 (32%)</td>
</tr>
<tr>
<td>Family History</td>
<td>18 (9%)</td>
</tr>
</tbody>
</table>

Ongoing study
MACE & ST

- On going study
- 217 patients have been treated
  - 0% MACE at 30 days
  - 1 non-cardiac death at 4 months
  - 2 (0.9%) patients had ischemia driven TLR at 4 months
  - 4 (1.8%) patients had TLR at 8 months Angio follow-up
  - 1 (0.5%) SAT
SUMMARY

- Drug release and tissue concentration is similar to Cypher
- Due to its low injury score, BioMimeTM demonstrates equivalent neo-intimal scores to Cypher despite having low drug loading
- BioPolyTM has demonstrable non-inflammatory behavior in pre-clinicals
- Neointimal thickness with BioMimeTM is 34% less than its bare metal platform NexGenTM (p=0.024)
- Optimal scaffolding and wall apposition (hybrid closed and open cell format), highly flexible and deliverable stent system, low balloon overhang, low forshortening and recoil.
- Excellent polymer structural integrity
Thank you for your attention!