Biolimus A9 Drug-Eluting Stents: The Biosensors STEALTH I Results

Eberhard Grube MD
FACC, FSCAI

Heart Center Siegburg, Siegburg, Germany
Stanford University, School of Medicine, CA, USA
Demonstrate safety and efficacy of new rapamycin derivative, Biolimus A9, eluted from bioabsorbable PLA-coated stent in *de novo* coronary lesions
Study Sites and Investigators

• Clinical Centers (Eberhard Grube, Principal Investigator):
  – Heart Center Siegburg, Germany
    *Eberhard Grube MD*
  – Institute Dante Pazzanese of Cardiology São Paulo, Brazil
    *Alex Abizaid MD PhD, Eduardo Sousa MD PhD*
  – Brüderkrankenhaus Trier, Germany
    *Karl-Eugen Hauptmann MD*

• Preclinical Animal Studies
  – Cedars-Sinai Medical Center: *S. Kar MD*

• BA9 Toxicology Studies
  – Terumo Corporation

• BA9 Metabolic Study
  – Univ. of Colorado HSC: *U. Christians MD PhD*
Core Labs

- Angiographic Core Lab
  - Cardiovascular Research Foundation: 
    E. Cristea MD, R. Costa MD, A. Lansky MD

- Data Management and Analysis
  - Harvard Clinical Research Institute: 
    A. Mercando RN, R. Kuntz MD
  - Cardiovascular Research Foundation: 
    M. Negoita MD, R. Mehran MD

- Blood and Tissue Analysis
  - Univ. of Colorado HSC: U. Christians MD PhD

- IVUS Core Lab
  - Stanford University: 
    Y. Shimada MD, Y. Honda MD, A. Hassan MD, P. Fitzgerald MD PhD

- Clinical Events & DSMB Committees
  - Harvard Clinical Research Institute: D. Cutlip, MD
BioMatrix™ Stent Components
(Biosensors International Group)

S-Stent™ (stainless steel)
- Quadrature-link design; increased flexibility
- Excellent scaffolding
- Reduced turbulence and wall injury

PLA Polymer
- Uniform thickness; bioresorbable
- Simultaneously releases drug and polymer
- Controlled biodegradability
- High drug-carrying capacity
- Minimizes polymer weight to minimize inflammation; polymer absorbed into tissue

Biolimus A9™ (rapamycin derivative)
- Powerful immunosuppressant, anti-inflammatory
- Prevents smooth muscle cell proliferation
- More lipophilic; elutes faster than rapamycin
Tissue Concentration of Biolimus A9 in Pre-Clinical, 24-hour Porcine Model

A9 acts locally, not systemically

Myocardium
- apex
- right ventricle
- distal myocardium
- posterior wall
- lateral wall
- mid anterior wall
- myocardium (proximal to the stent)
- myocardium (distal to the stent)
- myocardium beneath the stent

LAD Artery
- proximal vessel
- distal vessel
- stented vessel segment

n=3, Mean ± SD
STent Eluting A9 Biolimus Trial in Humans

First In-Man
Single-Dose Safety Trial
2:1 randomized
n = 120

Primary Endpoint:
Late Loss at 6 and 12 Months

- Biolimus A9 Eluting Stent
  n = 80
- Control Bare Metal Stent
  n = 40
Secondary Endpoints

- Angiographic **in-stent restenosis** (>50% diameter stenosis) at 6 month follow-up
- **MACE**
- **IVUS** changes evaluated at t₀, 6, and 12 months post implant.
- **Biolimus serum levels** measured at t₀, t₄, and before discharge
Inclusion Criteria

- Age > 18 years
- Single *de novo* lesions
- Stenosis > 50%
- Lesion length ≤ 24 mm
- Reference diameter (2.7 mm to 4 mm)
- No direct stenting
Exclusion Criteria

- LVEF < 30%
- Left main > 50%
- CTO, poor distal flow, thrombus
- Multiple stent (>2) implantation
- 7 days from AMI
- Significant medical comorbidities
- Staged procedures within 3 months
- Side branch > 2 mm
- Coexisting CHD, VHD, CRF
- Contraindication to anticoagulation
Pharmacologic Regimen

- **Pre-procedure**
  - Aspirin (100–325mg) starting 24 hrs prior to procedure
  - Plavix (loading dose, 300–375 mg within 24 hours pre or post procedure), or
  - Ticlid (loading dose, 500mg within 24 hours pre or post procedure)
- **During procedure**
  - Heparin (boluses to maintain ACT > 250 secs)
  - Plavix 75mg qd or Ticlid 250mg bid
- **Post-procedure**
  - Aspirin (100–325mg qd) indefinitely
  - Plavix (75mg qd) or Ticlid (250mg bid) for minimum 8 weeks
# Patient Demographics and Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Control BMS</th>
<th>Biolimus A9</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>61.0±9.2</td>
<td>62.0±10.0</td>
<td>0.61</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>82.5%</td>
<td>58.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>History of MI</td>
<td>35.0%</td>
<td>37.5%</td>
<td>0.84</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>12.5%</td>
<td>25.0%</td>
<td>0.15</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>2.5%</td>
<td>10.0%</td>
<td>0.27</td>
</tr>
<tr>
<td>Prior CVA or TIA</td>
<td>7.5%</td>
<td>3.8%</td>
<td>0.40</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>22.5%</td>
<td>26.6%</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85.0%</td>
<td>83.8%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Smoking</td>
<td>61.5%</td>
<td>46.3%</td>
<td>0.12</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>Control BMS</td>
<td>Biolimus A9</td>
<td>P value</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>Family History of CAD</td>
<td>30.6%</td>
<td>50.7%</td>
<td>0.06</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>12.8%</td>
<td>3.8%</td>
<td>0.11</td>
</tr>
<tr>
<td>LV Ejection Fraction</td>
<td>60.2±13.1%</td>
<td>62.4±11.1%</td>
<td>0.61</td>
</tr>
<tr>
<td>Peripheral Vasc. Disease</td>
<td>0.0%</td>
<td>2.5%</td>
<td>0.55</td>
</tr>
<tr>
<td>Anginal Status (CCS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>12.9%</td>
<td>10.5%</td>
<td>0.74</td>
</tr>
<tr>
<td>Class 2</td>
<td>67.7%</td>
<td>56.1%</td>
<td>0.36</td>
</tr>
<tr>
<td>Class 3</td>
<td>16.1%</td>
<td>26.3%</td>
<td>0.42</td>
</tr>
<tr>
<td>Class 4</td>
<td>3.2%</td>
<td>7.0%</td>
<td>0.65</td>
</tr>
</tbody>
</table>
Baseline Lesion Characteristics

Lesion Location

- **Control BMS**
  - Proximal: 42.50%
  - Mid: 47.50%
  - Distal: 10.00%
  - Ostial: 0.00%

- **Biolimus A9**
  - Proximal: 48.80%
  - Mid: 41.50%
  - Distal: 7.30%
  - Ostial: 2.40%
## Acute Results

<table>
<thead>
<tr>
<th></th>
<th>Control BMS</th>
<th>Biolimus A9</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. Vessel Diam. (mm)</td>
<td>2.97±0.42</td>
<td>2.95±0.40</td>
<td>0.79</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td>13.75±3.77</td>
<td>15.37±4.64</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Pre-Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Lesion MLD (mm)</td>
<td>1.07±0.28</td>
<td>1.02±0.27</td>
<td>0.30</td>
</tr>
<tr>
<td>In-Lesion DS (%)</td>
<td>64.07±7.72</td>
<td>65.50±7.76</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Post-Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Stent MLD (mm)</td>
<td>2.92±0.33</td>
<td>2.89±0.37</td>
<td>0.68</td>
</tr>
<tr>
<td>In-Lesion MLD (mm)</td>
<td>2.48±0.41</td>
<td>2.48±0.38</td>
<td>0.93</td>
</tr>
<tr>
<td>In-Stent DS (%)</td>
<td>2.62±8.86</td>
<td>4.61±9.70</td>
<td>0.28</td>
</tr>
<tr>
<td>In-Lesion DS (%)</td>
<td>18.08±8.02</td>
<td>18.64±7.74</td>
<td>0.71</td>
</tr>
</tbody>
</table>
Lesion Grade

<table>
<thead>
<tr>
<th></th>
<th>Control BMS</th>
<th>Biolimus A9</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.1</td>
<td>0</td>
</tr>
<tr>
<td>B1</td>
<td>61.5</td>
<td>43</td>
</tr>
<tr>
<td>B2</td>
<td>23.1</td>
<td>31.6</td>
</tr>
<tr>
<td>C</td>
<td>10.3</td>
<td>25.3</td>
</tr>
</tbody>
</table>

STEALTH
Stent Lengths Implanted

- **8mm**: 0%
- **14mm**: 1.3%
- **18mm**: 4.75%
- **28mm**: 10%

- **Control BMS**
- **Biolimus A9**

STEALTH
Stent Diameters Implanted

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Control BMS</th>
<th>Biolumin A9</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mm</td>
<td>2.5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>3.0 mm</td>
<td>62.5%</td>
<td>63.6%</td>
</tr>
<tr>
<td>3.5 mm</td>
<td>30%</td>
<td>35.1%</td>
</tr>
<tr>
<td>4.0 mm</td>
<td>2.5%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Follow-up

120 Patients

Control BMS  
n = 40

Biolimus A9 DES  
n = 80

30-Day Followup:  
99% (n=119)

6-Month Followup:  
95% (n=114)
## Cumulative MACE to 6 Months (Hierarchical)

<table>
<thead>
<tr>
<th>Event</th>
<th>BMS</th>
<th>BioMATRIX</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>2.5%</td>
<td>3.8%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Death</td>
<td>0.0%</td>
<td>0.0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Q Wave MI</td>
<td>0.0%</td>
<td>0.0%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Non-Q Wave MI</td>
<td>2.5%</td>
<td>2.5%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Emergent CABG</td>
<td>0.0%</td>
<td>0.0%</td>
<td>N/A</td>
</tr>
<tr>
<td>TLR-CABG</td>
<td>0.0%</td>
<td>0.0%</td>
<td>N/A</td>
</tr>
<tr>
<td>TLR-PTCA</td>
<td>0.0%</td>
<td>1.3%</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>
In-Stent Angiographic Results—6 Months

**% Diameter Stenosis**
- Control BMS: 27.4 ± 13.9%
- Biolimus A9: 11.9 ± 14.6%

Significance: P<0.001

**Late Loss (mm)**
- Control BMS: 0.74 ± 0.4 mm
- Biolimus A9: 0.26 ± 0.4 mm

Significance: P<0.001
In-Lesion Angiographic Results—6 Months

% Diameter Stenosis

- Control BMS: 30.9 ± 11.9%
- Biolimus A9: 22.0 ± 12.1%

P < 0.001

Late Loss (mm)

- Control BMS: 0.40 ± 0.41 mm
- Biolimus A9: 0.14 ± 0.45 mm

P = 0.004
Binary Restenosis—6 Months

In-Stent Binary Restenosis
- Control BMS: 7.7%
- Biolimus A9: 3.9%
- P = 0.40

In-Lesion Binary Restenosis
- Control BMS: 7.7%
- Biolimus A9: 3.9%
- P = 0.40
Late Loss—Edge Results

- **STEALTH**

**In-segment**

- **Proximal In-Stent Distal In-Segment**

  - **Control BMS**
  - **Biolimus A9**

  - **P=0.004**
  - **P=0.23**
  - **P<0.001**
  - **P=0.73**
  - **P=0.004**

- **50%**
- **65%**
- **20%**
- **69%**
The incidence of late incomplete apposition was 3% in both groups.
BioMatrix Case Example

preop

postop

6-month Follow-up
BioMatrix Case Example

preop

postop

6-month Follow-up
Biolimus-eluting stent

STEALTH-1 12 mths follow-up

\[0.28 \text{ mm}\]
Everolimus-eluting stent

FUTURE-1 29 mths follow-up

0.11 mm
Cypher DES

Cypher 10 mths follow-up

0.22 mm
Comparison of Neointimal Volume

- Taxol family
  - No Polymer
  - Polymer
- Limus family
  - No Polymer
  - Polymer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Neointimal Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>32.0</td>
</tr>
<tr>
<td>ASPECT Low</td>
<td>16.7</td>
</tr>
<tr>
<td>ASPECT High</td>
<td>12.8</td>
</tr>
<tr>
<td>TAXUS IV</td>
<td>12.2</td>
</tr>
<tr>
<td>TAXUS II</td>
<td>7.9</td>
</tr>
<tr>
<td>TAXUS I</td>
<td>7.2</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>3.1</td>
</tr>
<tr>
<td>FUTURE 1</td>
<td>2.9</td>
</tr>
<tr>
<td>STEALTH I</td>
<td>2.6</td>
</tr>
<tr>
<td>SVELTE</td>
<td>1.5</td>
</tr>
<tr>
<td>FUTURE II</td>
<td>1.1</td>
</tr>
<tr>
<td>RAISE</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Courtesy Shimada, Honda, Hassan, Fitzgerald
Summary

- **In-stent**: a low restenosis rate (3.9% vs. 7.7%, P=0.4) and decreased late loss (0.26mm vs. 0.74mm, P<0.001) was found in Biolimus A9 DES compared with control.
- Notably, the bare S-Stent (control) restenosis rate and in-stent % DS (23.5%) are lower than rates reported in other stent trials.
- No restenosis occurred at the edges in either cohort.
- By IVUS, % neointimal volume (2.6% vs. 23.5%, P<0.001) was significantly lower in Biolimus A9 DES compared with control.
- Late incomplete apposition was low (3% vs. 3%) in both groups.
Planned Studies

• BIG-SIR Study – 3rd Qtr 2005
  – Randomized, multi-center, comparison trial of BioMATRIX™ Stent with CYPHER™ Stent
• STEALTH US Pivotal Study – 4th Qtr 2005
  • Prospective, multi-center, randomized, non-inferiority trial of BioMATRIX™ Stent compared to TAXUS™ and CYPHER™ stents in the treatment of de novo coronary arteries
BIG-SIR STUDY
(Biolimus A-9 vs. Sirolimus)

- **Trial:**
  - Randomized, multi-center, comparison trial of BioMATRIX™ Stent with CYPHER™ Stent
- **Objective:**
  - To compare BioMATRIX™ Stent (Biolimus) with CYPHER™ Stent (Sirolimus)
- **Enrollment:**
  - 1,000 patients from ~3 sites in Europe. Patient data collection will occur at 1, 6, 8, 9, and 12 months following stent implant, and at 2, 3, 4, 5 years
- **Primary Endpoint:**
  - Major Adverse Cardiac Events (MACE) at 9 months
  - Target vessel revascularization (TVR) rates at 9 months
- **Secondary Endpoints:**
  - In-lesion and in-stent restenosis
  - In-lesion and in-stent MLD
STEALTH PIVOTAL

US Pivotal

• Trial:
  • Prospective, multi-center, randomized, non-inferiority trial of BioMATRIX™ Stent compared to TAXUS™ and CYPHER™ stents in the treatment of de novo coronary arteries

• Objective:
  – Demonstrate the safety and efficacy of the BioMATRIX™ Stent as compared to TAXUS™ (Paclitaxel) and CYPHER™ (Sirolimus) stents

• Enrollment:
  – 1700 patients from ~70 sites. Patient data collection will occur at 1, 6, 9, and 12 months post stent implant, and annually thereafter for 5 years

• Primary Endpoint:
  – Ischemia-driven target vessel revascularization (TVR) rates at 9 months

• Secondary Endpoints:
  – Late loss, binary restenosis, MLD, TLR, and TVF
  – Major Adverse Cardiac Events (MACE)
  – Device/Lesion/procedural success
STEALTH PIVOTAL

Study Design

Prospective, non-inferiority, 2:1 randomized
n = 1700

Primary Endpoint:
Ischemia-driven TVR at 9 months

BioMATRIX Stent
n = ~1140

Control TAXUS/CYPHER Stent
n = ~560
STEALTH Conclusions

• The BioMatrix stent, eluting the rapamycin derivative Biolimus A9 from a bioabsorbable PLA polymer coating, demonstrates significantly reduced NIH compared to S-Stent controls in this FIM experience.

• A low MACE rate (5%) and the absence of cardiac deaths suggest safety of this new DES.