My Crystal Ball – New Drug Delivery Platforms and Bioabsorbable Stents will Dominate in the Next 5-10 Years

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Presenter Disclosure Information for TCTAP 2010; April 27-30, 2010

Martin B. Leon, M.D.

Scientific Advisory Board:
Abbott Vascular, Boston Scientific, Medinol, and Medtronic
First Generation DES

**TAXUS**
- Paclitaxel Drug
- Polyolefin derivative Polymer
- Express Stent

**Cypher**
- Sirolimus
- PEVA + PBMA blend
- BX Velocity
DES - A Transforming Technology

My Rosey Prophecy: Restenosis is CURED!
Drug-Eluting Stents
the good, the bad, and the ugly!

- Late loss = 0
- BMS
- DES
- Giant cells
- Inflammation
- Sirolimus
- Control
- Abn Vasomotion
- *P<0.001 vs. control

- Late stent thrombosis
- Incomplete apposition
- Delayed Healing!
- 48 months
- 40 mos
- IVUS
Second Generation DES

Endeavor**

Zotarolimus
Drug

Phosphorylcholine
Polymer

Driver
Stent

Xience V*

Everolimus

VDF + HFP copolymer

Vision

*AKA Promus   **incl. Resolute
Second Generation DES

Endeavor**

Second Generation DES

Zotarolimus
Drug

BioLinx
Polymer

Driver
Stent

Xience V*

Everolimus

VDF + HFP copolymer

Vision

*AKA Promus  ** + Resolute
Next Generation DES

My Crystal Ball
Next Generation DES

The Holy Grail?

No restenosis
No clinical safety issues

Lucius Quinctius Cincinnatus (519–430 BCE?)

WHICH NEEDS TO GO AND WHICH NEEDS TO STAY

Stent
- vascular support
- limits recoil

Drug
- modulates vascular responses

Carrier
- elute appropriate drug load
- control kinetic release

Courtesy of E. Edelman

Lucius Quinctius Cincinnatus (519–430 BCE?)

WHICH NEEDS TO GO AND WHICH NEEDS TO STAY

Stent
- vascular support
- limits recoil

 Courtesy of E. Edelman
WHICH NEEDS TO GO AND WHICH NEEDS TO STAY

Lucius Quinctius Cincinnatus (519–430 BCE?)


Courtesy of E. Edelman
The Future

**New Drug Carrier Systems**

- **New DES with...**
  - Bioabsorbable polymers
  - Polymer-free drug delivery
- **Bioabsorbable DES**
- **Drug-eluting Balloons**
New DES Carrier Systems

**Bioabsorbable Polymers**

- Benefit – reduced polymer burden and bioabsorption should reduce chronic polymer effects (↑ safety)
- Issues – degradation rates, inflammatory by-products, more complex elution profiles
- Examples – Biosensors (BioMatrix), Cordis (Nevo), BSC (Jactax)
**BioMatrix Stent Platform**

**Bioabsorbable Polymer DES**

- **Biodegradable Drug Carrier:**
  - Biolimus A9® / Poly (Lactic Acid) 50:50 mix
  - abluminal surface only (contacts vessel wall)
  - 10 microns coating thickness
  - degrades in 9 months releasing CO₂+ water
1° endpoint: CV death, MI, clinically-indicated TVR (9 month)
2° endpoints:
- Death, CV death, MI, TLR, TVR
- Stent thrombosis according to ARC
- In-stent % diameter stenosis
- Late loss, binary restenosis

Angiographic study:
- BES BioMatrix Flex N=850
- SES Cypher Select N=850

N=1700 Patients

Assessor-blind
1:1 Randomisation

1:3 Randomisation

Clinical F/U N=640
Angio F/U N=210
Clinical F/U N=640
Angio F/U N=210

DAPT recommended for 12 month
Leaders – MACE

MACE = Cardiac Death, MI, or Clinically-Indicated TVR

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>BES</th>
<th>SES</th>
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<tbody>
<tr>
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<td>3</td>
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<td>6</td>
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<td>24</td>
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1-year HR

<table>
<thead>
<tr>
<th></th>
<th>BES 0.88 [0.65 to 1.08]</th>
<th>SES 0.88 [0.66 to 1.17]</th>
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<tbody>
<tr>
<td>P</td>
<td>0.37</td>
<td>0.18</td>
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</table>

2-year HR

<table>
<thead>
<tr>
<th></th>
<th>BES 0.84 [0.65 to 1.08]</th>
<th>SES 0.84 [0.65 to 1.17]</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>0.18</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Δ2.4%

Δ1.4%

Δ10.7%

Δ12.1%

Δ15.4%

Δ13.0%

 Δ: Absolute difference
Leaders – Cardiac Death or MI

1-year HR
1.01 [0.70 to 1.45]
P = 0.95

2-year HR
0.92 [0.66 to 1.27]
P = 0.59

BES
857 804 797 788 780 772 764 760 752

SES
850 801 798 793 779 770 758 755 742
Leaders – Clinically-Indicated TVR

1-year HR
0.82 [0.56 to 1.19]
$P = 0.29$

2-year HR
0.86 [0.62 to 1.20]
$P = 0.37$

Δ 1.1%

BES
SES

Number at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>BES</th>
<th>SES</th>
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<td>18</td>
<td>755</td>
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<td>21</td>
<td>750</td>
<td>729</td>
</tr>
<tr>
<td>24</td>
<td>741</td>
<td>717</td>
</tr>
</tbody>
</table>
Leaders – Definite ST Through 2 Years

Zoom at 1% scale

%  
0.0  0.5  1.0  1.5  2.0  2.5  3.0
0  3  6  9  12  15  18  21  24

BES
SES

2.0%
+0.5%
2.5%
+0.2%
2.2%
2.0%
NEVO™ Stent Design

- **Chromium-Cobalt Platform**
  - Flexible, thin struts, open cell design

- **Novel Reservoir Technology**
  - Minimizes polymer - vessel wall contact

- **Biodegradable Polymer**
  - Achieves Cypher-like sirolimus tissue levels
  - Rapid endotheliation
Polymer Structure and Degradation

- PLGA Polymer resorbs within 3-4 months
- Begins 75% BMS and becomes 100% BMS within 3-4 mos
NEVO RES-ELUTION I Study Overview

Single De Novo Native Coronary Artery Lesions
Reference Vessel Diameter: 2.5 - 3.5 mm
Lesion Length: ≤28 mm

40 sites worldwide
Europe, South America, Australia and New Zealand
394 subjects, stratified by diabetic status, and randomized 1:1

NEVO™
Sirolimus-eluting Stent (n=202)

TAXUS® Liberté™
Paclitaxel-eluting Stent (n=192)

Primary Endpoint: 6-month in-stent late loss
Sub-Study: IVUS subset (50 patients per arm)
Dual antiplatelet therapy for ≥6 months

Clinical/ MACE

30 Day 6Mo 1Yr 2Yr 3Yr 4Yr 5Yr

Angiographic/ IVUS

87% Angiographic follow up*
95% 180 day clinical follow up*

* Follow-up as of April 16, 2009
Late Lumen Loss at 6-Months

Primary Endpoint

- In-Stent
  - NEVO: 0.13 ± 0.31
  - Taxus Liberte: 0.36 ± 0.46
- In-Segment
  - NEVO: 0.06 ± 0.32
  - Taxus Liberte: 0.20 ± 0.39

P<0.001 for both comparisons.
# 6-Month In-Stent Late Loss, In-Stent BAR, and IVUS-Defined NIH Volume

<table>
<thead>
<tr>
<th>Late Loss (mm)</th>
<th>In-Stent BAR (%)</th>
<th>NIH Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.13 ± 0.31</td>
<td>1.1</td>
<td>5.82 ± 11.68</td>
</tr>
<tr>
<td>0.36 ± 0.46</td>
<td>8.0</td>
<td>19.45 ± 24.66</td>
</tr>
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</table>

- **Primary Endpoint:** $P<0.001$

- **$P=0.002$**

- **$P=0.004$**

≥50% diameter stenosis

<table>
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<tr>
<th>Group</th>
<th>Count 1</th>
<th>Count 2</th>
<th>Count 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEVO</td>
<td>2/180</td>
<td>13/162</td>
<td>2/35</td>
</tr>
<tr>
<td>Taxus Liberte</td>
<td>180</td>
<td>162</td>
<td>35</td>
</tr>
</tbody>
</table>

- NEVO
- Taxus Liberte
6-Month MACE and Components

- MACE: 8/193 (4.1%) for NEVO, 13/187 (7.5%) for Taxus Liberte; P=0.19
- Death: 1/193 (0.5%) for NEVO, 3/187 (1.6%) for Taxus Liberte; P=0.37
- MI: 4/193 (2.1%) for NEVO, 5/187 (2.7%) for Taxus Liberte; P=0.75
- Death or MI: 5/193 (2.6%) for NEVO, 8/187 (4.3%) for Taxus Liberte; P=0.37
- TLR: 3/193 (1.6%) for NEVO, 6/187 (3.2%) for Taxus Liberte; P=0.33

No reports of Emergent CABG
Properties of the JACTAX Stent

**JA®Coating**
- 9.2 μg of Paclitaxel and 9.2 μg DLPLA (16 mm)
- 2700 microdots (16 mm)
- Mass of polymer approx 3.4 ng per microdot
- > 1 micron thick, abluminal and lmw biodegradable polymer decreases persistence time

**Stent platform**
- Liberté™ pre-mounted stent (Boston Scientific)
**Jactax Clinical Trial**

**Design**

- **DESIGN**: Prospective, non-randomized, single-arm, multi-center clinical evaluation of the Jactax™ DES System (*patterned after ATLAS*)

- **OBJECTIVE**: To evaluate the acute and long-term safety of the Jactax System

- **PRINCIPAL INVESTIGATOR**
  Eberhard Grube, MD
  Helios Heart Center, Siegburg, Germany

- **PRIMAY ENDPOINT**: MACE at 9 mo
  (Cardiac Death, QMI, nonQMI, TVR)

**Participants and Follow-Ups**

- **103 patients** enrolled and implanted between July ’07 and Jan ’08 in 5 clinical sites in Europe
- **102 pts** with 1 mo f/u
  - 1 pt missed visit
- **102 pts** with 4 mo f/u
  - 1 pt missed visit
  - Currently
- **Clinical follow-up at 9 mo in 73 pts**
- **Angiographic f/u at 9 mo in 72 pts**
- **IVUS f/u at 9 mo in 59 pts**
- **Clinical follow-up at 12 mo in 19 pts**

**Notes**

- 1 pt missed visit
- Currently
<table>
<thead>
<tr>
<th></th>
<th>N=103 patients</th>
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</thead>
<tbody>
<tr>
<td><strong>MACE (in hospital)</strong></td>
<td>1.9% (2/103)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0</td>
</tr>
<tr>
<td>QMI</td>
<td>0</td>
</tr>
<tr>
<td>Non QMI</td>
<td>1.9% (2/103)</td>
</tr>
<tr>
<td>TVR</td>
<td>0</td>
</tr>
<tr>
<td><strong>MACE (30 Day)</strong></td>
<td>1.9% (2/103)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0</td>
</tr>
<tr>
<td>QMI</td>
<td>0</td>
</tr>
<tr>
<td>Non QMI</td>
<td>1.9% (2/103)</td>
</tr>
<tr>
<td>TVR</td>
<td>0</td>
</tr>
<tr>
<td><strong>MACE (9 months)</strong></td>
<td>7</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0</td>
</tr>
<tr>
<td>QMI</td>
<td>0</td>
</tr>
<tr>
<td>Non QMI</td>
<td>2</td>
</tr>
<tr>
<td>TVR</td>
<td>5% (2 TLRs)</td>
</tr>
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</table>
## Angio Outcomes @ 9 Months

<table>
<thead>
<tr>
<th></th>
<th>N=72 patients</th>
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<tbody>
<tr>
<td><strong>Pre Procedure</strong></td>
<td></td>
</tr>
<tr>
<td>RVD</td>
<td>2.72 ± 0.44</td>
</tr>
<tr>
<td>MLD</td>
<td>0.80 ± 0.38</td>
</tr>
<tr>
<td>% DS</td>
<td>71.71 ± 11.26</td>
</tr>
<tr>
<td><strong>Post Procedure</strong></td>
<td></td>
</tr>
<tr>
<td>MLD in-stent</td>
<td>2.59 ± 0.39</td>
</tr>
<tr>
<td>MLD in-segment</td>
<td>2.20 ± 0.45</td>
</tr>
<tr>
<td>% DS in-stent</td>
<td>6.69 ± 9.60</td>
</tr>
<tr>
<td>% DS in-segment</td>
<td>21.24 ± 9.46</td>
</tr>
<tr>
<td><strong>9 month</strong></td>
<td></td>
</tr>
<tr>
<td>MLD in-stent</td>
<td>2.27 ± 0.54</td>
</tr>
<tr>
<td>MLD in-segment</td>
<td>2.05 ± 0.51</td>
</tr>
<tr>
<td>% DS in-stent</td>
<td>17.15 ± 14.01</td>
</tr>
<tr>
<td>% DS in-segment</td>
<td>25.43 ± 12.33</td>
</tr>
<tr>
<td>Binary restenosis in stent (%)</td>
<td>4.2</td>
</tr>
<tr>
<td>Binary restenosis in segment (%)</td>
<td>5.6</td>
</tr>
<tr>
<td>Late Loss in-stent</td>
<td>0.32 ± 0.43</td>
</tr>
</tbody>
</table>

* Includes one pt with early TVR in branch vessel
# IVUS Results @ 9 Months

<table>
<thead>
<tr>
<th></th>
<th>Post Index Procedure</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent Volume (mm³)</strong></td>
<td>150.6 ± 45.9</td>
<td>157.4 ± 50.0</td>
</tr>
<tr>
<td><strong>Lumen Volume (mm³)</strong></td>
<td>150.6 ± 46.0</td>
<td>142.5 ± 47.8</td>
</tr>
<tr>
<td><strong>Neointima (mm³)</strong></td>
<td>14.9 ± 20.4</td>
<td></td>
</tr>
<tr>
<td><strong>Net Volume Obstruction (%)</strong></td>
<td>9.6 ± 10.3</td>
<td></td>
</tr>
</tbody>
</table>
Directional Sirolimus Biodegradable Abluminal Coating and Anti-CD34 Surface Modification

Genous Technology:
• Anti-CD34 surface to promote healing through rapid stent endothelialization

Genous-DES Technology:
• Rapamycin (5 µg/mm) applied in biodegradable SynBiosys polymer on the abluminal side

Genous CD34 Ab
Stent Strut
Abluminal Drug/ Polymer Layer
Stent Surface Coverage by SEM in Stented Arteries at 3 and 14 Days

Granada, Virmani et al; TCT 2008

* = p < 0.05; ** = p < 0.01; *** = p < 0.001

**% Endothelialization by SEM**

- **3 Days**
  - Genous
  - Combo
  - Cypher

- **14 Days**
  - Genous
  - Combo
  - Cypher
REMEEDEE (Sirolimus + EPC)

*Randomized Evaluation of an abluminal sirolimus coated bio-Engineered stEnt*

**First In-Man 2:1 randomized n = 180**
- Combo Stent n = 120
- Taxus Liberte n = 60

**Primary Endpoint:** Late Loss at 9 Months

- IVUS substudy
- OCT substudy
- Vasoreactivity substudy
New DES Carrier Systems

Polymer-Free Drug Delivery

• Benefit – “essentially” BMS after drug delivery (maximal safety)
• Issues – difficulties in prolonging drug elution
• Examples – Translumina (Yukon), Biosensors (BioFreedom), MIV (Vestasync)
Unique Microporous Stent Surface

Coating Capacity & Release Kinetics

Stent Surface

Coating Capacity

Rapamycin / stent surface area (µg/cm²)

0 100 200 300 400 500 600

0.5% 1.0% 2.0% rapamycin concentration

Release Kinetics

Fractional release [%]

0 20 40 60 80 100

0 5 10 15 20 25 30 days

microporous stent

Cypher stent

J Hausleiter et al. *Eur Heart J* 2005
ISAR TEST 2
Testing Dual-Drug Sirolimus + Probucol

1007 pts with de-novo lesions randomized

- Cypher (n=333)
- Dual DES (n=335)
- Endeavor (n=339)

Polymer-free, probucol + sirolimus-eluting stent

Primary Endpoint: angiographic restenosis
Secondary Endpoint: TLR

R Byrne et al., Eur Heart J 2009
ISAR TEST-2

Restenosis Analysis

Angiographic Restenosis (1\textsuperscript{ary} EP)

- Cypher: 12.0%
- Dual-DES: 11.0%
- Endeavor: 19.3%

Clinical Restenosis (TLR)

- Cypher: 7.2%
- Dual-DES: 6.8%
- Endeavor: 13.6%

Statistical significance:

- Angiographic Restenosis (1\textsuperscript{ary} EP): p=0.68, p=0.002
- Clinical Restenosis (TLR): p=0.83, p=0.001
**ISAR TEST-2**

**Clinical Follow-Up at 1 Year**

- **Death/MI**: 6.0% (Cypher), 6.0% (Dual-DES), 6.2% (Endeavor)
p = 0.66

- **MI**: 3.6% (Cypher), 4.2% (Dual-DES), 3.2% (Endeavor)
p = 0.80

- **Definite stent thrombosis**: 0.9% (Cypher), 0.9% (Dual-DES), 0.6% (Endeavor)
p = 0.87

R Byrne et al., *Eur Heart J* 2009
Ongoing Trial – ISAR TEST 5
Testing the 3rd Generation Non-Polymer DES

3000 patients
randomization

Dual-drug DES
(probulcol + sirolimus)

Endeavor
Resolute

Primary EP: composite of death, MI, TLR at 12 mo.
3D MicroPorous Nanofilm Hap

Polymer-free DES
### VESTASYNC Polymer-free
### Sirolimus-eluting Stent
### QCA results @ 4 mos and 9 mos

<table>
<thead>
<tr>
<th>Variable</th>
<th>4 months (n=15)</th>
<th>9 months (n=12)</th>
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<tbody>
<tr>
<td></td>
<td>In-Stent</td>
<td>In-Lesion</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.34 ± 0.33</td>
<td>2.05 ± 0.38</td>
</tr>
<tr>
<td>% Diameter stenosis</td>
<td>13.8 ± 7.0</td>
<td>23.6 ± 8.8</td>
</tr>
<tr>
<td>Late lumen loss, mm</td>
<td>0.29 ± 0.25</td>
<td>0.16 ± 0.29</td>
</tr>
<tr>
<td>Restenosis*, % (n)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abizaid et al. ACC 2008
**Hypothesis:** Polymer-free drug release via porous-eluting stents may reduce late events caused by polymer stent coatings

**Potential advantage**

- Avoid long term late adverse effects that might be attributable to the polymer
- Improved surface integrity since there is no polymer to be sheared or peeled away from the stent struts
- Possible Shorter need of dual antiplatelet therapy
BioFreedom FIM Design

First Cohort

BioFreedom Standard dose
BioFreedom Low dose

4 Months follow up
75 patients
Clinical FU 97%
Angio FU 92%
IVUS FU 77%

BioFreedom FIM
180 total patients

BioFreedom Standard dose
TAXUS® Liberté

Second Cohort

12 Months follow up
105 patients

BioFreedom Low dose
TAXUS® Liberté

Enrollment Complete
Sept 2008 – Jan 2009

Enrollment Complete
Jan 2009 – Jun 2009

75 patients
12 Months follow up
105 patients
Clinical FU 97%
Angio FU 92%
IVUS FU 77%
# 4-Month MACE (Hierarchical)

<table>
<thead>
<tr>
<th>MACE</th>
<th>BioFreedom Standard Dose (N=25)</th>
<th>BioFreedom Low Dose (N=26)</th>
<th>Taxus Liberté (N=24)</th>
<th>P-value BFM SD vs. Taxus</th>
<th>P-value BFM LD vs Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Death, MI, Emergent Bypass or TLR*)</td>
<td>0 (0.0%)</td>
<td>2 (8.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>0.17</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MI*</td>
<td>0 (0.0%)</td>
<td>1 (3.8%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>0.34</td>
</tr>
<tr>
<td>Q Wave MI</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Non-Q Wave MI*</td>
<td>0 (0.0%)</td>
<td>1 (3.8%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>NS</td>
</tr>
<tr>
<td>Emergent Bypass</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>TLR**</td>
<td>0 (0.0%)</td>
<td>1 (4.3%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>0.33</td>
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* In-hospital  ** Clinically indicated
## In-Stent Thrombosis
(Possible, probable, or definite as per ARC Def.)

<table>
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<tr>
<th></th>
<th>BioFreedom Standard Dose N=25</th>
<th>BioFreedom Low Dose N=26</th>
<th>Taxus Liberté N =24</th>
<th>P-value BFM SD vs. Taxus</th>
<th>P-value BFM LD vs Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Sub-acute</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Late</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
# 4-Months Angiographic Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>BioFreedom Standard Dose</th>
<th>BioFreedom Low Dose</th>
<th>Taxus Liberté</th>
<th>P-value BFM SD vs. Taxus</th>
<th>P-value BFM LD vs Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MLD (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-segment</td>
<td>2.0 [1.7,2.3]</td>
<td>2.1 [1.9,2.3]</td>
<td>2.0 [1.5,2.3]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>In-stent</td>
<td>2.5 [2.1,2.7]</td>
<td>2.5 [2.0,2.7]</td>
<td>2.2 [1.6,2.6]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>In-segment late loss</strong></td>
<td>23.2 [18.9,33.0]</td>
<td>18.2 [17.9]</td>
<td>24.6 [20.4,29.8]</td>
<td>&lt;0.0001</td>
<td>0.002</td>
</tr>
<tr>
<td>In-stent late loss</td>
<td>0.08 [0.02,0.14]</td>
<td>0.12 [0.07,0.26]</td>
<td>0.37 [0.14,0.58]</td>
<td>&lt;0.0001</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Late loss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-segment</td>
<td>0.12 [0.02,0.20]</td>
<td>0.12 [0.06,0.25]</td>
<td>0.18 [0.09,0.42]</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td>In-stent</td>
<td>0.08 [0.02,0.14]</td>
<td>0.12 [0.07,0.25]</td>
<td>0.37 [0.14,0.50]</td>
<td>&lt;0.0001</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Comparison of % Neointimal Volume
~ Among 4M Drug-Eluting Stent Trials~

- **Sirolimus**: 13.5, 10.9, 13.5
- **Paclitaxel**: 1.9, 2.2, 2.2
- **Biolimus**: 2.2, 1.3, 5.5
- **Zotarolimus**: 4.5, 6.5, 2.2
Drug Filled Stent (Medtronic)

Drug elution controlled by diffusion physics

No Polymer!
Drug Filled Stent (Medtronic)

Drug elution controlled by diffusion physics

Preliminary testing suggests a variety of elution profiles possible.
Bioabsorbable Stents

**Reasons for Bioabsorbable Stents**

- **Improved biocompatibility**...
  - less deep wall injury, inflammation and hypersensitivity responses
  - improved conformability (reduced compliance mismatch)
  - facilitates arterial remodeling
  - restored vasoreactivity
  - no stent fractures
- **Simplifies re-intervention (either PCI or CABG)**
Bioabsorbable Stents

**Reasons for Bioabsorbable Stents…**

- *Preserves sidebranch patency*
- *Improved deliverability (more flexible)*
- *Allows FU non-invasive imaging (CT and MRI)*
- *Improved clinical outcomes (?)*
  - less restenosis (requires drug elution)
  - reduced stent thrombosis (esp. late/very late)
  - reduced need for prolonged DAPT
- *Patients love the notion of a “temporary” disappearing implant!*
Bioabsorbable Stents

Challenges of Bioabsorbable Stents...

- **Profile (polymer thickness) and deliverability**
- **Mechanical stability** – radial force, early and esp. late recoil, and scaffolding
- **Biocompatibility** – inflammatory responses
- **Controlling bioabsorption** (? time and rate) and the consequences (by-products, retained polymer, macro-embolization)
- **Radiopacity**
- **Optimizing drug elution** (to prevent restenosis)
<table>
<thead>
<tr>
<th>Bioresorbable Stents</th>
<th>Igaki-Tamai</th>
<th>BVS</th>
<th>REVA</th>
<th>BTI</th>
<th>Biotronik</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLA</td>
<td>PLA</td>
<td>Tyrosine-Polycarbonate</td>
<td>PAE-Salicylate</td>
<td>Magnesium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Igaki-Tamai Stent (2000)

Hideo Tamai, MD
† 14 Feb, 2009
Arrow indicates a metallic marker
Absorb Trial: Patient Flow

Intent to treat

Per treatment

Per treatment

30 patients

n = 4 excluded in Per Treatment Population (3 received non-BVS stent, 1 device failure)

26 patients

n = 1 IVUS not analyzable (pullback issue)

25 patients

n = 2 missed F/U visits

n = 1 IVUS not analyzable (pullback issue)

28 patients

n = 2 missed F/U visits

n = 2 missed F/U visits

n = 2 missed F/U visits**

n = 5 refused angiography

n = 5 refused angiography, 1 CD recording error

19 patients

n = 5 refused angiography

18 patients

n = 2 missed F/U visits**

n = 1 IVUS not analyzable (pullback issue)

6-month follow-up

2-year follow-up

30 patients clinical

26 patients QCA

25 patients IVUS

28 patients clinical

19 patients QCA

18 patients IVUS

Clinical

QCA

IVUS
Absorb Trial: IVUS Results

1. Vessel size (EEL) did not change (blue)
2. Luminal area reduction of 16% by 6 months due to stent shrinkage (11%) and intimal hyperplasia of 5% (red)
Absorb Trial: IVUS Results

1. Between 6 months and 2 years the lumen (black) increased
2. Plaque plus media decreased by two yrs
3. No remodelling
4. Stent no longer seen
Absorb Trial: OCT Results

**Post-stenting**
Complete strut apposition

**6-month**
Late acquired incomplete stent apposition with tissue bridges between the struts
Corrugated endolumen

**24-month**
Smooth endoluminal lining
Struts largely disappeared although remnant just visible (arrow)

Serruys et al *Lancet* 2009
Absorb Trial: Vessel Reactivity

<table>
<thead>
<tr>
<th>Ach test (n=9)</th>
<th>Mean lumen diameter, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Ach</td>
</tr>
<tr>
<td>Proximal</td>
<td>2.17</td>
</tr>
<tr>
<td>Stented segment</td>
<td>1.81</td>
</tr>
<tr>
<td>Distal</td>
<td>1.76</td>
</tr>
</tbody>
</table>

P-values:
- Proximal: P=0.1
- Stented segment: P=0.03
- Distal: P=0.02

P-values for Ach test:
- Proximal: P=0.5, P=0.06
- Stented segment: P=0.3, P=0.4
- Distal: P=0.4, P=0.03
### Bioabsorbable Drug Everolimus Eluting Stent (BVS)
#### 2 Year Clinical Results – Intent to Treat

<table>
<thead>
<tr>
<th>Hierarchical</th>
<th>6 Months 30 Patients</th>
<th>12 Months 29 Patients**</th>
<th>2 Years 28 Patients**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia Driven MACE (%)</td>
<td>3.3% (1)*</td>
<td>3.4% (1)*</td>
<td>3.6% (1)*</td>
</tr>
<tr>
<td>Cardiac Death (%)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>MI (%)</td>
<td>3.3% (1)*</td>
<td>3.4% (1)*</td>
<td>3.6% (1)*</td>
</tr>
<tr>
<td>Q-Wave MI</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Non Q-Wave MI</td>
<td>3.3% (1)*</td>
<td>3.4% (1)*</td>
<td><strong>3.6% (1)</strong>*</td>
</tr>
<tr>
<td>Ischemia Driven TLR (%)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>by PCI</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>by CABG</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
</tr>
</tbody>
</table>

No new MACE events between 6 months and 2 years
No stent restenosis or thrombosis up to 2 years

* Same patient – this patient also underwent a TLR, not qualified as ID-TLR (DS = 42%)

BVS (Abbott): New Stent Design

- Gen 1.1 design is similar to MultiLink with zig-zag hoops linked by straight bridges
- More uniform support and drug application
- More radial strength and longer duration of support
- Increased stent security
- Storage room temp
- Delivery performance similar to metallic stent

SEM Gen 1.0 Cohort A clinical trial (2yr FU)
SEM Gen 1.1 Cohort B clinical trial (ongoing)
Drug-Eluting Balloons

**Rationale and Technology...1**

- **Clinical Rationale**
  - Improved safety – no chronic polymer effects + reduced drug exposure = optimal biocompatibility
  - Complements DES – use in situations where DES problematic or less effective; e.g. ISR, bifurcations (ostium sidebranch), diabetics, small vessels, diffuse disease, can’t deliver stent locations (distal, tortuous, etc.)
  - Non-coronary applications – PVD (both SFA and infra-popliteal) and intra-cranial lesions
Drug-Eluting Balloons

Rationale and Technology...2

• Technology
  - Local drug delivery system (déjà vu) using the balloon as a passive drug transfer conduit
  - Variables – drug lipophilicity, transfer efficiency (carrier agents), drug dose, balloon inflation times, and # inflations
  - Currently, paclitaxel preferred drug due to increased tissue residence times
  - Issues - predictable drug transfer and consistent tissue pharmacodynamics; efficacy with stents poorly understood
## DEB Competitive Landscape is Crowded

<table>
<thead>
<tr>
<th>DEB</th>
<th>IC/PI</th>
<th>Manufacturer</th>
<th>Drug/excipient</th>
<th>Dose density (ug/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paccocath</td>
<td>IC/PI</td>
<td>Bayer/Medrad</td>
<td>PTx/iopromide</td>
<td>3</td>
</tr>
<tr>
<td>Sequent Please</td>
<td>IC</td>
<td>B. Braun</td>
<td>PTx/iopromide</td>
<td>3</td>
</tr>
<tr>
<td>DIOR II</td>
<td>IC</td>
<td>Eurocor</td>
<td>PTx/shellac</td>
<td>3</td>
</tr>
<tr>
<td>Freeway</td>
<td>SFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elutax</td>
<td>IC</td>
<td>Aachen Resonance</td>
<td>PTx</td>
<td>2</td>
</tr>
<tr>
<td>IN.PACT Falcon</td>
<td>IC</td>
<td>Invatec/Medtronic</td>
<td>PTx/urea</td>
<td>3</td>
</tr>
<tr>
<td>IN.PACT Amphirion</td>
<td>BTK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IN.PACT Pacific</td>
<td>SFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IN.PACT Admiral</td>
<td>SFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutonix</td>
<td>IC/PI</td>
<td>Lutonix</td>
<td>PTx/surfactant</td>
<td>2</td>
</tr>
<tr>
<td>Biotronik</td>
<td>IC</td>
<td>Aachen Resonance</td>
<td>PTx</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HTQ</td>
<td>PTx/BTHC</td>
<td>3</td>
</tr>
<tr>
<td>Advance 18PTx</td>
<td>PI</td>
<td>Cook</td>
<td>PTx</td>
<td>?</td>
</tr>
<tr>
<td>JNJ</td>
<td>?</td>
<td>JNJ</td>
<td>Sirolimus/unknown</td>
<td>?</td>
</tr>
<tr>
<td>ABT</td>
<td>?</td>
<td>Abbott</td>
<td>Zotarolimus/iopromide</td>
<td>?</td>
</tr>
</tbody>
</table>
PACCOCATH Drug Coated Balloon

Technology Description

Paclitaxel + Hydrophilic Spacer (Iopromide)

The hydrophilic spacer leads to:

- **Porous coating with a high contact surface** between the lipophilic drug molecules and the vessel wall.
- Drug release through vessel contact following balloon expansion.
- **High bioavailability** of paclitaxel on the target side for rapid drug absorption by the vessel wall.
Paclitaxel Levels in Vessel Wall

Short Term PK Findings

- Dose: 2.2 µg/mm²
- 5 pigs per time point
- ~10% of the dose lost in transit
- ~12% transfer rate
- ~10% of the dose stays on balloon surface
- Plasma levels <LLOQ of 8 ng/ml

% of load

<table>
<thead>
<tr>
<th>Time After Intervention</th>
<th>% of load</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>12.00</td>
</tr>
<tr>
<td>1 h</td>
<td>10.00</td>
</tr>
<tr>
<td>2 h</td>
<td>8.00</td>
</tr>
<tr>
<td>24 h</td>
<td>4.00</td>
</tr>
<tr>
<td>72 h</td>
<td>2.00</td>
</tr>
</tbody>
</table>
Localized vascular retention of paclitaxel acting as micro “depots” producing secondary local drug delivery.
Treatment of Coronary In-Stent Restenosis with a Paclitaxel-Coated Balloon Catheter

Bruno Scheller, M.D., Christoph Hehrlein, M.D., Wolfgang Bocksch, M.D., Wolfgang Rutsch, M.D., Dariush Haghi, M.D., Ulrich Dietz, M.D., Michael Böhm, M.D., and Ulrich Speck, Ph.D.

1\textsuperscript{ry} endpoint (in-segm late lumen loss)

<table>
<thead>
<tr>
<th>Group</th>
<th>Minimal lumen diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncoated balloon group before procedure</td>
<td>0.74 ± 0.86 mm</td>
</tr>
<tr>
<td>Coated-balloon group before procedure</td>
<td>0.03 ± 0.48 mm</td>
</tr>
<tr>
<td>Uncoated-balloon group at 6 mo</td>
<td>0.03 ± 0.48 mm</td>
</tr>
<tr>
<td>Coated-balloon group at 6 mo</td>
<td>0.03 ± 0.48 mm</td>
</tr>
<tr>
<td>Coated-balloon group after procedure</td>
<td>0.74 ± 0.86 mm</td>
</tr>
<tr>
<td>Uncoated-balloon group after procedure</td>
<td>0.03 ± 0.48 mm</td>
</tr>
</tbody>
</table>

Cumulative Frequency (%)

Minimal lumen diameter (mm)

# The PEPCAD Program

**Paclitaxel-Eluting PTCA-Catheter in CAD**

<table>
<thead>
<tr>
<th>Title</th>
<th>Design</th>
<th>Status</th>
<th>PI/Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPCAD I SVD</td>
<td>Sequent in ≤2.8mm, 120pts, multi-center, Germany</td>
<td>6mo-FU √</td>
<td>MU, CRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12mo-FU √</td>
<td></td>
</tr>
<tr>
<td>PEPCAD II ISR</td>
<td>Sequent vs Taxus in ISR, 131pts, multi-center, Germany</td>
<td>6mo-FU √</td>
<td>MU, CRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12mo-FU √</td>
<td></td>
</tr>
<tr>
<td>PEPCAD III</td>
<td>Sequent + pre-loaded Coroflex Blue vs Cypher, 637 pts, Europe</td>
<td>Q2 / 07</td>
<td>B.Scheller</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9mo-FU √</td>
<td>C.Hamm</td>
</tr>
<tr>
<td>PEPCAD IV DM</td>
<td>Sequent vs Taxus in DM, 160pts, multi-center, Thailand, Malaysia</td>
<td>Q2 / 07 slow</td>
<td>D.Rosli, CRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recruiting √</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>after 85Px</td>
<td></td>
</tr>
<tr>
<td>PEPCAD V BIF</td>
<td>Sequent, 28pts, dual-center, Germany</td>
<td>Q3 / 07</td>
<td>D.Mathey</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recruiting √</td>
<td>F.Kleber</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CRI</td>
</tr>
<tr>
<td>PEPCAD CTO</td>
<td>Sequent, 50pts, single-center, Germany</td>
<td>Q3 / 07</td>
<td>J. Wöhrle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recruiting √</td>
<td></td>
</tr>
<tr>
<td>INDICOR</td>
<td>Coroflex Blue + Sequent, Real World, 125pts, India</td>
<td>recruiting</td>
<td>U.Kaul, CRI</td>
</tr>
</tbody>
</table>
“Paclitaxel-Eluting PTCA-Balloon in Combination with the Coroflex Blue Stent vs. the Cypher Stent in the Treatment of Advanced Coronary Artery Disease”

n = 644 patients, European multicenter trial, complex de-novo lesions

Christian Hamm, Bad Nauheim / Bruno Scheller, Homburg / Saar

Coroflex® Blue (uncoated balloon and CoCr stent)

Coroflex® DEBlue (SeQuent® Please / uncoated CoCr stent)

Coroflex® DEBlue is manufactured based on the PACCOCATH technology with 3 µg paclitaxel / mm²; CE mark since 11.03.2009

PEPCAD III randomization

Cypher stent, n=300
1 mos clinical FU
9 mos angio control

DEBlue stent, n=300
1 mos clinical FU
9 mos angio control

n = 644 patients, European multicenter trial, complex de-novo lesions
### PEPCAD III

**Primary and 2nd Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>DEB+BMS Coroflex DEBlue®</th>
<th>DES Cypher®</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Late Lumen Loss</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>0.41 ± 0.51 mm</td>
<td>0.16 ± 0.39 mm</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-segment</td>
<td>0.20 ± 0.52 mm</td>
<td>0.11 ± 0.40 mm</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Binary Restenosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent*</td>
<td>10.0 %</td>
<td>2.9 %</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>In-segment*</td>
<td>13.8 %</td>
<td>4.9 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TVR</strong></td>
<td>13.8 %</td>
<td>6.9 %</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>TLR</strong></td>
<td>10.5 %</td>
<td>4.7 %</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Hamm TCT09
## PEPCAD III

### Safety Endpoints

<table>
<thead>
<tr>
<th>Procedural Success</th>
<th>DEB+BMS (Coroflex DEBlue® N = 310)</th>
<th>DES (Cypher® N = 324)</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent placed + expanded</td>
<td>91.6%</td>
<td>94.1 %</td>
<td>0.22</td>
</tr>
<tr>
<td>QCA: TIMI3 + In-stent stenosis &lt; 30%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Death (9 months)</th>
<th>DEB+BMS</th>
<th>DES</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1.0 %</td>
<td>0.3 %</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>0.7 %</td>
<td>0.0 %</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MI (9 months)</th>
<th>DEB+BMS</th>
<th>DES</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>4.6 %</td>
<td>0.3 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>3.0 %</td>
<td>0.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0 %</td>
<td>0.3 %</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stent Thrombosis (ARC)</th>
<th>DEB+BMS</th>
<th>DES</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>2.0 %</td>
<td>0.3 %</td>
<td>&lt; 0.05</td>
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<tr>
<td>Probable</td>
<td>1.3 %</td>
<td>0.3 %</td>
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<td>0.6 %</td>
<td>0.0 %</td>
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</table>
Implantable Nanoparticle Drug Carriers

**Caliber’s** drug delivery platform: nanoparticle drug carrier via angioplasty with a long-acting therapeutic dose of **Rapamycin**.

**Platform configuration**

- Bio-Degradable Nanoparticles (NP)
- Sustained release of Rapamycin
- NPs delivered via angioplasty balloon
- Enhanced penetration via particle design, controlled size, material, and surface characteristics
- Enhanced efficiency with proprietary device configuration (liquid / dry delivery)
Future DES will focus largely on drug carrier enhancements to reduce safety concerns

- **Bioabsorbable polymer drug delivery** – many versions, much promise, insufficient long-term clinical data to grade value-added features
- **Polymer-free drug delivery** – more difficult to achieve optimal drug elution profiles, best chance for “BMS-like” safety profile, BUT almost no clinical data thus far
Bioabsorbable stents have important potential advantages, each system is unique (all will require iterative stent designs and drug elution), but early proof-of-concept has already been accomplished (Abbott BVS–ABSORB trial + new studies) suggesting that a more biocompatible solution with excellent safety and efficacy may be a breakthrough DES technology in the future!
New Drug Carrier Systems

**Final Thoughts...3**

- *Drug-eluting balloons* – interesting and potentially useful *complementary technology to “fill gaps” and enhance overall PCI safety/efficacy* (not just coronary applications); early results with paclitaxel systems promising, BUT need (1) more consistent drug elution profiles and tissue pharmacodynamics, (2) better solutions when combined with either BMS or DES, (3) more carefully conducted clinical trials (larger RCTs with optimal endpoints and FU), and (4) drug carrier systems with sirolimus analogues
Next Generation DES

The Holy Grail?

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No clinical safety issues
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