Why Polymer Coated Paclitaxel Stents
Insight from Clinical Trials

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Why Paclitaxel?

• Stable and potent at nanomolar concentrations
• Multifunctional
  - Anti-inflammatory, -proliferative, -migratory, -secretory, -extracellular matrix
• Hydrophobic/liphophilic
• Large doses can be loaded in polymers
• Can be applied to metal as a durable simple coating, without need for a polymer
• Extensive human experiences
Paclitaxel
Taxol™
**Paclitaxel** inhibits cell processes dependent on microtubule turnover including mitosis, cell proliferation and cell migration while the cells remain viable (cytostatic).
Dose Dependent Mitotic Arrest

Control  6 nM  100 nM Paclitaxel

Flow cytometry (mitotic index)

Microscopy (round, detached cells)

DAPI stain (fragmented nuclei, mitotic arrest)

Dose Dependent Inhibition of Intimal Hyperplasia

Uncoated
8.6 µg
Chondroitin Sulfate Gelatin Coated
20.2 µg
1.5 µg
42 µg

Farb A et al. Circ 2001;104:473
Toxicity by high drug concentration (42 ug/stent) of paclitaxel

Intimal fibrin deposition
- Medial necrosis
- Hemorrhage

Focal intimal acute and chronic inflammatory cell

Farb A et al. Circ 2001;104:473
Dose Dependent Cellular Effect

Smooth muscle cells

Endothelial cells

Axel et al (Circulation 1997)
Impact of Anti-restenotic action

**Tacrolimus**
- FK506 IC50 (M): 3.30E-06
- SMC: 5.10E-07
- EC: 3.30E-06

**Rapamycin**
- Rapamycin IC50 (M): 4.10E-09
- SMC: 4.10E-10
- EC: 7.10E-10

**Paclitaxel**
- Paclitaxel IC50 (M): 4.90E-09
- SMC: 3.00E-09
- EC: 4.90E-09

**IC50:** drug concentration to kill 50% in in-vitro cell culture
Paclitaxel has a good vascular compatibility

Complete healing, re-endothelization, minimal inflammation…
Paclitaxel coated stents produce significant inhibition of neointimal hyperplasia
Non-Polymer Coating Stent

Dose Rating Clinical Studies

ASPECT / ELUTE
Paclitaxel coated stent

- Paclitaxel was adhered to the abluminal surface of stents using a proprietary process without the use of a polymer.
## Dose-Ranging Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Diameter:</th>
<th>Length:</th>
<th>PTX Doses:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPECT:</td>
<td>Randomized, Controlled, Triple-Blinded Supra G™ 316L SS Coronary Stent</td>
<td>2.5, 3.0, 3.5 mm</td>
<td>15 mm</td>
<td>0.0/ 1.3/ 3.1 (μg/mm²)</td>
</tr>
<tr>
<td>(Asia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELUTES:</td>
<td>Randomized, Controlled, Triple-Blinded V-Flex Plus™ 316L SS Coronary Stent</td>
<td>3.0, 3.5 mm</td>
<td>16 mm</td>
<td>0.0/ 0.2/ 0.7/ 1.4/ 2.7 (μg/mm²)</td>
</tr>
<tr>
<td>(Europe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comparison of Paclitaxel Dose

Paclitaxel Dose Density ($\mu g/mm^2$)

- ELUTES V-Flex Plus™
  - 0.0
  - 0.2
  - 0.7
  - 1.4
  - 2.7

- ASPECT Supra G™
  - 0.0
  - 1.3
  - 3.1
## Dose-Ranging Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Investigative Sites</th>
<th>Enrolled Patients</th>
<th>Treatment Duration</th>
<th>Primary Follow-up</th>
<th>Ongoing Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPECT: (Asia)</td>
<td>3</td>
<td>177</td>
<td>1 month or 6 months</td>
<td>MACE at 1 &amp; 6 months, Angiographic at 6 months, IVUS subset at 6 months</td>
<td>Clinical every year</td>
</tr>
<tr>
<td>ELUTES: (Europe)</td>
<td>9</td>
<td>192</td>
<td>3 months</td>
<td>MACE at 1 &amp; 6 months, Angiographic at 6 months</td>
<td>Clinical every year</td>
</tr>
</tbody>
</table>

(37 pts cilostazol)
## Demographics

<table>
<thead>
<tr>
<th>Feature</th>
<th>ASPECT</th>
<th>ELUTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ±10</td>
<td>60 ±11</td>
</tr>
<tr>
<td>Male</td>
<td>76%</td>
<td>82%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13%</td>
<td>49%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
<td>46%</td>
</tr>
<tr>
<td>Smokers</td>
<td>59%</td>
<td>64%</td>
</tr>
<tr>
<td>Multiple Vessel Disease</td>
<td>40%</td>
<td>43%</td>
</tr>
</tbody>
</table>
# Lesion Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASPECT</th>
<th>ELUTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type B1</td>
<td>40%</td>
<td>64%</td>
</tr>
<tr>
<td>Type B2</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Tortuosity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>37%</td>
<td>45%</td>
</tr>
<tr>
<td>Moderate</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>14%</td>
<td>38%</td>
</tr>
<tr>
<td>Moderate</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Eccentric</td>
<td>55%</td>
<td>51%</td>
</tr>
<tr>
<td>Angulation &gt;45 degrees</td>
<td>1%</td>
<td>6%</td>
</tr>
</tbody>
</table>
# Baseline QCA

<table>
<thead>
<tr>
<th></th>
<th>ASPECT</th>
<th>ELUTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTX Dose ($\mu g/mm^2$)</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td>10.9</td>
<td>11.1</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>2.94</td>
<td>2.95</td>
</tr>
<tr>
<td>MLD pre (mm)</td>
<td>0.64</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Cardiovascular Research Foundation

ANGIOPLASTY SUMMIT
6-Month QCA Results:

**ASPECT**

- Control: 39%
- 1.3: 23%
- 3.1: 14%

*p<0.001*

**ELUTES**

- 0.2: 33%
- 0.7: 28%
- 1.4: 23%
- 2.7: 14%

*p<0.01*
% Diameter Stenosis

-Dose response

6-Month QCA Results:

- High dose vs. Control significant for both studies
**Binary Restenosis - Dose response**

6-Month QCA Results:

![Graph showing dose density vs. binary restenosis rate](image)

- **Dose Density (µg/mm²)**
  - 0.0
  - 1.0
  - 2.0
  - 3.0
  - 4.0

- **Rate (%)**
  - 0
  - 10
  - 20
  - 30

*High dose vs. Control significant for ASPECT study*
Late Loss

6-Month QCA Results:

**ASPECT**

![Graph showing late loss and dose density for ASPECT](image)

- Late Loss: 1.04, 0.57, 0.29
- Dose Density (µg/mm²): 0, 1.3, 3.1
- p < 0.001

**ELUTES**

![Graph showing late loss and dose density for ELUTES](image)

- Late Loss: 0.73, 0.71, 0.2
- Dose Density (µg/mm²): 0, 0.2, 0.7, 1.4, 2.7
- p < 0.005
Lesion Length

6-Month QCA Results

Paclitaxel Dose (µg/mm²)

0.0 0.0 0.2 0.7 1.3 1.4 2.7 3.1

Lesion Length (mm)

* p = < 0.0001
† p = < 0.05

Grzegorz Kaluza / Al Raizner  QCA Core Lab

Cardiovascular Research Foundation

ANGIOPLASTY SUMMIT
## Safety: ELUTES Study

<table>
<thead>
<tr>
<th></th>
<th>1-Month</th>
<th>6-Month</th>
<th>12-Month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTX Dose:</strong></td>
<td>2.7</td>
<td>0.0</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>n:</strong></td>
<td>37</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>QMI</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAT</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-Q MI</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PCI</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

|                  |         |         |         |
|                  | (8%)    | (3%)    | (11%)   |
|                  | (13%)   | (13%)   | (13%)   |
|                  | (18%)   |         |         |
### Safety: ASPECT Study

<table>
<thead>
<tr>
<th></th>
<th>1-Month</th>
<th>6-Month</th>
<th>12-Month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTX Dose:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td>0.0</td>
<td>3.1</td>
<td>0.0</td>
</tr>
<tr>
<td>n:</td>
<td>48</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QMI</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAT</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-Q MI</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PCI</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SAE</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>(2%)</td>
<td>(0%)</td>
<td>(4%)</td>
<td>(4%)</td>
</tr>
</tbody>
</table>
12-Month TLR-free Survival

ASA+Ticlid/Plavix

Log rank p=0.93

- Control: 89.6±4.4%
- Low dose: 90.7±4.4%
- High dose: 91.7±4.0%
12-Month TLR-free Survival

ASA+Cilostazol

TLR-free survival (%)

Control: 90.0±9.5%
Low dose: 93.3±6.4%
High dose: 58.3±1.4%

Log rank p=0.06

Months
The Cook Logic PTX stent (n=50)

- Coating applied to abluminal surface using Cook’s proprietary surface modification technology
- 2.0 ug/mm² (nominal)
9-month Angiographic Data

Diameter Stenosis (%)

- Control: 41%
- Logic PTX: 41%

Binary Restenosis (%)

- Control: 6/17 (35%)
- Logic PTX: 8/21 (39%)
Non-Polymer Coating Stent

Dose Rating Clinical Studies

ASPECT | ELUTE
Lessons from Experimental and Clinical studies

Nonpolymer Coating Paclitaxel Eluting Stent

• A paclitaxel eluting stent suppresses neointimal formation in a dose-dependent manner. However, a higher dose of paclitaxel is likely to be associated with delayed healing and local toxicity.

• The ASPECT, ELUTE, and PATENCY trials support the concept that an optimal dose density is essential for a sufficient restenosis-reducing effect.
Lessons from Experimental and Clinical studies

Nonpolymer Coating Paclitaxel Eluting Stent

• The high dose density (3 mcg/mm$^2$) paclitaxel coating was the most effective in reducing restenosis.

• The paclitaxel effect is maintained at 12 months
Polymer Coating Stent

TAXUS Studies
TAXUS stent
Three Component System

Stent design

Drugs
Paclitaxel

Drug
Eluting
Stent

Translute

Stent
Basecoat
TAXUS Program

Preclinical

TAXUS I

Feasibility

Slow release

TAXUS II (Cohort I)

Moderate release

TAXUS II (Cohort I)

TAXUS IV

TAXUS V

Higher Risk

TAXUS VI

Standard Risk

Higher Risk

Moderate release
**TAXUS-II: Efficacy study**

NIRx™-Paclitaxel-coated stent

De novo, 3.0 and 3.5 mm, <12 mm
532 pts at 61 sites in 19 countries
1:1 Randomization
Enrollment completed, results at TCT 2002

**TAXUS-III: Feasibility study**

Coated stent for ISR lesions
30 pts at 2 sites
TAXUS-IV: Pivotal study I

De novo 10-28 mm lesions
1,172 pts at 80 U.S. sites
1:1 Randomization with single stent
2.5, 3.0, 3.5 mm Express (16, 24, 32 mm)
Enrollment to begin 1st quarter 2002
TAXUS-V: Pivotal study II

De novo 10-48 mm lesions
1,110 pts at 80 sites
1:1 Randomization, multiple stents allowed
2.5, 3.0, 3.5 mm Express (8, 16, 24, 32 mm)
Enrollment anticipated 3rd quarter 2002

TAXUS-VI: European arm
TAXUS-VII: Pivotal study III

ISR, 10-40 mm lesions
528 pts at up to 60 US sites
1:1 vs. brachytherapy
2.5, 3.0, 3.5 mm Express (8, 16, 24, 32 mm)
Enrollment anticipated 3rd quarter 2002
TAXUS I

MACE over Time

Sustained benefit of TAXUS SR over 2 years
No difference at edges between TAXUS and control

TCT, Oct 2002
TAXUS II

Moderate Release: 6-Month Restenosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Control</th>
<th>TAXUS MR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal Edge 5mm</td>
<td>4.7</td>
<td>2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stented Segment</td>
<td>20.2</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Distal Edge 5mm</td>
<td>3.1</td>
<td>2.3</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

No difference at edges between TAXUS and control

TCT, Oct 2002
# TAXUS II

## 6-Month MACE

<table>
<thead>
<tr>
<th>Event</th>
<th>Combined Control (n=270)</th>
<th>TAXUS\textsuperscript{NIRx} SR (n=131)</th>
<th>TAXUS\textsuperscript{NIRx} MR (n=135)</th>
<th>P-value SR vs. Control</th>
<th>P-value MR vs. Control</th>
<th>P-value overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>6-Month MACE</td>
<td>19.8 (52)</td>
<td>8.5 (11)</td>
<td>7.8 (10)</td>
<td>0.0035</td>
<td>0.0019</td>
<td>0.0007</td>
</tr>
<tr>
<td>Death</td>
<td>0.4 (1)</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Q-Wave MI</td>
<td>0.8 (2)</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Non Q-Wave MI</td>
<td>4.6 (12)</td>
<td>1.5 (2)</td>
<td>2.3 (3)</td>
<td>0.1567</td>
<td>0.4029</td>
<td>0.2692</td>
</tr>
<tr>
<td>TVR - Overall</td>
<td>16.0 (42)</td>
<td>7.7 (10)</td>
<td>6.2 (8)</td>
<td>0.0262</td>
<td>0.0059</td>
<td>0.0053</td>
</tr>
<tr>
<td>TLR</td>
<td>13.3 (35)</td>
<td>4.6 (6)</td>
<td>3.1 (4)</td>
<td>0.0080</td>
<td>0.0010</td>
<td>0.0005</td>
</tr>
<tr>
<td>TVR Remote</td>
<td>2.7 (7)</td>
<td>3.1 (4)</td>
<td>2.3 (3)</td>
<td>0.7572</td>
<td>1.0000</td>
<td>0.9406</td>
</tr>
<tr>
<td>CABG</td>
<td>0.8 (2)</td>
<td>0.8 (1)</td>
<td>1.0 (1)</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

*TCT, Oct 2002*
## TAXUS II

### 12-Month MACE

<table>
<thead>
<tr>
<th></th>
<th>Combined Control (n=270)</th>
<th>TAXUS\textsuperscript{NIRs} SR (n=131)</th>
<th>TAXUS\textsuperscript{NIRs} MR (n=135)</th>
<th>P-value SR vs. Control</th>
<th>P-value MR vs. Control</th>
<th>P-value overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.3267</td>
<td>0.3333</td>
<td>0.2458</td>
</tr>
<tr>
<td>12-Month MACE</td>
<td>21.7 (57)</td>
<td>10.9 (14)</td>
<td>9.9 (13)</td>
<td>0.0082</td>
<td>0.0048</td>
<td>0.0023</td>
</tr>
<tr>
<td>Death</td>
<td>0.8 (2)</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Q-Wave MI</td>
<td>1.1 (3)</td>
<td>0.8 (1)</td>
<td>1.5 (2)</td>
<td>1.0000</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Non Q-Wave MI</td>
<td>4.2 (11)</td>
<td>1.6 (2)</td>
<td>2.3 (3)</td>
<td>0.2354</td>
<td>0.4026</td>
<td>0.3552</td>
</tr>
<tr>
<td>TVR - Overall</td>
<td>17.5 (46)</td>
<td>10.1 (13)</td>
<td>6.9 (9)</td>
<td>0.0704</td>
<td>0.0034</td>
<td>0.0069</td>
</tr>
<tr>
<td>TLR</td>
<td>14.4 (38)</td>
<td>4.7 (6)</td>
<td>3.8 (5)</td>
<td>0.0035</td>
<td>0.0010</td>
<td>0.0003</td>
</tr>
<tr>
<td>TVR Remote</td>
<td>3.0 (8)</td>
<td>3.1 (4)</td>
<td>1.5 (2)</td>
<td>1.0000</td>
<td>0.5069</td>
<td>0.7279</td>
</tr>
<tr>
<td>CABG</td>
<td>1.1 (3)</td>
<td>3.1 (4)</td>
<td>1.5 (2)</td>
<td>0.2244</td>
<td>1.0000</td>
<td>0.3716</td>
</tr>
<tr>
<td>Euro PCR, 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
12-Month MACE Free Survival

Days after randomization

Sustained benefit of TAXUS stents from 6 to 12 months

8.8% 10.5%
TAXUS VI: Study Design

448 pts 1:1

Stratified for Diabetes

1 ug/mm² MR Paclitaxel-Eluting Express Stent

Uncoated Express Stent

• Clopidogrel and aspirin for 6 months
• Clinical F/U at 1, 3, 6, and 9 months and annually
• Angiographic F/U (n=446) at 9 months
• IVUS substudy (n=171) F/U at 9 months
## 30-Day MACE

<table>
<thead>
<tr>
<th></th>
<th>MR TAXUS (n=350)</th>
<th>Control (n=309)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis (%)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>30-Day MACE</td>
<td>5.3</td>
<td>7.3</td>
<td>0.379</td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Overall MI (%)</td>
<td>9 (4.0)</td>
<td>16 (7.3)</td>
<td>0.125</td>
</tr>
<tr>
<td>Q-MI (%)</td>
<td>2 (0.9)</td>
<td>2 (0.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Non-Q MI (%)</td>
<td>7 (3.1)</td>
<td>14 (6.4)</td>
<td>0.099</td>
</tr>
<tr>
<td>TVR (%)</td>
<td>3 (1.3)</td>
<td>1 (0.5)</td>
<td>0.624</td>
</tr>
</tbody>
</table>
WISDOM Registry

Real world

9 countries, 26 sites

Real world safety data on the TAXUS EXPRESS Slow Release Stent System

529 patients from June 2002 to May 2003

- Diabetes mellitus: 32%
- AMI: 10%
- Average lesion length: 15.0 ± 6.5 mm
- Average RVD: 2.9 ± 0.6 mm
- No of stents per pts: 1.23
Feasibility and Efficacy

Polymer Coating Paclitaxel Eluting Stent

• TAXUS I study demonstrated that polymer coated paclitaxel eluting stent is safe and feasible.

• TAXUS studies showed that polymer coated paclitaxel eluting stent has a dramatic effectiveness for inhibition of intimal hyperplasia compared to bare metal stent.

• Moreover its role was maintained for 2 years.
Safety and Efficacy by Experimental Studies

Paclitaxel should be OK!
Why could not demonstrate the same efficacy of the Non-polymer Paclitaxel eluting stents in DELIVER?

By chance or inevitable?
The Guidant ACHIEVE stent

- Coating applied to abluminal surface using Cook’s proprietary surface modification technology
- 3.0 ug/mm² (nominal)
Study Design

- **Test** – ACHIEVE™†
  - n = 521

- **Control** – ML PENTA®
  - n = 521

**de novo Coronary Lesions in Native Vessels**
- n = 1042

Prospective, randomized, single-blinded, parallel-group (two-arm), multi-center clinical trial
Inclusion Criteria

• Target vessel RVD 2.5 – 4.0 mm
• Target lesion length ≤25 mm visually estimated
• Up to two native vessels treated, one target and one non-target, with only one de novo lesion per vessel
• Target lesion %DS ≥50 and <100, and TIMI flow ≥1
DELIVER: 30-Day MACE

Control (n=519)
- Death: 0.2%
- Q-MI: 0.2%
- Non Q-MI: 0.4%

Achieve (n=524)
- Death: 0.2%
- Q-MI: 0.2%
- Non Q-MI: 0.6%
- TLR-CABG: 0.2%

Incidence:
- Control: 1 SAT – 0.2% (day 3)
- Achieve: 1 SAT – 0.2% (day 12)

Incidence (%)
**DELIVER:** 9-Month Death, MI

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Q-MI</th>
<th>Non Q-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.2</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Achieve</td>
<td>1.0</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Control: 1 (0.2%) late SAT  
Achieve: 1 (0.2%) late SAT
DELIVER: Restenosis Rate

Achieve stent: 16.7%
Penta stent: 22.4%

P = NS
DELIVER

The complete data was not presented yet. However, it was reported that major clinical and angiographical end point were not met as powered.
We may speculate reasons why …

1. The drug paclitaxel and its concentration
We may speculate reasons why …

1. The drug paclitaxel and its concentration

   It should be OK
We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system
Optimal Stent Design
For Even Distribution of Drug

- Open diamond design
  - Uneven distribution
  - With curved links

- Closed cell design
  - Even distribution
  - With curved links

- Corrugated ring cell design
Comparison of Stents

Closed cell design
- **Bx Velocity**
- Sirolimus
- Eluting stent

Corrugated ring cell design
- **Supra G, V Flex**
- Non-polymer
- Paclitaxel stent
- **PENTA**
- Non-polymer
- Paclitaxel stent
Comparison of Stents

<table>
<thead>
<tr>
<th></th>
<th>PENTA 3.0x18mm</th>
<th>BX Velocity 3.0x18mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsupported Surface Area</td>
<td>3.85mm²</td>
<td>3.29mm²</td>
</tr>
<tr>
<td>Metal:Artery</td>
<td>14.16%</td>
<td>13.32%</td>
</tr>
<tr>
<td>Max. Circular USA</td>
<td>0.930mm²</td>
<td>1.290mm²</td>
</tr>
</tbody>
</table>

3.5x28mm PENTA

3.5x28mm BX Velocity
Diameter of Curvature: 15.33mm
Balloon Injury in Both Edges

Stent To Shoulder Distance

Mean Distal STS = 1.333mm

Mean Distal STS = 0.555mm

3.0x18mm BX Velocity

3.0x18mm PENTA

Less edge balloon injury...
We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system

It should be OK
We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system
3. The manufacturing of drug coating and the release kinetics
Why Polymer coating?

1. Consistent dosing
2. Controlled release kinetics
3. Structural integrity
Why Polymer coating?

Reproducible release over time

From TAXUS trial

1.0 ug/mm², slow release
3 different lengths
Why Non-Polymer Coating?

- Less complex
- Less expensive

Polymer coating leads to …

Initiation of tissue reaction  Cracking and Embolization
However, non-polymer coating leads to...

Up to 40% drug loss on expansion without a “carrier” in bench testing
Boston Scientific Polymer Coated stent

*In vivo* Paclitaxel Elution

**Fast release**
- 1 ug/mm² (108ug)

**TAXUS trial**

**Moderate release**
-4 ug/mm² (432ug)
-2 ug/mm² (216ug)
-1 ug/mm² (108ug)

**Slow release**
- 1 ug/mm² (108ug)
Vascular Inflammation

Fast release vs. Slow release

Fast release

Slow release
Non-Polymer SUPRA G stent (Cook)

**In vivo Paclitaxel Elution**

<table>
<thead>
<tr>
<th>Days</th>
<th>0.17</th>
<th>4</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Release Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>50</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

3.1 ug/mm² taxol

Faster Release?
We may speculate reasons why …

1. The drug paclitaxel and its concentration
2. The stent and delivery system
3. The manufacturing of drug coating and the release kinetics

Doubtful,
Doubtful…

1. Non-polymer surface modification technique simplifies the manufacturing of the drug coated stent, whereas it is difficult to guarantee the controlled release of paclitaxel.

2. Based on the *in vivo* release kinetics, the Cook non-polymer surface modification technique might release the paclitaxel faster than the polymer coated stents.
Doubtful...

3. Clinical studies about non-polymer paclitaxel eluting stent have a substantially different dose, delivery system and pharmacokinetic profiles. As a result, the diversity may lead to different outcomes.

4. Determinant of the right dose drug concentration for coating might be required for expected clinical outcomes.
Why Polymer?

Potential Advantages
- Consistent dosing
- Controlled release
- Difficulties with loading, sterilization, and expansion
- Inflammatory responses
- Less complex
- Less expensive

Potential Disadvantages
- Drug retention and uniformity
- Consistent release kinetics
Efficacy of Paclitaxel Coated Stents

- **Non-polymer coated stent** …
  DELIVER trial give us doubt.

- **Polymer coated stent**….
  TAXUS trials give us trust.
Taxus vs. Cypher
Which stent would be better?

Stent design

Drugs ↔ Drug Eluting Stent ↔ Drug carrier vehicle
Taxus vs. Cypher

Which stent would be better?

Drug

Paclitaxel

Sirolimus
Taxus vs. Cypher
Which stent would be better?
Taxus vs. Cypher

Which stent would be better?

Polymer

Translute

Two coat

Stent

Basecoat

Stent

Basecoat
Taxus vs. Cypher
Which stent would be better?

Based on Current data base

No clear Difference…
Taxus vs. Cypher

Then, Which will be the winner?

- Preoccupation of Cypher in the market, depending on the management skill of BSC
- **Price**, depending on the policy of each company
- **Stent design**, depending on lesion characteristics
- Doctor’s preference, depending on sponsorship…^-^