Boston Scientific Corporation
Drug-Eluting Stent Program
Program Overview

- World Wide Status
- Restenosis
- Paclitaxel
- Polymers
- Dose and Release Kinetics
Current Worldwide Status

• There are currently three drug eluting stents on the market
  – TAXUS™
  – Cypher™
  – Abbot Biodivisio™ Dexamet stent

• Drug-Eluting Stents are Available in Many Countries at this Time

• Adoption Rates Vary from 2% in France to 50% in Australia

• Early Clinical Performance is Promising, However there are many differences between the products
Restenosis

A Vessel may be Injured During the Stent Implant Process.

Baro Trauma may Cause the Vessel Wall to Fracture.
Restenosis

White Blood Cells, Platelets, and Red Blood Cells Adhere to the Injury Site.

White Blood Cells Migrate to the Media and Degranulate

Caution: Investigational device. Limited by Federal law to investigational use. Not available for sale in the U.S. Rev 03.02
Restenosis

Smooth Muscle Cells Begin to Proliferate, Migrate and Excrete Extracellular Matrix

SMC Proliferation, Migration and Secretion may Cause Excessive Neointimal Formation

The Body’s Response to Injury may be Amplified Resulting in Excessive Neointimal Formation
Targeting Restenosis

The Ideal Pharmaceutical Should Control:
- Platelet Aggregation
- Inflammatory Cells
- SMC Proliferation
- SMC Migration
- ECM

The Ideal Pharmaceutical Should Promote:
- Endothelialization

Restenotic Cascade:
- 0-2 days
- 2-4 days
- 4-10 days
- 10-14 days
- 2-4 weeks
Targeting Restenosis

Characteristics of the Ideal Pharmaceutical

- Highly Lipophilic
  - May Minimize Wash-Out and Enhance Cellular Uptake

Paclitaxel

Lipid Bi-Layer
Targeting Restenosis

• Post-Implantation, Drug-Eluting Stents Should not Arrest the Healing Process, they should:
  – Not Compromise Healthy Formation of Neointima
    • Low and Consistent Late Loss
  – Allow Normal Endothelialization
Paclitaxel

- Multi-Functional Effects on Restenosis
  - Inhibits Proliferation
  - Inhibits Migration
  - Inhibits Extracellular Matrix Secretion
  - Inhibits Inflammation

- Lipophilic
  - Rapid Vascular Uptake
  - 10,000 Times More Lipophilic than Sirolimus*

- Dose-Dependent and Selective Effects
  - Impacts SMCs, Platelets and White Blood Cells While Allowing Re-Endothelialization to Occur

* Data on File.
# Paclitaxel and Taxol® are Different

<table>
<thead>
<tr>
<th>Composition</th>
<th>Paclitaxel</th>
<th>Taxol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% Paclitaxel</td>
<td>Paclitaxel + Cremophor EL + Dehydrated alcohol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Elution from Stent</th>
<th>Intravenous</th>
</tr>
</thead>
</table>

| Dose        | 1.5 µg/kg*          | - 3,280 µg/kg ovarian CA  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- 4,250 µg/kg in breast CA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>Restenosis</th>
<th>Cancer</th>
</tr>
</thead>
</table>

*Based on Implantation of a Single 3.5mm X 16mm TAXUS® Express² Stent with Total Loaded Dose of 108 µg/kg. Dose in µg/kg Calculated Using Average Body Surface Area of 1.7m² and 70kg Body Weight.

Taxol is a registered trademark of Bristol Meyers Squibb

Caution: Investigational device. Limited by Federal law to investigational use. Not available for sale in the U.S.
Rev 03.02
How does Paclitaxel Work?

- Microtubules Impact Cell Functions Such as Proliferation, Migration, Secretion and Inflammation
- Paclitaxel has been Shown to Promote the Formation of Extremely Stable Microtubules, thereby Inhibiting Many Cellular Functions

Image Courtesy of Dr. Vladimir Rodionov
Cytotoxic or Not

- Paclitaxel Used in Formulation on TAXUS Stents has not Shown Any Signs of Toxicity
  - Toxicity is a Dose Dependent Term
  - A Very Large Pre-clinical Program Identified a Safe Dose Range
  - No Signs of Toxicity in the TAXUS Clinical Trial Programs
  - Marketing Spin
Benefits of a Polymer

- Dose Control
  - Uniform Drug Distribution
  - Ability to Modify Release Rate
  - Consistent Release

- Protects the Drug
  - No Loss in Handling or Delivery
  - Consistent Dose

Stent Strut Coated With Polymer Carrier
Polymers

TAXUS™ Express² Stent

Cypher™ Stent

*Single Layer Translute™ polymer with Paclitaxel

*Dual Layer Polymer

PEVA with Sirolimus

PBMA Diffusion Barrier

*These Images are Artist Renditions and are not Intended to Represent Actual Stent Designs.

Caution: Investigational device. Limited by Federal law to investigational use. Not available for sale in the U.S.

Rev 03.02
Translute™ Polymer

- Healing Similar to Control
- Ensures Vascular Compatibility

Images Courtesy of Dr. Robert Schwartz

Caution: Investigational device. Limited by Federal law to investigational use. Not available for sale in the U.S. Rev 03.02
Drug-Eluting Stent Clinical Trial Update
TAXUS II Study Overview

- Randomized (1:1)
- Triple-Blind
- International, Multi-Center
- 536 Patients
  - TAXUSÔ Stent SR - 267
  - TAXUS Stent MR - 269
- 30D, 6 Mo., 1-5 Year F/U
- Endpoints:
  - Clinical
  - QCA
  - IVUS

Inclusion Criteria
- Standard Risk de novo Lesions
- Length ≤ 12 mm
- RVD ≥ 3.0 & ≤ 3.5mm
- Anti Platelet Regimen
  - ASA ≥ 75mg
    - Loading Dose and Maintained Indefinitely
  - Clopidogrel
    - Loading Dose 300 mg
    - 75 mg q.d for 6 Months
**TAXUS II Incomplete Apposition**

Small increase in late acquired IA without statistical significance

<table>
<thead>
<tr>
<th></th>
<th>TAXUS SR n=117</th>
<th>Combined Control n=224</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo. F/U</td>
<td>15 /119 (12.6%)</td>
<td>20/230 (8.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Resolved</td>
<td>7/117 (5.9%)</td>
<td>11/224 (4.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Persistent</td>
<td>5/117 (4.2%)</td>
<td>8/224 (3.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Late Acquired</td>
<td>10/117 (8.5%)</td>
<td>12/224 (5.3%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Total incidence of IA at follow up is 12.8%. No patients with late IA had positive remodeling.

Caution: Investigational device. Limited by Federal law to investigational use. Not available for sale in the U.S. Rev 03.02
Late Loss

• Neointima (Late Loss) may be Desirable to Ensure Complete and Adequate Coverage of Stent Struts therefore Creating a Smooth, Non-Thrombogenic Surface that Helps Prevent Thrombotic Events

• A Drug-Eluting Stent Should not Completely Eliminate the Body’s Healing Response

• Consistent and Adequate Late Loss Values Across Studies may be an Important Indicator of Healing
SIRIUS Late Loss Data

Sirius late loss 0.17mm ± 0.64

Caution: Investigational device. Limited by Federal law to investigational use. Not available for sale in the U.S.
Rev 03.02
Late Loss

Late Loss for all Clinical Trials

<table>
<thead>
<tr>
<th>Device</th>
<th>Late Loss</th>
<th>± (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL</td>
<td>-0.01</td>
<td></td>
</tr>
<tr>
<td>SIRIUS</td>
<td>0.17</td>
<td>±0.42</td>
</tr>
<tr>
<td>E-SIRIUS</td>
<td>Not Reported</td>
<td></td>
</tr>
<tr>
<td>C-Sirius</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>TAXUS I</td>
<td>0.36</td>
<td>±0.48</td>
</tr>
<tr>
<td>TAXUS II</td>
<td>0.31</td>
<td>±0.38</td>
</tr>
<tr>
<td>TAXUS II Diabetics</td>
<td>0.37</td>
<td>±0.35</td>
</tr>
</tbody>
</table>
## Diabetic Patients in TAXUS II

Diabetic Patients Showed Consistent Benefit at 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Control SR (n=22)</th>
<th>TAXUS SR (n=14)</th>
<th>Control MR (n=17)</th>
<th>TAXUSMR (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Loss</td>
<td>.90mm</td>
<td>.37mm</td>
<td>m</td>
<td>.26mm</td>
</tr>
<tr>
<td>Restenosis Rate</td>
<td>18.2%</td>
<td>0%</td>
<td>13.2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Restenosis Rates Exclude Non-Study (Control) Stents
TAXUS II Conclusions

- **Biologic Reproducibility for TAXUS\textsuperscript{\textregistered} Stent Technology:**
  - No Edge effect
  - No statistically Significant Late Incomplete Apposition
  - Consistent Performance in TAXUS I and II Using Different Sites and Core Labs

- *Post hoc analysis of TAXUS II suggests that . . .*
  - Might be more effective in some high patient populations (e.g., diabetics)
**Purpose:** To Demonstrate Safety and Efficacy of TAXUS Express² Stent System for Treatment of *de novo* Lesions

- Prospective, Randomized, Placebo Controlled, Triple Blind
- 74 Centers, 1,326 Patients
- Lesions: *de novo* ³10 mm to £28mm
- Stent Diameters from 2.5 mm - 3.5mm
- Stent Lengths from 16 mm - 32mm
- Slow Release Formulation
- Primary Endpoint: 9 Month TVR, Superiority
- Enrollment completed July 2002
- Results Expected at TCT 2003
Purpose: To Demonstrate Superior 9-Month Target Vessel Revascularization (TVR) for TAXUS SR Compared to ExpressÔ Stent.

*de novo* Arm - Began Enrollment March 2003
- 1,108 Patients
- 10 to 40 mm Lesions Length
- Stents: 2.25 - 4.0 mm, Lengths: 8 - 32 mm
- Slow Release Formulation
- Multiple Stents Allowed

*In-Stent Restenosis Arm*
- 500 Patients
- TAXUS Stent Randomized to Brachytherapy
TAXUS VI

**Purpose:** To Evaluate TVR Rate for TAXUS™ Express2™ Stent System in Long Lesions
  - Prospective, Randomized, Placebo Controlled, Triple Blind Study
  - 44 Sites, 448 Patients
  - Lesion length 18-40mm
  - Primary Endpoint: 9 Month TVR
  - Stent Diameters 2.50 mm to 3.50 mm
  - Stent Lengths 16 mm - 32 mm
  - Moderate Release Formulation
  - Enrollment Completed December 2002
Summary

• Traditional Measures of Performance are Changing

• Consistent Late Loss, Absence of Edge Effect, Low Restenosis Rates and the incidence of Incomplete Apposition may be the best indicators of Safety and Efficacy