Device Description

- Combination Product
- Stent Platform: Driver balloon-expandable cobalt alloy (MP35N) stent
  - 2.5 to 3.5mm Ø and 8 to 30mm in length
  - approved October 1, 2003
- Polymer: phosphorylcholine (PC)
- Drug: zotarolimus (ABT-578)
- Catheter delivery systems
  - Over-The-Wire (OTW)
  - Rapid Exchange (RX)
  - Multi Exchange (MX2)
The Endeavor Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to de novo lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5mm to ≤ 3.5mm.
FDA Review Team

- Center for Drug Evaluation & Research (CDER)
  - Office of Clinical Pharmacology (OCP)
  - Office of New Drug Evaluation I (ODEI)
  - Office of New Drug Quality Assessment (ONDQA)

- Center for Devices & Radiological Health (CDRH)
  - Office of Device Evaluation (ODE)
  - Office of Surveillance & Biometrics (OSB)
  - Office of Compliance (OC)
  - Office of Science & Engineering Laboratories (OSEL)
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- Elizabeth Hillebrenner, Engineering (CDRH/ODE)
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- Wolfgang Kainz, PhD, MR Safety (CDRH/ODE)
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- Melissa Burns, QS/GMP (CDRH/OC)
- Mary Ann Fitzgerald, QS/GMP (CDRH/OC)
- Michelle Noonan, QS/GMP (CDRH/OC)
- Bradley Quinn, QS/GMP (CDRH/OC)
- Melissa Torres, QS/GMP (CDRH/OC)
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- Susan Bowley, PhD
- Ashley Boam
- Nallaperumal Chidambaram, PhD
- Benita Dair, PhD
- Srilekha Das, PhD
- Angelica Dorantes, PhD
- Andrew Farb, MD
- Jonette Foy, PhD

- Jennifer Goode
- Stephen Hilbert, PhD, MD
- Gary Kamer, PhD
- Thomas Marciniak, MD
- Ramsharan Mittal, PhD
- Neal Muni, MD, MSPH
- Kimberly Peters
- LeRoy Schroeder, PhD
- Belay Tesfamariam, PhD
Review of Drug Substance Safety Data

- Safety Pharmacology
- Toxicology
- Absorption, Distribution, Metabolism, and Excretion (ADME) Studies
- Human IV Dosing
Pre-Clinical Review of the Finished Product

- Stent Functional Testing
- Stent Coating Testing
- Stent Delivery System Testing
- Animal Studies
- Chemistry, Manufacturing, and Controls (CMC)
- Sterilization
- Biocompatibility
- Manufacturing (QS/GMP)
# Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>US</th>
<th>Enrollment</th>
<th>Primary Endpoints</th>
<th>dAPT: ASA indefinitely + Plavix/Ticlid ≥3m</th>
<th>Available Follow-up</th>
</tr>
</thead>
</table>
| ENDEAVOR I  |    | Endeavor: 100 | 30d MACE  
4m Late Loss |                                        | 48m                 |
| ENDEAVOR II |    | Endeavor: 598  
Driver: 599 | 9m TVF  
8m Late Loss* |                                        | 36m                 |
| ENDEAVOR II CA | | Endeavor: 296 | 30d MACE | ASA indefinitely + Plavix/Ticlid ≥3m | 24m                 |
| ENDEAVOR III | X | Endeavor: 323  
Cypher: 113 | 8m Late Loss | ASA indefinitely + Plavix/Ticlid ≥3m | 24m                 |
| ENDEAVOR IV | X | Endeavor: 773  
Taxus: 775 | 9m TVF  
8m Late Loss* | ASA indefinitely + Plavix/Ticlid ≥6m | 9m                  |
| ENDEAVOR PK | X | Endeavor: 43 | 30d PK parameters | ASA indefinitely + Plavix/Ticlid ≥3m | 9m                  |
| ENDEAVOR Japan | | Endeavor: 99 | 9m TVF | ASA indefinitely + Plavix/Ticlid ≥3m | 9m                  |

* Powered secondary endpoints
FDA Presentation

- Clinical Review – Andrew Farb, MD
- Statistical Review – Yonghong Gao, PhD
- Summary – Andrew Farb, MD
- Epidemiology Review – Hesha Duggirala, PhD
FDA Clinical Review
Endeavor Zotarolimus-Eluting Coronary Stent

Andrew Farb, M.D.
Division of Cardiovascular Devices
Office of Device Evaluation
October 10, 2007
Relevant Study Definitions

- **Procedural Outcomes**
  - Device Success: Attainment of <50% in-stent residual stenosis of the target lesion using only the assigned device
  - Device-Specific Procedure Success: Device success and no in-hospital MACE

- **Angiographic Outcomes**
  - Late Lumen Loss: Difference between the post-procedure MLD and MLD at follow-up angiography
  - Binary Restenosis: Angiographic follow-up % diameter stenosis of ≥50%
Relevant Study Definitions

- **TVR**: Clinically driven repeat intervention (PCI or CABG) of the target vessel.
- **TLR**: Clinically-driven repeat intervention of the target lesion of the target vessel.
- **TVF**: Composite of TVR, cardiac death, or MI that could not be clearly attributed to a vessel other than the target vessel.
- **MACE**: Composite of death, MI, emergent bypass surgery, or TLR.
Stent Thrombosis Per Protocol

- Any death not attributed to a non-cardiac cause within the first 30 days

- Late Stent Thrombosis
  - MI >30 days after index and attributable to the target vessel
  - Angiographic documentation
  - Freedom from interim revascularization of the target vessel
ARC Stent Thrombosis
Time Frame Classification

- **Acute**: 1 day
- **Subacute**: 2-30 days
- **Early**: 1-30 days
- **Late**: >30 days to 1 year
- **Very Late**: >1 year
ARC Stent Thrombosis
Levels of Evidence

- **Definite/Confirmed**
  - Acute coronary syndrome AND
  - [Angiographic confirmation of thrombus or occlusion OR]
  - Pathologic confirmation of acute thrombosis]

- **Probable**
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion

- **Possible**
  - Unexplained death after 30 days
Endeavor Program
Key Inclusion/Exclusion Criteria

- **Key Inclusion Criteria:**
  - Stable or unstable angina, silent ischemia, or a positive functional study
  - The target lesion was a *single de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$.
  - The target lesion length:
    - $\leq 27$ mm (ENDEAVOR II, IICA, III, IV and PK)
    - $\leq 15$ mm (ENDEAVOR I only)
  - Target vessel reference diameter
    - $\geq 2.25$ mm (ENDEAVOR II and II CA) and $\leq 3.5$ mm
    - $\geq 2.5$ mm (ENDEAVOR III, IV, and PK) and $\leq 3.5$ mm
    - $\geq 3.0$ mm (ENDEAVOR I) and $\leq 3.5$ mm
Endeavor Program
Key Inclusion/Exclusion Criteria

- **Key Exclusion Criteria:**
  - Acute MI within 72 hours
  - Left ventricular ejection fraction <30%
  - Serum creatinine >2.0 mg/dl
  - Left main, ostial lesion, or bifurcation lesion
  - Thrombus within the target vessel
Randomized Trials

- ENDEAVOR II
- ENDEAVOR III
- ENDEAVOR IV
ENDEAVOR II

- Randomized double-blind **superiority** trial

- **Objective:** To demonstrate the safety and efficacy of the Endeavor stent vs. the uncoated Driver Stent for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter

- **Primary endpoint**
  - TVF at 9 months

- **Important secondary endpoints**
  - Device specific procedure success
  - Total MACE and rates of death, MI, revascularization, and stent thrombosis at 30 days and 6, 9, and 12-months and annually to 5 years
  - Angiographic in-segment late lumen loss at 8 months (powered secondary superiority endpoint)
    - Angiography and IVUS follow-up in first 600 and 300 patients, respectively
ENDEAVOR II

- Conducted OUS
  - Europe
  - Asia Pacific
  - Israel
  - Australia
  - New Zealand
ENDEAVOR II
Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endeavor (N=598)</th>
<th>Driver (N=599)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>461</td>
<td>77.2%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>108/595</td>
<td>18.2%</td>
</tr>
<tr>
<td>Insulin Dependent Diabetes*</td>
<td>27/594</td>
<td>4.5%</td>
</tr>
<tr>
<td>Single Vessel Disease</td>
<td>387</td>
<td>64.8%</td>
</tr>
<tr>
<td>Double Vessel Disease</td>
<td>140</td>
<td>23.5%</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>268/545</td>
<td>49.2%</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>181/545</td>
<td>33.2%</td>
</tr>
<tr>
<td>Ilb/Illa inhibitors</td>
<td>79/597</td>
<td>13.2%</td>
</tr>
</tbody>
</table>

*higher rate of Insulin Dependent Diabetes in Driver group (p=0.05)
<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter, mm*</td>
<td>2.73±0.48</td>
<td>2.76±0.49</td>
</tr>
<tr>
<td>Lesion length, mm*</td>
<td>14.04±5.56</td>
<td>14.38±5.73</td>
</tr>
<tr>
<td>Pre-procedure % Stenosis*</td>
<td>69.74±10.89</td>
<td>69.58±11.00</td>
</tr>
<tr>
<td>Vessel Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>43.2%</td>
<td>47.5%</td>
</tr>
<tr>
<td>LCX</td>
<td>22.4%</td>
<td>21.2%</td>
</tr>
<tr>
<td>RCA</td>
<td>34.4%</td>
<td>31.3%</td>
</tr>
<tr>
<td>LMCA</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Post-procedure % Stenosis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Stent</td>
<td>6.04±10.43</td>
<td>6.23±10.03</td>
</tr>
<tr>
<td>In-Segment</td>
<td>20.39±10.26</td>
<td>20.11±9.38</td>
</tr>
</tbody>
</table>

*Mean±SD
**ENDEAVOR II**

Procedural Success and 30 Day MACE

- Device-specific procedure success in Endeavor-stented patients: 96.5%

- 30 Day MACE

<table>
<thead>
<tr>
<th>ENDEAVOR II 30 Day MACE</th>
<th>Endeavor</th>
<th>Driver</th>
<th>Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>2.9%</td>
<td>3.7%</td>
<td>-0.9% (-2.9%, 1.2%)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0.3%</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Non Q-wave MI</td>
<td>2.3%</td>
<td>2.7%</td>
<td></td>
</tr>
</tbody>
</table>
## ENDEAVOR II

### Primary Endpoint Results

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Driver Control</th>
<th>Difference [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVF Rate at 9 months</td>
<td>7.9% (47/592)</td>
<td>15.1% (89/591)</td>
<td>-7.1% [-10.7%, -3.5%]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

48% relative reduction in TVF

Primary endpoint met
ENDEAVOR II

Major Clinical Endpoint Results at 9 months

Death: 1.2% (Endeavor), 0.5% (Driver)
Cardiac Death: 0.8% (Endeavor), 0.5% (Driver)
MI: 2.7% (Endeavor), 3.9% (Driver)
TLR: 4.6% (Endeavor), 5.6% (Driver)
TVR: 11.8% (Endeavor), 12.5% (Driver)
ST Protocol: 0.5% (Endeavor), 1.2% (Driver)
ST ARC Def+Prob: 0.5% (Endeavor), 1.4% (Driver)
ENDEAVOR II
Angiographic Results at 8 months

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Driver Control</th>
<th>Difference [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-segment late loss, mm (n)</td>
<td>0.36±0.46 (264)</td>
<td>0.72±0.61 (263)</td>
<td>-0.36 [-0.45,-0.27]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% diameter stenosis, (n)</td>
<td>32.67±16.27 (264)</td>
<td>44.33±20.45 (265)</td>
<td>-11.66 [-14.82,-8.50]</td>
<td>-</td>
</tr>
<tr>
<td>Binary in-segment restenosis, % (n)</td>
<td>13.3 (35/264)</td>
<td>34.7 (92/265)</td>
<td>-21.5 [-28.5%,-14.4%]</td>
<td>-</td>
</tr>
<tr>
<td>IVUS Volume Obstruction, % (n)</td>
<td>17.34±10.27 (90)</td>
<td>29.55±17.58 (81)</td>
<td>-12.22 [-16.51,-7.92]</td>
<td>-</td>
</tr>
</tbody>
</table>

Secondary angiographic endpoint met
ENDEAVOR II
Major Clinical Endpoint Results at Latest Available Follow-Up (36 months)
ENDEAVOR III

- Randomized single-blind non-inferiority trial
  - Randomized 3:1 Endeavor:Cypher

- **Objective:** To demonstrate the equivalency in in-segment late loss at 8 months between the Endeavor Stent and the Cypher Stent for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter

- **Primary endpoint:** Angiographic in-segment Late Lumen Loss at 8 months
  - Equivalency margin ($\delta$) = 0.20 mm
  - H0: Endeavor stent would have a mean late loss equal to or exceeding that of the Cypher stent by 0.2 mm or more
  - HA: Endeavor would have a mean in-segment late lumen loss less than the control Cypher stent plus 0.2 mm

- **Important secondary endpoints**
  - Device specific procedure success
  - Clinically-driven TLR, TVR, and TVF at 9 months
  - Total MACE and rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually to 5 years
### ENDEAVOR III Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endeavor (N=323)</th>
<th>Cypher (N=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Male*</td>
<td>211</td>
<td>65.3%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>96/323</td>
<td>29.7%</td>
</tr>
<tr>
<td>Insulin Dependent Diabetes</td>
<td>21/322</td>
<td>6.5%</td>
</tr>
<tr>
<td>Single Vessel Disease</td>
<td>201</td>
<td>62.2%</td>
</tr>
<tr>
<td>Double Vessel Disease</td>
<td>94</td>
<td>29.1%</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>118/274</td>
<td>43.1%</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>140/274</td>
<td>51.1%</td>
</tr>
<tr>
<td>Ilb/Illa inhibitors</td>
<td>142/323</td>
<td>44.0%</td>
</tr>
</tbody>
</table>

*higher percentage of women in Endeavor group (p=0.001)
## ENDEAVOR III
Baseline Lesion and Vessel Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Cypher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter, mm*</td>
<td>2.75 ± 0.46</td>
<td>2.79 ± 0.46</td>
</tr>
<tr>
<td>Lesion length, mm*</td>
<td>14.96±6.20</td>
<td>14.95±7.28</td>
</tr>
<tr>
<td>Pre-procedure % Stenosis*</td>
<td>66.81±12.40</td>
<td>67.91±12.42</td>
</tr>
<tr>
<td>Vessel Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>41.2%</td>
<td>39.8%</td>
</tr>
<tr>
<td>LCX</td>
<td>23.2%</td>
<td>28.3%</td>
</tr>
<tr>
<td>RCA</td>
<td>35.6%</td>
<td>31.9%</td>
</tr>
<tr>
<td>LMCA</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Post-procedure % Stenosis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Stent</td>
<td>4.33±9.77</td>
<td>5.92±9.07</td>
</tr>
<tr>
<td>In-Segment</td>
<td>19.38±9.25</td>
<td>20.17±11.74</td>
</tr>
</tbody>
</table>

*Mean±SD
ENDEAVOR III
Procedural Success and 30 Day MACE

- Device-specific procedure success in Endeavor-stented patients: 98.1%
- 30 Day MACE

<table>
<thead>
<tr>
<th>ENDEAVOR III 30 Day MACE</th>
<th>Endeavor</th>
<th>Cypher</th>
<th>Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.6%</td>
<td>3.5%</td>
<td>-2.9% (-6.4%, 0.6%)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Non Q-wave MI</td>
<td>0.6%</td>
<td>3.5%</td>
<td></td>
</tr>
</tbody>
</table>
# ENDEAVOR III
## Primary Endpoint Results

<table>
<thead>
<tr>
<th></th>
<th>Endeavor n=323</th>
<th>Cypher n=113</th>
<th>Difference [One-sided 95% CI]</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-segment late loss at 8 months, mm (n)</td>
<td>0.36 ±0.46 (277)</td>
<td>0.13 ±0.33 (94)</td>
<td>0.24 [-∞, 0.32] (Prespecified non-inferiority margin 0.20)</td>
<td>0.791</td>
</tr>
</tbody>
</table>

*test for non-inferiority

Primary endpoint not met
## ENDEAVOR III
### Other Angiographic and IVUS Results at 8 Months

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Cypher</th>
<th>Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>% diameter stenosis (n)</td>
<td>30.42±15.57 (277)</td>
<td>23.86±13.87 (94)</td>
<td>6.56 [3.01,10.12]</td>
</tr>
<tr>
<td>Binary in-segment restenosis, % (n)</td>
<td>12.3 (34/277)</td>
<td>4.3 (4/94)</td>
<td>8.0 [2.4%,13.6%]</td>
</tr>
<tr>
<td>IVUS Volume Obstruction, % (n)</td>
<td>15.94±10.94 (187)</td>
<td>2.66±3.11 (61)</td>
<td>13.27 [10.48,16.07]</td>
</tr>
</tbody>
</table>
ENDEAVOR III
Major Clinical Outcomes at 9 Months

- TVF: 11.8%
- Death: 0.6%
- Cardiac Death: 0%
- MI*: 3.5%
- TLR: 6.2%
- TVR: 11.2%
- ST Protocol: 0%
- ST ARC Def+Prob: 0%

*Non-Q MI

**Endeavor** blue, **Cypher** yellow

39
ENDEAVOR III
Major Clinical Endpoint Results at Latest Available Follow-Up (24 months)

- TVF: 14.4% Endeavor, 13.4% Cypher
- Death: 1.6% Endeavor, 4.5% Cypher
- Cardiac Death: 0% Endeavor, 0.9% Cypher
- MI*: 0.6% Endeavor, 3.6% Cypher
- TLR: 7.0% Endeavor, 4.5% Cypher
- TVR: 13.7% Endeavor, 9.8% Cypher
- ST Protocol: 0% Endeavor, 0% Cypher
- ST ARC Def+Prob cens: 0% Endeavor, 0% Cypher
- ST ARC Def+Prob uncens: 0.3% Endeavor, 0% Cypher

*Non-Q MI
ENDEAVOR IV

- **Randomized single-blind non-inferiority trial**

- **Objective**: To assess the equivalence in safety and efficacy of the Endeavor stent compared to the Taxus stent for the treatment of single *de novo* lesions in native coronary arteries with a RVD of 2.5-3.5 mm

- **Primary endpoint**: TVF at 9 months
  - Assumed TVF rate for Endeavor and Taxus = 7.6%
  - Equivalency margin ($\delta$) = 3.8%
  - H0: Endeavor stent would have a TVF rate equal to or exceeding that of the Taxus stent by 3.8% or more
  - HA: Endeavor would have a TVF rate less than the Taxus stent plus 3.8%
Important secondary endpoints

- Device specific procedure success
- Total MACE and rates of death, MI, revascularization, and stent thrombosis at 30 days and 6, 9, and 12-months and annually to 5 years
- Angiographic in-segment late lumen loss at 8 months (powered secondary non-inferiority endpoint)
  - Angiographic and IVUS follow-up in first 328 patients
  - Equivalency margin ($\delta$) = 0.20 mm
  - H0: Endeavor stent would have a mean late loss equal to or exceeding that of the Taxus stent by 0.2 mm or more
  - HA: Endeavor would have a mean in-segment late lumen loss less than the Taxus stent plus 0.2 mm
## Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endeavor (N=773)</th>
<th>Taxus (N=775)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>517</td>
<td>66.9%</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>241/773</td>
<td>31.2%</td>
</tr>
<tr>
<td><strong>Insulin Dependent DM</strong></td>
<td>80/773</td>
<td>10.3%</td>
</tr>
<tr>
<td><strong>Single Vessel Disease</strong></td>
<td>424</td>
<td>54.9%</td>
</tr>
<tr>
<td><strong>Double Vessel Disease</strong></td>
<td>221</td>
<td>28.6%</td>
</tr>
<tr>
<td><strong>Stable Angina</strong></td>
<td>281/616</td>
<td>45.6%</td>
</tr>
<tr>
<td><strong>Unstable Angina</strong></td>
<td>318/616</td>
<td>51.6%</td>
</tr>
<tr>
<td><strong>IIb/IIIa inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-Procedure</strong></td>
<td>50/209</td>
<td>23.9%</td>
</tr>
<tr>
<td><strong>During Procedure</strong></td>
<td>195/209</td>
<td>93.3%</td>
</tr>
<tr>
<td><strong>Post-Procedure</strong></td>
<td>154/209</td>
<td>73.7%</td>
</tr>
</tbody>
</table>
## ENDEAVOR IV

### Baseline Lesion and Vessel Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference vessel diameter, mm</strong>*</td>
<td>2.73±0.47</td>
<td>2.70±0.46</td>
</tr>
<tr>
<td><strong>Lesion length, mm</strong>*</td>
<td>13.41±5.67</td>
<td>13.80±6.09</td>
</tr>
<tr>
<td><strong>Pre-procedure % Stenosis</strong>*</td>
<td>64.83±13.29</td>
<td>65.68±13.10</td>
</tr>
<tr>
<td><strong>Vessel Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>42.2%</td>
<td>41.5%</td>
</tr>
<tr>
<td>LCX</td>
<td>26.9%</td>
<td>26.1%</td>
</tr>
<tr>
<td>RCA</td>
<td>30.8%</td>
<td>32.4%</td>
</tr>
<tr>
<td>LMCA</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Post-procedure % Stenosis</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Stent</td>
<td>5.50±9.61</td>
<td>5.01±10.49</td>
</tr>
<tr>
<td>In-Segment</td>
<td>20.47±9.54</td>
<td>20.97±11.12</td>
</tr>
</tbody>
</table>

*Mean±SD
Device-specific procedure success in Endeavor-stented patients: 96.5%

30 Day MACE

<table>
<thead>
<tr>
<th>ENDEAVOR IV 30 Day MACE</th>
<th>Endeavor</th>
<th>Taxus</th>
<th>Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>1.2%</td>
<td>3.0%</td>
<td>-1.8% (-3.2%, -0.4%)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0.3%</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>Non Q-wave MI</td>
<td>0.5%</td>
<td>2.2%</td>
<td></td>
</tr>
</tbody>
</table>
## ENDEAVOR IV
### Primary Endpoint Results

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Taxus</th>
<th>Difference [One-sided 95%CI]</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVF at 9 Months</td>
<td>6.8% (50/740)</td>
<td>7.4% (54/734)</td>
<td>-0.6% [-100%, 1.6%] (Prespecified non-inferiority margin 3.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*test for non-inferiority

**Primary endpoint met**
ENDEAVOR IV
Major Clinical Outcomes at 9 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Endeavor</th>
<th>Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-wave MI</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>1.2%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

### Event Rates

- **Death**: 0.7% Endeavor, 0.8% Taxus
- **Cardiac Death**: 0.4% Endeavor, 0.3% Taxus
- **MI**: 1.5% Endeavor, 2.5% Taxus
- **TLR**: 4.2% Endeavor, 2.7% Taxus
- **TVR**: 5.5% Endeavor, 5.0% Taxus
- **ST Protocol**: 0.8% Endeavor, 0.1% Taxus
- **ST ARC Def+Prob**: 0.9% Endeavor, 0.1% Taxus
## ENDEAVOR IV
Powered Secondary Endpoint Results

<table>
<thead>
<tr>
<th>In-segment late loss at 8 months, mm (n)</th>
<th>Endeavor N=164</th>
<th>Taxus n=164</th>
<th>Difference [One-sided 95% CI]</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.36±0.47 (143)</td>
<td>0.23±0.45 (135)</td>
<td>0.13 [-∞, 0.22] (Prespecified non-inferiority margin 0.20)</td>
<td>0.089</td>
</tr>
</tbody>
</table>

*test for non-inferiority

Secondary angiographic endpoint not met
### ENDEAVOR IV
Other Angiographic and IVUS Results at 8 Months

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Taxus</th>
<th>Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>% diameter stenosis (n)</td>
<td>32.28±17.02</td>
<td>26.61±15.52</td>
<td>5.68 [1.83, 9.52]</td>
</tr>
<tr>
<td></td>
<td>(144)</td>
<td>(135)</td>
<td></td>
</tr>
<tr>
<td>Binary in-segment restenosis, % (n)</td>
<td>15.3 (22/144)</td>
<td>10.4 (14/135)</td>
<td>4.9 [-2.9, 12.7]</td>
</tr>
<tr>
<td>IVUS Volume Obstruction, % (n)</td>
<td>15.72±10.40</td>
<td>9.88±9.24</td>
<td>5.84 [2.68, 9.00]</td>
</tr>
<tr>
<td></td>
<td>(74)</td>
<td>(77)</td>
<td></td>
</tr>
</tbody>
</table>
Non Randomized Studies

- ENDEAVOR I
- ENDEAVOR II Continued Access
- ENDEAVOR PK
ENDEAVOR I

- Non-randomized single arm feasibility trial

- **Objective**: To demonstrate the feasibility of the Endeavor stent for the treatment of single native coronary *de novo* lesions in

- **Primary endpoint**
  - MACE at 30 days

- **Important secondary endpoints**
  - TVF at 9 months
  - Clinically-driven TLR at 9 months
## ENDEAVOR I Clinical Results

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Endeavor (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE at 30 days</td>
<td>1.0% (1/100)</td>
</tr>
</tbody>
</table>

### Clinical Endpoint Results at 9 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Endeavor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVF</td>
<td>2.0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>1.0</td>
</tr>
<tr>
<td>TLR</td>
<td>2.0</td>
</tr>
<tr>
<td>TVR</td>
<td>2.0</td>
</tr>
<tr>
<td>ST Protocol</td>
<td>1.0</td>
</tr>
<tr>
<td>ST ARC Def+Prob</td>
<td>1.0</td>
</tr>
</tbody>
</table>
ENDEAVOR II Continued Access (CA)

- Non-randomized single arm registry

- **Objective**: To expand the acute safety information and performance data of the Endeavor stent for the treatment of single *de novo* lesions in native coronary arteries

- **Primary endpoint**: MACE at 30 days

- **Important secondary endpoints**
  - Device specific procedure success
  - Total MACE and rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually out to five years
  - TLR, TVR, and TVF at 9 months
## ENDEAVOR II CA Clinical Results

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Endeavor (n=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE at 30 days</td>
<td>5.4% (16/296)</td>
</tr>
</tbody>
</table>

### Clinical Endpoint Results at 9 months

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Endeavor (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVF (Death)</td>
<td>13.0</td>
</tr>
<tr>
<td>Death</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0.7</td>
</tr>
<tr>
<td>MI</td>
<td>5.1</td>
</tr>
<tr>
<td>TLR</td>
<td>5.1</td>
</tr>
<tr>
<td>TVR (ST Protocol)</td>
<td>8.9</td>
</tr>
<tr>
<td>ST Def+Prob</td>
<td>0</td>
</tr>
<tr>
<td>ST ARC Def+Prob</td>
<td>0</td>
</tr>
</tbody>
</table>
ENDEAVOR PK

- Non-randomized single arm trial
- **Objective**: To assess the acute pharmacokinetics and safety of zotarolimus from the Endeavor stent used to treat single *de novo* lesions in native coronary arteries
- **Primary endpoint**: Pharmacokinetic parameters
- **Important secondary endpoints**
  - Device specific procedure success
  - Total MACE and individual rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually out to 5 years
  - Clinically-driven TLR, clinically-driven TVR, and TVF at 9 months
- **Patients enrolled**: n=43
Endeavor Stent PK Profile

Mean Zotarolimus Blood Concentration Over Time
Post-Endeavor Stent Implantation
ENDEAVOR PK
Major Clinical Outcomes at 9 months

- TVF: 11.9%
- Death: 4.8%
- Cardiac Death: 4.8%
- MI: 2.4%
- TLR: 2.4%
- TVR: 7.1%
- ST Protocol: 0%
- ST ARC Def+Prob: 0%

[Bar chart showing the percentages for each outcome]
Clinical results from single arm registries were qualitatively in-line with the RCT results with no apparent new safety concerns.
Pooled Analysis

- FDA requested post-hoc analyses of clinical outcomes for patients treated with Endeavor stents pooled from the available clinical trials (ENDEAVOR I, II, II CA, III, IV, and PK)
  - All patients
  - Diabetic Patients
  - Stent thrombosis

- Follow-up through 3 years

- Patients treated with Driver stents in ENDEAVOR II are shown for comparison
  - Number at risk at 3 years = 579

- Results unadjusted for baseline covariates and multiple comparisons
Pooled Analysis: All Patients

- For NMEs such as zotarolimus, FDA requests a minimum 2,000 patient exposure for demonstration of drug safety.
- Across the ENDEAVOR program, 2,123 patients have received the Endeavor stent, of which 1,279 have been followed through 2 years.

<table>
<thead>
<tr>
<th>Latest Available Follow-Up: Endeavor Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>ENDEAVOR I</td>
</tr>
<tr>
<td>ENDEAVOR II</td>
</tr>
<tr>
<td>ENDEAVOR II CA</td>
</tr>
<tr>
<td>ENDEAVOR III</td>
</tr>
<tr>
<td>ENDEAVOR IV</td>
</tr>
<tr>
<td>ENDEAVOR PK</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients
Freedom From Death, Cardiac Death, Non-Cardiac Death, MI
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients
Freedom From Cardiac Death or MI, Stent Thrombosis

Freedom from Cardiac Death + MI
p=0.002 (log rank)

Freedom from Stent Thrombosis (protocol)
p=NS

Freedom from Stent Thrombosis (ARC definite + probable, TLR-censored)
p=NS

Freedom from Stent Thrombosis (ARC definite + probable, uncensored)
p=NS
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

Freedom From TVR and TLR

Freedom from TVR
p<0.001 (log rank)

Freedom from TLR
p<0.001 (log rank)
Diabetic Patients

- Diabetics comprise an important patient subgroup at increased risk for cardiovascular morbidity and mortality.
- Like previous DES applications diabetic patients were included in the Endeavor clinical trials.
- Although there were no pre-specified hypotheses or trial design features to warrant a specific labeled indication for the use of the Endeavor stent in diabetics, FDA believes that clinical outcomes in diabetics should be considered in the review of the Endeavor stent program.

### Patients Analyzed With 270 days Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Non-Diabetics</th>
<th>All Diabetics</th>
<th>Insulin-Dependent Diabetics</th>
<th>Non Insulin-Dependent Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled Endeavor EI, II, II CA, III, IV, PK</td>
<td>1549</td>
<td>537</td>
<td>154</td>
<td>381</td>
</tr>
<tr>
<td>Driver ENDEAVOR II</td>
<td>463</td>
<td>132</td>
<td>44</td>
<td>88</td>
</tr>
</tbody>
</table>
Pooled Analysis: Diabetic Patients

- FDA requested post-hoc analyses of clinical outcomes for diabetic patients treated with Endeavor stents pooled from the available clinical trials (ENDEAVOR I, II, II CA, III, IV, and PK)
  - Endeavor diabetics patients vs. Endeavor non-diabetic patients
  - Endeavor diabetic patients vs. Driver diabetic patients (ENDEAVOR II)
  - Analysis for all diabetics and stratified by insulin and non-insulin-dependent
- Clinical outcomes assessed 270 days
Pooled Endeavor Stent-Treated Patients
Death, Cardiac Death, MI, Death or MI, Stent Thrombosis, TLR, TVR
Diabetics vs. Non-Diabetics Through 270 Days

Diabetics vs. Non-Diabetics Through 270 Days

<table>
<thead>
<tr>
<th>Event</th>
<th>Non-Diabetics</th>
<th>All Diabetics</th>
<th>Insulin-Dependent</th>
<th>Non-Insulin-Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.80%</td>
<td>0.80%</td>
<td>0.70%</td>
<td>0.80%</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0.50%</td>
<td>0.50%</td>
<td>0.60%</td>
<td>0.50%</td>
</tr>
<tr>
<td>MI</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cardiac Death or MI</td>
<td>2.4%</td>
<td>2.8%</td>
<td>2.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Protocol ST</td>
<td>1.5%</td>
<td>1.9%</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>ARC Def+Prob ST</td>
<td>1.4%</td>
<td>1.9%</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>TLR</td>
<td>4.1%</td>
<td>6.3%</td>
<td>6.5%</td>
<td>4.1%</td>
</tr>
<tr>
<td>TVR</td>
<td>5.8%</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

%
Pooled Endeavor vs. Driver
Death, Cardiac Death, MI, Death or MI Through 270 Days
All Diabetics, IDDM, Non-IDDM

All Diabetics, Endeavor
IDDM, Endeavor
Non-IDDM, Endeavor
Non-IDDM, Driver
Pooled Endeavor vs. Driver
Stent Thrombosis, TLR, TVR Through 270 Days
All Diabetics, IDDM, Non-IDDM
Pooled Analysis: Diabetic Patients

- Endeavor stent treated diabetic patients pooled from ENDEAVOR I, II, II CA, III, IV, PK
- Survival analysis through 3 years
- Diabetic patients treated with Driver stents in ENDEAVOR II shown for comparison
- Results are post hoc and unadjusted for other baseline covariates and multiple comparisons
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients
Death, Cardiac Death, MI, Cardiac Death or MI in Diabetics

Freedom from Death
p=NS

Freedom from Cardiac Death
p=0.029 (log rank)

Freedom from MI
p=NS

Freedom from Cardiac Death + MI
p=0.006 (log-rank)
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

Freedom From Stent Thrombosis in Diabetics

- Freedom from ST (protocol) p=NS
- Freedom from Stent Thrombosis (ARC definite + probable, TLR-censored) p=NS
- Freedom from ST (ARC definite + probable, uncensored) p=NS
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients Freedom From Stent TVR and TLR in Diabetics

Freedom from TVR
p=0.003 (log rank)

Freedom from TLR
p<0.001 (log rank)
Stent Thrombosis Rates
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients

EI, EII, EII CA, EIII, EIV, & E PK

0-30 days 0.3 0.3
0-180 days 0.5 0.5
0-270 days 0.5 0.5
0-720 days 0.3 0.5
0-1080 days 0.6 0.9

EI & EII

0-30 days 1.2
0-180 days 1.2
0-270 days 1.2
0-720 days 1.4
0-1080 days 1.4

Endeavor, Protocol ST
Driver, Protocol ST
Endeavor, ARC ST*
Driver, ARC ST*

*ARC ST reflects the definite + probable, TLR-censored definition
Late Stent Thrombosis

- DES that utilize drugs that interfere with the cell cycle (such as Sirolimus, Paclitaxel, and Zotarolimus) inhibit in-stent neointimal growth but also delay neointimal healing and endothelialization.
  - Prolongs the window of thrombotic risk vs. BMS

- Autopsy studies suggest that incomplete or delayed neointimal healing may be an important mechanism of late DES thrombosis.

- Although overall rates of stent thrombosis may be similar between DES and BMS, any observed increased rate of late stent thrombosis in DES patients is an important safety concern.
FDA requested post-hoc analyses of data pooled from all Endeavor trials for potential signals of late cardiac death, MI, or stent thrombosis.

The following Kaplan-Meier curves depict late safety outcomes beyond the one year landmark in patients treated with Endeavor stents pooled from the Endeavor trials.

- Patients treated with Driver stents in ENDEAVOR II are shown for comparison.
- Results are unadjusted for covariate imbalance and multiplicity.

<table>
<thead>
<tr>
<th></th>
<th>Number at Risk</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled Endeavor</td>
<td>1301</td>
<td>1287</td>
<td>675</td>
<td></td>
</tr>
<tr>
<td>Driver (ENDEAVOR II)</td>
<td>589</td>
<td>586</td>
<td>579</td>
<td></td>
</tr>
</tbody>
</table>
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients
Freedom From Stent Thrombosis, Death Beyond 1 Year
Pooled Endeavor (EI, EII, EII CA, EIII, EIV, & E PK) Patients vs. Driver (ENDEAVOR II) Patients
Cardiac Death, MI, Cardiac Death or MI Beyond 1 Year

Freedom from Cardiac Death
p=0.002 (log rank)

Freedom from MI
p=NS

Freedom from Cardiac Death + MI
p=0.01 (log rank)
## ENDEAVOR Patients
### Incomplete Stent Apposition

<table>
<thead>
<tr>
<th>Difference</th>
<th>ENDEAVOR I*</th>
<th>ENDEAVOR II</th>
<th>ENDEAVOR III</th>
<th>ENDEAVOR IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISA at Post-Procedure</td>
<td>12.6% (12/95)</td>
<td>24.8% (36/145)</td>
<td>12.4% (31/251)</td>
<td>12.5% (17/136)</td>
</tr>
<tr>
<td>ISA at 8 Month Follow-up</td>
<td>4.7% (4/86)</td>
<td>16.8% (21/125)</td>
<td>7.5% (17/226)</td>
<td>10.0% (12/120)</td>
</tr>
<tr>
<td>Resolved</td>
<td>8.1% (7/86)</td>
<td>7.0% (8/114)</td>
<td>5.8% (11/189)</td>
<td>3.8% (4/106)</td>
</tr>
<tr>
<td>Persistent</td>
<td>4.7% (4/86)</td>
<td>17.5% (20/114)</td>
<td>7.9% (15/189)</td>
<td>8.5% (9/106)</td>
</tr>
<tr>
<td>Late Acquired</td>
<td>0.0% (0/86)</td>
<td>0.0% (0/114)</td>
<td>0.5% (1/189)</td>
<td>0.9% (1/106)</td>
</tr>
</tbody>
</table>

*ENDEAVOR I values are based on 12 month follow up
**Dual Antiplatelet Therapy Per Protocol**

<table>
<thead>
<tr>
<th>ENDEAVOR I, II, II CA, III, PK</th>
<th>ASA indefinitely + Clopidogrel or Ticlopidine for at least 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDEAVOR IV*</td>
<td>ASA indefinitely + Clopidogrel or Ticlopidine for at least 6 months</td>
</tr>
</tbody>
</table>

*At least 6 months of dual antiplatelet therapy used in ENDEAVOR IV to match the Taxus stent labeled recommendation*
# ENDEAVOR Patients

## Dual Antiplatelet Therapy Use At 6 Months

<table>
<thead>
<tr>
<th></th>
<th>ENDEAVOR II (N=598)</th>
<th>ENDEAVOR II CA (N=296)</th>
<th>ENDEAVOR III (N=323)</th>
<th>ENDEAVOR IV (N=773)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>96.9% (561/579)</td>
<td>95.1% (272/286)</td>
<td>95.9% (303/316)</td>
<td>95.8% (713/744)</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></td>
<td>65.5% (377/576)</td>
<td>59.4% (170/286)</td>
<td>90.1% (264/293)</td>
<td>94.8% (697/735)</td>
</tr>
<tr>
<td><strong>Ticlopidine</strong></td>
<td>2.1% (12/569)</td>
<td>0% (0/287)</td>
<td>6.1% (2/33)</td>
<td>29.4% (5/17)</td>
</tr>
<tr>
<td><strong>Aspirin + Clopidogrel or Ticlopidine</strong></td>
<td>64.8% (375/579)</td>
<td>55.9% (161/288)</td>
<td>81.6% (258/316)</td>
<td>92.3% (687/744)</td>
</tr>
</tbody>
</table>
Summary

- **Clinical endpoints**
  - Endeavor stent *met* its primary TVF superiority endpoint vs. the bare metal Driver stent (ENDEAVOR II)
  - Endeavor stent *met* its primary TVF non-inferiority endpoint vs. the Taxus stent (ENDEAVOR IV)

- **Angiographic endpoints**
  - Endeavor stent *met* its late loss endpoint vs. the bare metal Driver stent (ENDEAVOR II)
  - Endeavor stent *failed to meet* its non-inferiority late loss endpoint endpoints vs. the Cypher (ENDEAVOR III) and Taxus (ENDEAVOR IV) stents
Safety

- The Endeavor clinical studies include a total of 2,133 patients assigned to receive Endeavor stents with 1,287 patients followed out to 24 months.

- For the individual randomized trials (ENDEAVOR II, III, and IV), increased rates of death, cardiac death, MI, cardiac death or MI, or noncardiac death for the Endeavor stent vs. the control stents have not been observed.

- Outcomes from an analysis of patients treated with Endeavor stents pooled from the submitted Endeavor clinical trials did not demonstrate unanticipated safety signals.
FDA Statistical Review
Endeavor Zotarolimus-Eluting Coronary Stent

Yonghong Gao, PhD
Gary Kamer, MS

Division of Biostatistics
Office of Surveillance and Biometrics
October 10, 2007
Trial Overview

Six prospectively designed studies to evaluate the Endeavor Zotarolimus-Eluting Coronary Stent System

<table>
<thead>
<tr>
<th>Trial</th>
<th>#Center</th>
<th>Endeavor Patients</th>
<th>Control Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>EI</td>
<td>8</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>EII</td>
<td>72</td>
<td>598</td>
<td>599 BMS</td>
</tr>
<tr>
<td>EII CA</td>
<td>15</td>
<td>296</td>
<td>0</td>
</tr>
<tr>
<td>EIII</td>
<td>29 (US)</td>
<td>323</td>
<td>113 Cypher</td>
</tr>
<tr>
<td>EIV</td>
<td>80 (US)</td>
<td>773</td>
<td>775 Taxus</td>
</tr>
<tr>
<td>EPK</td>
<td>6 (US)</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>
Endeavor II

- Objective: superiority to Driver bare metal stent (BMS)
- Primary endpoint: TVF at 9-month
- Powered secondary endpoint: in-segment late loss at 8-month
- 1:1 randomization to DES or BMS:
  598 DES patients and 599 BMS patients, all OUS powered at 90% with 2-sided 5% type I error rate
- Angiographic subgroup: first 600 consecutively enrolled were evaluated for late loss
Results of Endeavor II: TVF

- Primary endpoint: TVF at 9-month
- Superiority hypotheses:
  
  \[ H_0: P_e = P_c \]
  
  \[ H_a: P_e \neq P_c \]

14 pts (6 Endeavor vs. 8 Driver) were excluded from the analysis

<table>
<thead>
<tr>
<th></th>
<th>Enrolled</th>
<th>Available</th>
<th>TVF rate</th>
<th>DES - BMS 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>598</td>
<td>592</td>
<td>7.9%</td>
<td>-7.1% (-10.7%, -3.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMS</td>
<td>599</td>
<td>591</td>
<td>15.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMS <0.001
### Missing Data: EII TVF

#### Sensitivity analysis:

<table>
<thead>
<tr>
<th>TVF at 9-month</th>
<th>Endeavor DES (N=598)</th>
<th>Driver BMS (N=599)</th>
<th>Endeavor –Driver (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple imputation</td>
<td>8.1%</td>
<td>15.4%</td>
<td>-7.3% (9.0%, -5.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worst case</td>
<td>8.9% (53/598)</td>
<td>14.9% (89/599)</td>
<td>-6.0% (9.6%, -2.3%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Available case</td>
<td>7.9% (47/592)</td>
<td>15.1% (89/591)</td>
<td>-7.1% (10.7%, -3.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Same conclusion for all analyses: met the endpoint
Results of Endeavor II: Late Loss

- Powered secondary endpoint: 8-month late loss in mm
- Superiority hypotheses:
  \[ H_0: \mu_e = \mu_c \]
  \[ H_a: \mu_e \neq \mu_c \]

<table>
<thead>
<tr>
<th>Available patients</th>
<th>mean</th>
<th>SD</th>
<th>Difference (DES - BMS) 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>262</td>
<td>0.36</td>
<td>-0.36, (-.452, -.267)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMS</td>
<td>263</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 73 pts (34 DES vs. 39 BMS) were excluded from the analysis
## Missing Data: Ell Late Loss

### Sensitivity analysis:

<table>
<thead>
<tr>
<th>Late Loss</th>
<th>Endeavor (N=298)</th>
<th>Driver (N=302)</th>
<th>Endeavor – Driver, 2-sided 95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputation</td>
<td>0.35± 0.53</td>
<td>0.73± 0.63</td>
<td>-0.38, (-0.47,0.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Worst case</td>
<td>0.57± 0.74</td>
<td>0.57± 0.68</td>
<td>0.00, (-0.12, 0.11)</td>
<td>0.975</td>
</tr>
<tr>
<td>Available case</td>
<td>0.36± 0.46 (264)</td>
<td>0.72± 0.61 (263)</td>
<td>-0.36, (-0.45, -.27)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Multiple imputation and the available case analysis: met the endpoint
- Worst case analysis: failed to meet the criteria
Endeavor III

- Objective: non-inferior to Cypher in 8-month late loss
  \[ H_0: \mu_e \geq \mu_c + \delta \]
  \[ H_a: \mu_e < \mu_c + \delta \]
  non-inferiority margin \( \delta = 0.2 \text{mm} \)

- 3:1 randomization to Endeavor DES versus Cypher:
  323 Endeavor patients vs. 113 Cypher patients

- Powered at 90% with 1-sided alpha of 5%
Non-inferiority Testing

• To demonstrate the test device is not worse than the control by more than the allowable margin
• Allowable margin is called non-inferiority margin (delta)
• Non-inferiority hypotheses
  \[ H_0: \mu_e \geq \mu_c + \delta \]
  \[ H_a: \mu_e < \mu_c + \delta \]
• Pre-specify the margin in the protocol
• One-tailed testing and one-sided confidence interval
## Results of Endeavor III: Late Loss

<table>
<thead>
<tr>
<th></th>
<th>Available (treated)</th>
<th>Mean (SD)</th>
<th>Endeavor - Cypher</th>
<th>Upper bound of 1-sided 95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIII</td>
<td>277 (323)</td>
<td>0.36 (0.46)</td>
<td>0.23</td>
<td>0.32</td>
<td>0.791</td>
</tr>
<tr>
<td>Cypher</td>
<td>94 (113)</td>
<td>0.13 (0.33)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 14.6% = 65/436 pts were excluded from the analysis
- 46 Endeavor pts vs. 19 Cypher pts
## Missing Data: EIII Late Loss

### Sensitivity analysis

<table>
<thead>
<tr>
<th>Late Loss</th>
<th>Endeavor (N=323) Mean±SD</th>
<th>Cypher (N=113) Mean±SD</th>
<th>Difference, Upper Bound of 1-sided 95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple imputation</td>
<td>0.35± 0.50</td>
<td>0.17± 0.74</td>
<td>DIFF = 0.18 UB = 0.30</td>
<td>0.607</td>
</tr>
<tr>
<td>Worst case</td>
<td>0.63± 0.77</td>
<td>0.01± 0.40</td>
<td>DIFF = 0.62 UB = 0.74</td>
<td>0.995</td>
</tr>
<tr>
<td>Available case</td>
<td>0.36± 0.46 (277)</td>
<td>0.13± 0.33 (94)</td>
<td>DIFF = 0.24 UB = 0.32</td>
<td>0.791</td>
</tr>
</tbody>
</table>

- Same conclusion for all analyses: failed to show non-inferiority
Baseline Covariates

- EIII: statistically-significant covariate imbalance between the two arms was observed for gender:
  - 34.7% females for Endeavor vs. 18.6% for Cypher
- Propensity score analysis was performed, but the results of EIII remained essentially unchanged
Endeavor IV

- Objective: non-inferior to Taxus DES
- Primary endpoint: 9-month TVF
- Powered secondary endpoint: 8-month late loss
- 1:1 randomization to Endeavor DES or Taxus
  - 773 Endeavor patients vs. 775 Taxus patients
  - Powered at 84% with 1-sided 5% type I error rate
- First 328 consecutively enrolled pts (164 pts per arm) were evaluated for 8-month late loss
  - Powered at 80% with 1-sided 5% type I error rate
Results of Endeavor IV: TVF

- **Primary endpoint:** TVF at 9-month
- **Non-inferiority hypotheses:**
  \[ H_0: P_e \geq P_c + \delta \]
  \[ H_a: P_e < P_c + \delta, \text{ non-inferiority margin } \delta = 3.8\% \]

<table>
<thead>
<tr>
<th></th>
<th>Available (enrolled)</th>
<th>TVF rate</th>
<th>Endeavor – Taxus</th>
<th>Upper bound of 1-sided 95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIV</td>
<td>740 (773)</td>
<td>6.8%</td>
<td>-0.6%</td>
<td>1.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Taxus</td>
<td>734 (775)</td>
<td>7.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 74 pts excluded: 33 Endeavor vs. 41 Taxus
**Missing Data: EIV TVF**

**Sensitivity analysis**

<table>
<thead>
<tr>
<th>TVF</th>
<th>Endeavor (N=773)</th>
<th>Taxus (N=775)</th>
<th>Difference</th>
<th>Upper Bound of 1-sided 95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple imputation</strong></td>
<td>7.7%</td>
<td>8.0%</td>
<td>DIFF=-0.4%</td>
<td>UB=1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Worst case</strong></td>
<td>10.7% (83/773)</td>
<td>7.0% (54/775)</td>
<td>DIFF=3.8%</td>
<td>UB=6.1%</td>
<td>0.492</td>
</tr>
<tr>
<td><strong>Available case</strong></td>
<td>6.8% (50/740)</td>
<td>7.4% (54/734)</td>
<td>DIFF=-0.6%</td>
<td>UB=1.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Multiple imputation and available case analyses: supported non-inferiority
- Worst case analysis: failed to show non-inferiority
- Odds ratio in missing patients must be >8.1 to overturn non-inferiority
Results of Endeavor IV: Late Loss

- Secondary endpoint: Late loss at 8-month
- Non-inferiority hypotheses:
  \[ H_0: \mu_e \geq \mu_e + \delta \]
  \[ H_a: \mu_e < \mu_e + \delta, \text{ non-inferiority margin } \delta = .2\text{mm} \]

<table>
<thead>
<tr>
<th></th>
<th>Available (planned)</th>
<th>Mean (SD)</th>
<th>Endeavor-Taxus</th>
<th>Upper bound of 1-sided 95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIV</td>
<td>143 (164)</td>
<td>0.36 (0.47)</td>
<td>0.13</td>
<td>0.22</td>
<td>0.089</td>
</tr>
<tr>
<td>Taxus</td>
<td>135 (164)</td>
<td>0.23 (0.45)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 50 pts excluded: 21 Endeavor vs. 29 Taxus
### Missing Data: EIV Late Loss

#### Sensitivity analysis

<table>
<thead>
<tr>
<th>Late Loss</th>
<th>Endeavor (N=164) Mean±SD</th>
<th>Taxus (N=164) Mean±SD</th>
<th>Difference Upper Bound of 1-sided 95%CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple imputation</td>
<td>0.35± 0.54</td>
<td>0.23± 0.49</td>
<td>DIFF=0.12 UB=0.20</td>
<td>0.057</td>
</tr>
<tr>
<td>Worst case</td>
<td>0.55± 0.68</td>
<td>0.05± 0.56</td>
<td>DIFF=0.50 UB=0.62</td>
<td>1</td>
</tr>
<tr>
<td>Available case</td>
<td>0.36± 0.47 (143)</td>
<td>0.23± 0.45 (135)</td>
<td>DIFF=0.13 UB=0.22</td>
<td>0.089</td>
</tr>
</tbody>
</table>

- Same conclusion for all analyses: failed to show non-inferiority
Summary of Statistical Inference

- For 9-month TVF:
  showed superiority to Driver (EII)
  showed non-inferiority to Taxus (EIV)

- For 8-month in segment late loss:
  showed superiority to Driver (EII)
  failed to show non-inferiority to Cypher (EIII)
  failed to show non-inferiority to Taxus (EIV)
Summary

- **Clinical endpoints**
  - Endeavor stent *met* its primary TVF superiority endpoint vs. the bare metal Driver stent (ENDEAVOR II)
  - Endeavor stent *met* its primary TVF non-inferiority endpoint vs. the Taxus stent (ENDEAVOR IV)

- **Angiographic endpoints**
  - Endeavor stent *met* its late loss endpoint vs. the bare metal Driver stent (ENDEAVOR II)
  - Endeavor stent *failed to meet* its non-inferiority late loss endpoint endpoints vs. the Cypher (ENDEAVOR III) and Taxus (ENDEAVOR IV) stents
Putting Clinical and Angiographic Endpoints into Perspective

- Reconcile a less effective stent with respect to inhibition of in-segment neointimal growth compared to approved DES with...

- A stent that is non-inferior to approved DES with respect to TVF
  - A composite clinical endpoint that combines safety (cardiac death and MI) and effectiveness (TVR) elements
Clinical Endpoints
DES vs. BMS Superiority Trials

- Historically (for the currently approved DES) and the Endeavor stent
  - Randomized trials show a significant reduction in the TVF composite endpoint by DES vs. BMS
    - E.g., 48% reduction in TVF in Endeavor vs. Driver in ENDEAVOR II (7.9% vs. 15.1%)
  - Superiority of DES driven by reduction in repeat revascularization rates (TLR and TVR)
    - E.g., 61% reduction in TLR in Endeavor vs. Driver
  - No significant differences in low rates of cardiac death or MI

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>MI</td>
<td>2.7%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>
Angiographic Endpoints
DES vs. BMS Superiority Trials

- Angiography can directly assess the effect of a DES in preventing restenosis

- Historically (for the currently approved DES) and the Endeavor stent
  - Angiographic studies within randomized trials show that DES are significantly more effective in inhibiting neointimal growth
    - Reduced late lumen loss
    - Reduced percent stenosis
    - Reduced rates of binary restenosis
  - E.g., 50% reduction in late lumen loss in Endeavor stent vs. Driver stent in ENDEAVOR II
Angiographic Surrogate Markers for Stent Effectiveness

- Serial angiographic studies from randomized trials of DES vs. BMS show that late loss and percent diameter stenosis are strong surrogate markers predictive of repeat revascularization.

Pocock S, et al., European Society of Cardiology Congress, September 2007
Pivotal DES vs. DES Non-inferiority Trials
Focus on Endeavor IV

- First head-to-head DES vs. DES trial powered for both clinical (TVF) and angiographic (late loss) endpoints
  - TVF endpoint for non-inferiority met
  - Late loss endpoint for non-inferiority not met

<table>
<thead>
<tr>
<th></th>
<th>Endeavor</th>
<th>Taxus</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVF at 9 Months</td>
<td>6.8% (50/740)</td>
<td>7.4% (54/734)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Endeavor N=164</th>
<th>Taxus n=164</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-segment late loss at 8 months, mm</td>
<td>0.36±0.47</td>
<td>0.23±0.45</td>
<td>0.089</td>
</tr>
</tbody>
</table>
Exploring Dichotomous Results in ENDEAVOR IV

- Rates of the components of TVF were low in both Endeavor and Taxus groups

<table>
<thead>
<tr>
<th>Events at 270 Days</th>
<th>Endeavor</th>
<th>Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>MI</td>
<td>1.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>TVR</td>
<td>5.5%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

- TLR a superior clinical measure of stent effectiveness at the treated arterial segment compared with TVR

- Differences in rates of TLR were consistent with greater angio effectiveness of the TAXUS stent albeit with low rates of TLR in both groups

<table>
<thead>
<tr>
<th>Events at 270 Days</th>
<th>Endeavor</th>
<th>Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Lesion Revascularization</td>
<td>4.2%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

- Since numerous factors that may affect whether a repeat revascularization is performed, the clinical impact of small differences in low rates of TVR or TLR is uncertain
Angiographic Inferiority in ENDEAVOR IV

- The late loss/TLR graph is curvilinear
- Differences in late loss in Endeavor vs. Taxus stent located at the flat part of the curve associated with relatively small differences in revascularization rates compared to Endeavor vs. Driver stents

Pocock S, et al., European Society of Cardiology Congress, September 2007
Clinical Effectiveness

DES vs. DES

- Based on the results of ENDEAVOR IV, it is uncertain whether the less effective angiographic results of the Endeavor stent will translate into a significantly greater frequency of repeat revascularization compared to the Taxus stent in a larger study population or with longer-term follow-up.
  - Follow-up for ENDEAVOR IV only available through 9 months
  - Longer-term follow-up of ENDEAVOR IV patients will provide important information on this issue.

- From a review of the Endeavor program, cases of TLR and TVR continue to accrue over time in all treatment groups (Endeavor, Driver, and Cypher) without a pattern of reduced clinical effectiveness of the Endeavor stent.
Safety and Effectiveness

Studies of DES vs. BMS or DES

- PMA approval is dependent on a reasonable expectation of safety and effectiveness

- What we have learned in the DES era:
  - In DES vs. BMS studies, any short or long-term risks of putting a drug on a stent need to be clearly outweighed by the clinical benefit of a drug-eluting device
  - Effectiveness over time should be evaluated in the context of long-term safety (death, MI, and stent thrombosis)
Post-Approval Considerations
Endeavor Zotarolimus-Eluting Coronary Stent

Hesha Duggirala, PhD
Epidemiology Branch
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
October 10, 2007
Outline

- General Principles
- Rationale/Postmarket Questions
- Proposed Post-Approval Study (PAS) Protocol
- Assessment of PAS Protocol
- PAS Issues for Panel Discussion
Disclaimer

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.

- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.

- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.
Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.

Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.
General Objectives for Post-Approval Studies

- Gather postmarket information
  - Longer-term performance
  - Community performance
  - Effectiveness of training programs
  - Sub-group performance
  - Rare adverse events and real world experience
- Account for Panel recommendations
Views on Post-Approval Studies for Drug Eluting Stents (DES)

- Not known if ST rate plateaus or continues to increase over time
- Study incidence rate of cardiac death and MI
- Study routine clinical use of DES
Issues to be Considered in Endeavor PAS

- Stent thrombosis
  - Confirm incidence is <1% for each 12 month period after 1 year

- 5-year patient informed consent

- Evaluate higher risk subgroups
  - Patient characteristics
  - Lesion characteristics
Overview of Sponsor’s Approach

- Endeavor US Postmarketing Registry (n=2000)
- OUS PROTECT - Patient Related Outcomes with Endeavor versus Cypher stenting Trial (n=4000)
## Overview of US Postmarketing Registry

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Non-randomized, prospective, multi-center, single-arm registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Consecutive patient who receive Endeavor stent and consent to participate</td>
</tr>
<tr>
<td>Sample Size</td>
<td>2000 patients</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Up to 5 years</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Stent thrombosis rate up to 5-years</td>
</tr>
<tr>
<td>Co-Primary Endpoint</td>
<td>Rates of cardiac death and MI</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Composite total death and non-fatal MI; composite cardiac death and non-fatal MI</td>
</tr>
<tr>
<td>Antiplatelet regimen</td>
<td>Per proposed labeling</td>
</tr>
</tbody>
</table>
### Overview of PROTECT Study

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Prospective, multi-center, randomized, two-arm trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>1:1 Endeavor versus Cypher</td>
</tr>
<tr>
<td>Sample Size</td>
<td>8800 patients</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Up to 5 years</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Overall stent thrombosis rate at 3 years</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Composite total death and non-fatal MI; composite cardiac death and non-fatal MI</td>
</tr>
<tr>
<td>Antiplatelet regimen</td>
<td>Minimum 3 months</td>
</tr>
</tbody>
</table>

- A portion of PROTECT patients will be pooled with U.S. registry patients for an analysis of stent thrombosis rates.
Proposed Statistical Analysis Plan

- **Primary endpoint**
  Alternative hypothesis – the Endeavor Definite/Probable Stent Thrombosis rate per ARC definition during each yearly interval post-implant is less than 1.0% when used in accordance with the labeled indication.

- **Co-primary endpoint**
  Alternative hypothesis - the incidence of cardiac death and MI in patients treated with the Endeavor DES will not exceed the endpoint incidence by 50% or more for patients treated with the Driver stent.

- **Pool U.S. Registry patients with portion of PROTECT patients**
The post-market study has been designed to:

- Identify rates of stent thrombosis through five years.
- Assess rates of cardiac death and MI to confirm long-term safety of the Endeavor stent when implanted in accordance with its labeled indications for use compared to the Driver bare metal stent.
- Evaluate use of the Endeavor stent for potential safety signals associated with higher risk lesion and patient subsets, recognizing from published literature that such patients are likely to receive drug-eluting stents in clinical practice.

*Are the objectives identified above appropriate? Please discuss what additional objectives should be considered.*
PAS Issues for Panel Discussion

- Not powered for sub-group analysis
- Unclear if 5-year follow-up is sufficient for long-term stent thrombosis evaluation
- Potential differences on anti-platelet therapy recommendations

*Please discuss if the study protocol should be revised to address these issues.*
Questions?