Endeavor-Combining Safety with Efficacy

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Primary limiting factor in long term vessel patency

Time course variable
- In ~30% of patients within 9 months after procedure
- Median at 3 months
- Reported to occur up to 7 years after procedure with a rate of 1–2% per year = as for progression of disease

Poor understanding of cause
- Predictors only explain 20–30% of restenosis

Accounts for significant
- Morbidity
- Health care expenditures
Deliverability
Efficacy
Safety
DES - OPTIMAL SAFETY - EFFICACY BALANCE

Incomplete vascular healing
+ Endothelial dysfunction

Hypothesis - link has not been established so far

Overall results of DES implantation

Restenosis

Late Thrombosis

N. Kipshidze and M. Leon, J Am Coll Cardiol 2005, 47(9): 1911-1913
Early Trials

TLR Rates

2 Year Clinical Results of TAXUS II, TCT.
4 Year Clinical Results TAXUS II WCC.
3 Year Results of RAVEL Trial, Circulation DOI:10.11661/01.CIR.0000156334.24955.B2.
RAVEL 4 Year Results, Sousa, PCR.
RAVEL 5 Year Results, Morice, WCC.

Clinical results are not suitable for comparison
ENDEAVOR II

Randomized, Double-Blind Trial Design

Single De Novo Native Coronary Artery Lesions
Stent Diameters: 2.25-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14-27 mm
Pre-dilatation required

Endeavor Stent
Active Arm
n = 600

Driver Stent
Control Arm
n = 600

N = 1,200 patients
72 sites
Europe, Asia Pacific, Israel, New Zealand and Australia

Clinical/MACE

Angiography/IVUS

Angio N = first 600
IVUS N = first 300
IVUS for overlapping stents

Primary Endpoint: TVF (cardiac death, MI, TVR) at 9 months
Dual antiplatelet therapy for 3 months. 10 µg Zotarolimus per mm stent length

ENDEAVOR II
ENDEAVOR II

TLR at 9 Months

Rate

Driver (n=591/599)
Endeavor (n=592/598)

11.8%
4.6%

↓ 61%

P<0.001

Target Vessel Failure*  Major Adverse Cardiac Events

<table>
<thead>
<tr>
<th></th>
<th>Driver</th>
<th>Endeavor</th>
<th>Driver</th>
<th>Endeavor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>15.1%</td>
<td>7.9%</td>
<td>14.4%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

*Target Vessel Failure is a composite of target vessel revascularization, Q- or non Q-wave MI, or cardiac death.
Pivotal Trials: Late loss vs. TLR

**Late loss (mm)**

<table>
<thead>
<tr>
<th>In-stent LL (mm)</th>
<th>In-segment LL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDEAVOR II</td>
<td>0.62, 0.36</td>
</tr>
<tr>
<td>TAXUS IV</td>
<td>0.39, 0.23</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>0.17, 0.24</td>
</tr>
</tbody>
</table>

**TLR at 9 months (%)**

<table>
<thead>
<tr>
<th></th>
<th>ENDEAVOR II</th>
<th>TAXUS IV</th>
<th>SIRIUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.6</td>
<td>3.0</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*12 month analysis

Data from different clinical trials are not suitable for comparison.

ENDEAVOR II

Event Free Survival at 2 Years

EII TLR-Free Survival Sustained Over Time

Event Free Survival at 2 Years

Efficacy Measures

TLR Rates

Clinical results are not suitable for comparison.
Clinical Events (%)

12-Month Follow-Up

DES Arms from Pivotal Trials

- 12-Month Follow-Up
  - ENDEAVOR II
  - TAXUS IV
  - SIRIUS

Fajadet et al. Circulation. 2006; 114:98-806
Clinical Events (%)

24-Month Follow-Up

DES Arms from Pivotal Trials

**Clinical Events (%)**

<table>
<thead>
<tr>
<th></th>
<th>TLR</th>
<th>TVR</th>
<th>TVF</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDEAVOR II</td>
<td>6.5</td>
<td>8.4</td>
<td>11.1</td>
<td>9.9</td>
</tr>
<tr>
<td>TAXUS IV</td>
<td>5.6</td>
<td>10.6</td>
<td>14.0</td>
<td>14.7</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>6.3</td>
<td>11.7</td>
<td>13.0</td>
<td>10.9</td>
</tr>
</tbody>
</table>

Sirius Study 2 year Results Kereiakes. TCTMD.
TAXUS IV 2 Year Results. Stone TCTMD.
ENDEAVOR III
Multicenter Randomized Trial
3:1 Randomization
Single Blind - Single Vessel - No Staging

Single De Novo Native Coronary Lesion
Vessel Diameter: 2.5-3.5 mm
Lesion Length: 14-27 mm
Stent Lengths: 18-30 mm (8/9) mm bailout
Pre-dilatation required

Endeavor Stent
n = 327

Control Cypher Stent
n = 109

N = 436 patients
30 sites
United States

Clinical/MACE
Angio/IVUS

Primary Endpoint: In-segment late lumen loss by QCA at 8 months
Secondary Endpoints: TLR, TVR, TVF at 9 months & ABR at 8 months
Antiplatelet therapy for ≥3 months 10 µg Zotarolimus per mm stent length
ENDEAVOR III

Confirms Endeavor Deliverability

Device Procedure

Endeavor 98.8 99.4
Cypher 94.7 95.6

P = .02  P = .02

En-doevar
Cypher

P-value

In-hospital events

<table>
<thead>
<tr>
<th>Event</th>
<th>Endeavor</th>
<th>Cypher</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<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 (2)</td>
<td>3.5 (4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

ENDEAVOR III

Primary Endpoint at 8 Months

- Non-Inferiority Margin of Difference: 0.20 mm
  - 90% Power, 5% \( \alpha \) one-sided

- Observed Difference: 0.23 mm

ENDEAVOR III

Event Free Survival to 360 Days

Kandzari et al. ACC, 2006.
ENDEAVOR Clinical Program

TLR Across High Risk Groups EI, EII, EIICA and EIII

Kandzari et al. ACC, 2006.
Deliverability

Efficacy

Safety
ENDEAVOR I

Safety Profile

ENDEAVOR I Clopidogrel Therapy for ≥3 months

N = 100

1.0%

12 // 10 14 // 30 // 100 270 360
1 year

720
2 years

1080
3 years

Days Post Procedure

Defined as angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic re-study for documented ischemia (chest pain and ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Seoul, 2007
ENDEAVOR II Clopidogrel Therapy for ≥3 months

Endeavor

0.5% (3)

1 2 3 // 12 13 14 // 30 100 200 270 360 500 600 720

1 year 2 years

Driver

1.2% (7)

Days Post Procedure

Defined as angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic re-study for documented ischemia (chest pain and ECG changes). Any death not attributed to a non-cardiac cause within the first 30 days is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

No Late Stent Thrombosis in Over 1300 Patients
No Late Stent Thrombosis in 994 Patients ³ 2 yr f/u

ENDEAVOR I–III Clopidogrel Therapy for ≥3 months

Overall Thrombosis = 0.3%

Fajadet et al. TCT. 2006.
Cypher and Taxus

Combined Stent Thrombosis*

N = 4037

% of ST after 9 mo

DES

BMS

≤ 30 days 1 - 9 mo 9 - 12 mo 12 - 24 mo 24 - 36 mo**

P-value on Total ST: NS

≤ 30 days

1 - 9 mo

9 - 12 mo

12 - 24 mo

24 - 36 mo**

P - value on ST after 9 months: <.001

* TAXUS-II, TAXUS-IV, TAXUS-VI (2 yr); RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS (3 yrs).

**24-36 months for Cypher data only.
Meta-analysis of Published Data

Combined Stent Thrombosis: DES vs BMS

- **TAXUS-II, TAXUS-IV, TAXUS-VI (2 yr); RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS (3 yrs).**
- **24-36 months for Cypher data only.**

N = 4037

P-value on ST after 9 months: <.001

- Taxus and Cypher
- BMS

0 days <30 days 1-9 months 9-12 months 12-24 months 24-36 months

Seoul, 2007
Total Stent Thrombosis Among DES
HCRI CEC and ARC Definitions

<table>
<thead>
<tr>
<th></th>
<th>Endeavor (KM to 3 years)</th>
<th>Cypher (KM to 4 years)</th>
<th>Taxus (KM to 4 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEC</td>
<td>0.3%</td>
<td>1.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Def+ Prob</td>
<td>0.6%</td>
<td>1.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>All</td>
<td>1.0%</td>
<td>3.5%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Cutlip, HCRI, TCT 2006.

Clinical results are not suitable for comparison.
Stent thrombosis rates with DES

Pre-specified HCRI CEC Defined Stent Thrombosis

4x relative increase required in next year to “catch up”

Clinical results are not suitable for comparison.
Lack of Endothelial Strut Coverage

DES vs BMS >3 years in Humans

Percentage Endothelialization vs Duration in months

- Taxus and Cypher
- BMS

P = .0001

Conclusions:
- BMS showed far greater endothelialization than DES
- Lack of coverage highlighted in areas of overlap
- Less surface coverage by endothelial cells in PES than SES

Finn et al. (Circulation. 2005;112:270-278.)
Strut Coverage and Endothelialization

Driver Endeavor

[Graph showing mean % Endothelialization for Driver and Endeavor]

Virmani et. al; PCR 2006. Rabbit Model at 21 days.
Strut Coverage and Endothelialization

Virmani et. al; PCR 2006. Rabbit Model at 21 days

Seoul, 2007
Endeavor: “Complete” NIH

Smooth Lumen, Even Neointimal Distribution

Source: Dr. Peter Fitzgerald EII 9 month (IVUS 8 months).

Seoul, 2007
**NO and Endothelial Cell Function**

**Endothelial Nitric Oxide Synthase (eNOS)**

- eNOS is the protein that produces NO and is a marker of endothelial cell function.

- Both proximal and stent vessels have significantly more eNOS present than either Taxus or Cypher.

**Graph:**
- Graph showing the comparison of eNOS levels among Endeavor, Cypher, and Taxus.

*Seoul, 2007*
E-Five Registry

Interim Results: Procedural Outcomes on 8,260 patients

Chaim Lotan, Ian Meredith and Martin Rothman on behalf of the E-Five Investigators
<table>
<thead>
<tr>
<th>Country</th>
<th>Centers</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>31</td>
<td>1904</td>
</tr>
<tr>
<td>Germany</td>
<td>24</td>
<td>1220</td>
</tr>
<tr>
<td>Italy</td>
<td>16</td>
<td>813</td>
</tr>
<tr>
<td>India</td>
<td>7</td>
<td>586</td>
</tr>
<tr>
<td>Greece</td>
<td>7</td>
<td>451</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>11</td>
<td>422</td>
</tr>
<tr>
<td>Netherlands</td>
<td>6</td>
<td>318</td>
</tr>
<tr>
<td>Malaysia</td>
<td>6</td>
<td>307</td>
</tr>
<tr>
<td>Israel</td>
<td>10</td>
<td>290</td>
</tr>
<tr>
<td>China</td>
<td>7</td>
<td>252</td>
</tr>
<tr>
<td>Austria</td>
<td>6</td>
<td>241</td>
</tr>
</tbody>
</table>

Seoul, 2007
### E-Five

#### Patient Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8260</td>
</tr>
<tr>
<td>Male Gender (%)</td>
<td>76.7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.3 ± 11.1</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>33.6</td>
</tr>
<tr>
<td>Q wave MI</td>
<td>21.4</td>
</tr>
<tr>
<td>Non-Q wave MI</td>
<td>12.2</td>
</tr>
<tr>
<td>Prior PCI (%)</td>
<td>25.2</td>
</tr>
<tr>
<td>Prior CABG (%)</td>
<td>7.5</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>32.7</td>
</tr>
<tr>
<td>(Recent) MI (%)</td>
<td>21.8</td>
</tr>
<tr>
<td>Unstable Angina (%)</td>
<td>34.0</td>
</tr>
</tbody>
</table>
### E-Five

#### Procedure Characteristics

<table>
<thead>
<tr>
<th>Number Endeavor Stents / Lesion</th>
<th>1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Endeavor stent (%)</td>
<td>84.7</td>
</tr>
<tr>
<td>2 Endeavor stents (%)</td>
<td>12.6</td>
</tr>
<tr>
<td>3 Endeavor stents (%)</td>
<td>2.3</td>
</tr>
<tr>
<td>4+ Endeavor stents (%)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Overlapping Endeavor stents (%)**

<table>
<thead>
<tr>
<th>Only Endeavor stents (%)</th>
<th>94.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination with other DES only (%)</td>
<td>2.8</td>
</tr>
<tr>
<td>Combination with other BMS only (%)</td>
<td>2.1</td>
</tr>
<tr>
<td>Combination with other DES and BMS (%)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

N=10259

The calculation includes all lesions with Endeavor Stents implanted or attempted.
## E-Five

### 30-Day MACE – First Subset

**n=1930**

<table>
<thead>
<tr>
<th>Event</th>
<th>Non Hierarchical</th>
<th>MACE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (all) (%)</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Death (all) (%)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>MI (all) (%)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Q-wave</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Non Q-wave</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>TLR (%)</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>
Fifty nine year old male admitted with chest pain.

Risk factors: HTA & smoking

ECG: ST depression V2-V6.
Negative T waves V1-V6

Echocardiogram: WNL. EF 50%
LM: ulcerated plaque w/o important compromise of the lumen

LAD: Critical lesion proximal segment

CX: Severe lesion OM1

RCA: Ostial lesion
Cutting balloon & stent Endeavor (3.5x10 mm) ostium RCA
Stent Endeavor (3.5x24) in LAD
Stent Endeavor (2.75x18mm) OM1
Stent Endeavor (3.5x24 mm) LM-LAD
Kissing balloon in LM-LAD-Cx
6 mo. angiographic evaluation
No restenosis in any of the stents
**Deliverability**
- Endeavor drug-eluting stent deliverability documented in multiple patient populations and trials

**Efficacy**
- Efficacy of the Endeavor drug-eluting stent was maintained out to 24 months

**Safety**
- Safety of Endeavor stent may be unique among the DES programs
Ideal Scenarios for Endeavor Stent

- Lesions with reference vessel diameter \( \geq 2.5 \text{ mm} \)
- Patients with questionable compliance for antiplatelet therapy
- Lesions with high risk for restenosis and foreseeable surgery
- ACS where the lesion principal component is thrombus
- STEMI?