An Update on ABT-578 - PC Coated Stent Studies

Abbott Prefer-IVUS
Medtronic Endeavor 1

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Monash Medical Centre and Monash University,
Melbourne, Australia
Strategic Alliance

**Medtronic**

- Load Abbott stent on Medtronic delivery system
- ABT-578 and PC coating on Medtronic AVE stents
- Provide OTW, RX Int’l & new stent delivery system to Abbott

**Abbott Laboratories**

- License ABT-578 and PC coating to Medtronic Vascular
- Load Abbott stent on Medtronic delivery system
ABT-578 Chemical Structure

ABT-578

Sirolimus

Everolimus
ABT-578 Mechanism of Action

- **Primary mode of action is anti-proliferative:** by inhibiting the function of the cell cycle regulatory protein, mTOR.

- **Inflammatory response may be limited by blocking local cytokines.**

**ABT-578 Mechanism**

- **Complex prevents …**
  - Rb phosphorylation
  - p70S6 kinase
  - cyclin-dependent kinase (CDK) activation
  - p27 down regulation

- **ABT-578 binds with FKBP<sub>12</sub> protein**

- **Complex blocks mTOR signal transduction**
The PC coating is a synthetic copy of the predominant phospholipid of red blood cell membranes.
ABT-578 In vivo Drug Elution Data

% Drug Eluted

% Total Drug Load in Tissue Surrounding Stent

Endeavor Preclinical Study Rabbit Iliac Artery
10μg/mm ABT-578 PC-coated Driver Stent

A. Carter, ACC 2003
PREFER – IVUS
FIM Trial of an ABT-578 eluting stent.
N=50 patients with *de novo* or restenotic Coronary Lesions

11 Subjects Studied

Aspirin 300mg & clopidogrel (300mg loading), then 75mg daily for 3 months

Lesion diam. 3.0mm Length ≤ 15mm

3 mths IVUS & Angio Clinical FU 6,12 mths Yearly clinical for 5 yrs
PREFER – IVUS Objectives

Primary Objective
- Demonstrate the safety and efficacy of the ABT-578 coated BiodivYsio™ stent

Primary end point
- MACE at 30 days

Secondary Objectives
- Evaluate clinical, angiographic, IVUS and device performance

Secondary Endpoints
- In hospital MACE rate, 6 month MACE rate, TVR rate at 6 mths, 1 year and yearly for 5 years.

Additional Evaluations
- Device, lesion and procedural success
PREFER – IVUS

Investigators
Ian Meredith, Melbourne, Australia  4pts
Robert Whitbourn, Melbourne, Australia  4pts
John Ormiston, Auckland, New Zealand  3pts

Analysis
QCA: Brigham and Womens , Boston  USA
IVUS: Stanford Interventional Cardiology, California
ECG: Harvard Clinical Research Institute, Boston
## PREFER-IVUS

### 90 day QCA Peri-stent Analysis

<table>
<thead>
<tr>
<th></th>
<th>Late Loss (mm)</th>
<th>Binary Restenosis (%)</th>
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<tbody>
<tr>
<td>In-stent</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Proximal margin</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Distal margin</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>In-segment</td>
<td>0.1</td>
<td>0</td>
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</table>

![Diagram showing late loss and binary restenosis metrics for different segments.](attachment:image.png)
PREFER- IVUS
Post PCI & 90 day IVUS Analysis

Lumen & Neointima Volume
(n=10)

- Post: 148.5 mm³
- 3M-FU: 139.4 mm³

Average Lumen & Neointima Area

- Lumen: 7.25 mm²
- Neointima: 0.18 mm²

Volume index: Volume/Stent Length
Drug eluting stent trials
Comparison of % Neointimal Volume

<table>
<thead>
<tr>
<th>Drug Family</th>
<th>BMS</th>
<th>ASPECT</th>
<th>SCORE</th>
<th>TAXUS SR</th>
<th>TAXUS MR</th>
<th>SIRIUS</th>
<th>FUTURE</th>
<th>RAVEL</th>
<th>PREFER</th>
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<tr>
<td>&quot;Taxol&quot;</td>
<td>30.0</td>
<td>11.8</td>
<td>9.2</td>
<td>7.9</td>
<td>7.8</td>
<td>2.9</td>
<td>2.6</td>
<td>1.0</td>
<td>2.6</td>
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<td>&quot;Limus&quot;</td>
<td></td>
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</table>

*Courtesy of Peter Fitzgerald*
PREFER - IVUS Summary

- No safety concerns associated with the PC coated ABT-578 drug-eluting stent
- Negligible neointimal response both in stent and in segment.
- Zero binary restenosis rate
- No acquired malappositions, aneurysms stent thromboses
Primary Endpoints: MACE at 30 days and late loss (QCA) at 4 mo
Secondary Endpoints: TVF and TLR at 9 months; late loss at 12 mo
IVUS at 4 and 12 months
Stent Sizes: 3.0-3.5 mm x 18 mm
Pre- and post-dilatation specified with balloon length < stent length
Antiplatelet therapy for 3 months
Endeavor DES System
Key Components

- Driver Cobalt Alloy Stent
- Stent Delivery System
- PC Technology
- Drug: ABT-578

Angioplasty Summit Korea 2004 ITM
E1 PI & Core Labs

**Principal Investigator**
Ian T. Meredith, Monash Medical Centre, Melbourne, Aust

**QCA Core Lab**
Brigham and Women’s Hospital, Boston, MA, USA
Jeffrey J. Popma, MD

**IVUS Core Lab**
Cardiovascular Core Analysis Lab
Stanford Interventional Cardiology, CA, USA
Peter Fitzgerald, MD

**Data Coordinating Center**
Harvard Clinical Research Institute
Richard E. Kuntz, MD, MSc and Ross Prpic, MBBS

**ECG Core Lab**
Harvard Clinical Research Institute, Boston, MA, USA
Peter Zimetbaum, MD

**Clinical Events Committee/DSMB**
Harvard Clinical Research Institute, Boston, MA, USA
Donald Cutlip, MD
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Hospital</th>
<th># Patients</th>
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<tbody>
<tr>
<td>John Ormiston</td>
<td>Green Lane/Mercy, NZ</td>
<td>32</td>
</tr>
<tr>
<td>Robert Whitbourn</td>
<td>St. Vincent’s, Melbourne</td>
<td>20</td>
</tr>
<tr>
<td>Patrick Kay</td>
<td>Dunedin, NZ</td>
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<tr>
<td>Ian Meredith</td>
<td>Monash Medical Centre</td>
<td>14</td>
</tr>
<tr>
<td>David Muller</td>
<td>St. Vincent’s, Sydney</td>
<td>12</td>
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<tr>
<td>Mark Adams</td>
<td>Royal Prince Alfred Hosp.</td>
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<td>Con Aroney</td>
<td>The Prince Charles Hosp.</td>
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<tr>
<td>Mark Pitney</td>
<td>Eastern Heart Clinic</td>
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# E I Milestones

<table>
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<tr>
<th>Milestone</th>
<th>Date</th>
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<tbody>
<tr>
<td>First Ethics Approval</td>
<td>December, 2002</td>
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<tr>
<td>TGA Approval</td>
<td>December, 2002</td>
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<tr>
<td>First Patient Enrolled</td>
<td>January, 2003</td>
</tr>
<tr>
<td>Last Patient Enrolled</td>
<td>April, 2003</td>
</tr>
<tr>
<td>Last 4 mo Follow up</td>
<td>August, 2003</td>
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<tr>
<td>Database Lock</td>
<td>September, 2003</td>
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<tr>
<td><strong>4 mo Data TCT Presentation</strong></td>
<td><strong>September, 2003</strong></td>
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<tr>
<td>Last 12 mo Follow up</td>
<td>29&lt;sup&gt;th&lt;/sup&gt; April, 2004</td>
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<tr>
<td>12 mo Clinical Data PCR</td>
<td>25&lt;sup&gt;th&lt;/sup&gt; May, 2004</td>
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<tr>
<td>12 mo Angio/ IVUS Data PCR</td>
<td>25&lt;sup&gt;th&lt;/sup&gt; May, 2004</td>
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### Endeavor I
#### Patient Demographics

<table>
<thead>
<tr>
<th>n=100</th>
<th>Baseline</th>
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<tbody>
<tr>
<td>Male</td>
<td>79.0%</td>
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<tr>
<td>Average age (years)</td>
<td>58.8 (35-76)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>47.0%</td>
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<tr>
<td>Prior PCI</td>
<td>19.0%</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>16.0%</td>
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<tr>
<td>Unstable Angina</td>
<td>39.0%</td>
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<tr>
<td>Hyperlipidemia</td>
<td>91.8%</td>
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<tr>
<td>Current Smoker</td>
<td>34.0%</td>
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</table>
### Endeavor I
30 day & 4mth Hierarchical MACE

<table>
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<tr>
<th>n=100</th>
<th>30 Days</th>
<th>4 Months</th>
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<tbody>
<tr>
<td>MACE</td>
<td>1%</td>
<td>2%</td>
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<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
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<tr>
<td>MI (all)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Q-wave</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Non Q-wave</td>
<td>1%</td>
<td>1%</td>
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<tr>
<td>TLR</td>
<td>0</td>
<td>1%</td>
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<tr>
<td>TVR (non-TL)</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

Acute device, lesion and procedural success: 100%
4 mth clinical follow up achieved: 100%
<table>
<thead>
<tr>
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<th>In-Stent</th>
<th>In-Segment</th>
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</thead>
<tbody>
<tr>
<td>RVD, mm</td>
<td>2.96 ± 0.47</td>
<td></td>
</tr>
<tr>
<td>Lesion Length, mm</td>
<td>10.9 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>MLD Pre, mm</td>
<td>0.88 ± 0.33</td>
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<tr>
<td>Post, mm</td>
<td>2.84 ± 0.35</td>
<td>2.52 ± 0.42</td>
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<tr>
<td>4 m follow-up</td>
<td>2.52 ± 0.43</td>
<td>2.31 ± 0.44</td>
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<tr>
<td>Acute Gain, mm</td>
<td>1.96 ± 0.38</td>
<td>1.64 ± 0.42</td>
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<tr>
<td>Late Loss, mm</td>
<td>0.33 ± 0.35</td>
<td>0.20 ± 0.40</td>
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<tr>
<td>Late Loss Index</td>
<td>0.17</td>
<td>0.11</td>
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4 mth angio follow up achieved: 99%
E1 4 mth QCA

% DS

In-Stent

In-Segment

% Diam. Stenosis

Pre Post 4 F/U

70.3% 5.4% 14.4% 0%

70.3% 16.5% 21.7% 0%
E1 4 mth QCA Edge Data

Prox. 5 mm  |  Distal 5 mm

Proximal In-Stent Distal In-Segment

Late Loss

-0.40  -0.20  0.00  0.20  0.40  0.60  0.80

0%  2.1%  0%  2.1%

0.11  0.33  0.09  0.20
E1
Pt # 006

Pre PCI

Post

4mth

12mth
# E1 4mth IVUS Data

<table>
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<tr>
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<th>Post Mean</th>
<th>Follow up Mean</th>
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<tr>
<td>EEM volume</td>
<td>300 mm³</td>
<td>321 mm³</td>
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<tr>
<td>Stent Volume</td>
<td>142 mm³</td>
<td>149 mm³</td>
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<tr>
<td>Neointimal Volume</td>
<td>NA</td>
<td>6.1 mm³</td>
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<tr>
<td>Lumen Volume</td>
<td>142 mm³</td>
<td>143 mm³</td>
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<tr>
<td>Percent Volume</td>
<td>NA</td>
<td>4.5%</td>
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<tr>
<td>Obstruction</td>
<td></td>
<td></td>
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<tr>
<td>Late Acquired</td>
<td>—</td>
<td>0</td>
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<tr>
<td>Incomplete Apposition</td>
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4 mth IVUS follow up achieved: 98%
Baseline (post stenting)

Four Month Follow-up

(233_012)
E1 4 & 12 mth IVUS F/U

Pt # 0012 RCA

Post Stent

4 mth follow up

12 mth follow up
E1 4 & 12 mth IVUS F/U

Post Stent

4 mth follow up

12 mth follow up
Endeavor II

Randomized, Double-blind Trial
Single De Novo Native Coronary Artery Lesions (Type A-C)
Vessel diam: 2.25-3.5 mm, Lesion Length: 14-27 mm
N = 1200

Control Driver Stent
n=600

Endeavor Stent
n=600

90 site Europe, Canada, Israel, South-East Asia, Australia, and New Zealand

Clinical/MACE

Angio/IVUS

Primary Endpoint: TVF (cardiac death, MI, TVR) at 9 months
Stent Sizes: 2.25-3.5 mm x 18-30 mm (8/9 mm bailout)
Pre dilatation specified, Antiplatelet therapy for 3 mo, PK sub-study
E II Study Design

Randomized Population
n = 1200

Uncoated Control
Driver Stent
n = 600

ABT-578 Eluting
Driver Stent
n = 600

First 300 pts
All Sites

QCA
n = 300

No QCA
n = 300

First 150 pts
At IVUS Sites

IVUS
n = 150

No IVUS
n = 150

No IVUS
n = 150

QCA
n = 300

No IVUS
n = 150

No QCA
n = 300

No IVUS
n = 150
Endeavor II

**Primary objective**
To demonstrate the safety & efficacy of the Endeavor™ Coronary Stent (10 μg/mm ABT-578) compared to the uncoated DRIVER™ Stent for the treatment of single de novo lesions in native coronary arteries (2.25-3.5 mm diam).

**Primary End-Point**
Target Vessel Failure (TVF) rate, defined as a composite of target vessel revascularization, recurrent MI (Q or Non Q-Wave), or cardiac death that could not be clearly attributed to a vessel other than the target vessel at 9 months post procedure.
Endeavor II: Inclusion Criteria

Age $\geq 18$ years

Evidence of ischemic heart disease or a +ve functional study

Acceptable for PTCA, stenting and CABG

SVD or MVD with only moderate stenosis

Target lesion/ vessel

Single de novo, native lesion $\geq 50\%$ and $< 100\%$

Lesion length: $\geq 14$ mm and $\leq 27$ mm

Reference diameter: $\geq 2.25$ mm and $\leq 3.5$ mm

-ve pregnancy test before the procedure if applic

Subject has provided written informed consent
<table>
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<th>Count</th>
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<td>Austria</td>
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<tr>
<td>G Laarman</td>
<td>Netherlands</td>
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<td>K-H Kuck</td>
<td>Germany</td>
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<td>E Hauptmann</td>
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<td>M Suttrop</td>
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<td>J Drzewiecki</td>
<td>Poland</td>
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<td>J Ormiston</td>
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<td>H-P Schultheiss</td>
<td>Germany</td>
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<tr>
<td>M Pieper</td>
<td>Switzerland</td>
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</table>
ENDEAVOR III
Randomized Multi-center Trial

N=436
3:1 Randomization

Single De Novo Native Coronary Artery (NCA) Lesion (Type A-B)
Stent Diameter: 2.5-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14 - 24 mm
Pre-dilatation required
Direct Stenting is not allowed

Control Cypher Stent
n=109

Endeavor Stent
n=327

30 sites
United States

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 mths

Clinical/MACE
Angio/IVUS

QCA
IVUS
# E III PI & Core Labs

## Principal Investigators
- Martin B. Leon, Lennox Hill Heart Vasc Inst, CRF, NY

## QCA Core Lab
- Brigham and Women’s Hospital, Boston, MA, USA
  - Jeffrey J. Popma, MD

## IVUS Core Lab
- Cardiovascular Core Analysis Lab
  - Stanford Interventional Cardiology, CA, USA
  - Peter Fitzgerald, MD

## Data Coordinating Center
- Harvard Clinical Research Institute
  - Richard E. Kuntz, MD, MSc

## ECG Core Lab
- Harvard Clinical Research Institute, Boston, MA, USA
  - Peter Zimetbaum, MD

## Clinical Events Committee/DSMB
- Harvard Clinical Research Institute, Boston, MA, USA
  - Donald Cutlip, MD
Primary objective
To demonstrate the equivalency of the Endeavor™ Coronary Stent (10 μg/mm ABT-578) with Cordis’ Co CYPHER™ Sirolimus-Eluting Coronary Stent System for the treatment of single de novo lesions in native coronary arteries 2.5-3.5 mm in diameter.

Primary End-Point
In-segment late loss at 8 months as measured by QCA, defined as the difference between the post-procedure minimal lumen diameter (MLD) and the follow-up angiography MLD.
Inclusion criteria (Target lesion):
Same as Endeavor II, except:
- Target vessel must have $\geq$ TIMI flow 2
- Target lesion length must be $\geq 10$ & $\leq 24$ mm
- Target vessel ref diam must be $\geq 2.5$ & $\leq 3.5$ mm

Exclusion criteria (Target lesion):
Same as Endeavor II, except:
- Treatment of one additional (non-target) lesion is permitted
ENDEAVOR Continued Access OUS
Single-arm Multi-center Registry

Single De Novo NCA Lesion
(Type A-B2)
Stent Diameter: 2.25-3.5 mm
Stent Lengths: 8-30 mm (8/9 mm bailout)
Lesion Length: 14 - 27 mm

10 μg ABT-578 per mm stent length
Direct Stenting – Per Investigator Discretion
for lesions ≤ 20 mm

N = 300

≤ 15 sites

Clinical/MACE

30d 6mo 8mo 9mo 12mo 2yr 3yr 4yr 5yr

Angio/IVUS

MACE

QCA N=150
IVUS N=100

Primary Endpoint:
MACE at 30 days

Secondary Endpoints:
TLR, TVR, TVF @ 9 mo, QCA & IVUS @ 8 mo

Antiplatelet therapy for ≥ 3 months
Medtronic Endeavor Update

**Endeavor Preclinical**
ABT-578 is a synthetic cytostatic agent similar to sirolimus that has been demonstrated to be safe and effective in reducing NIH in animal models.

**Endeavor I**
First in man trial - 4 mth results suggest that the ABT-578 eluting Endeavor Stent is safe and efficacious in the reduction of in-stent restenosis.

**Endeavor II and III**
Large scale randomized controlled trials: will provide definitive data regarding the safety and efficacy of the ABT-578 eluting Endeavor Stent.