

FDA Executive Summary Memorandum

Prepared for the October 10, 2007, meeting of the
Circulatory System Devices Advisory Panel

P060033

Medtronic, Inc.

Endeavor Zotarolimus Drug-Eluting Coronary Stent System &
Over-the-Wire (OTW), Rapid Exchange (RX), and
Multi-Exchange II (MX²) Stent Delivery Systems

Table of Contents

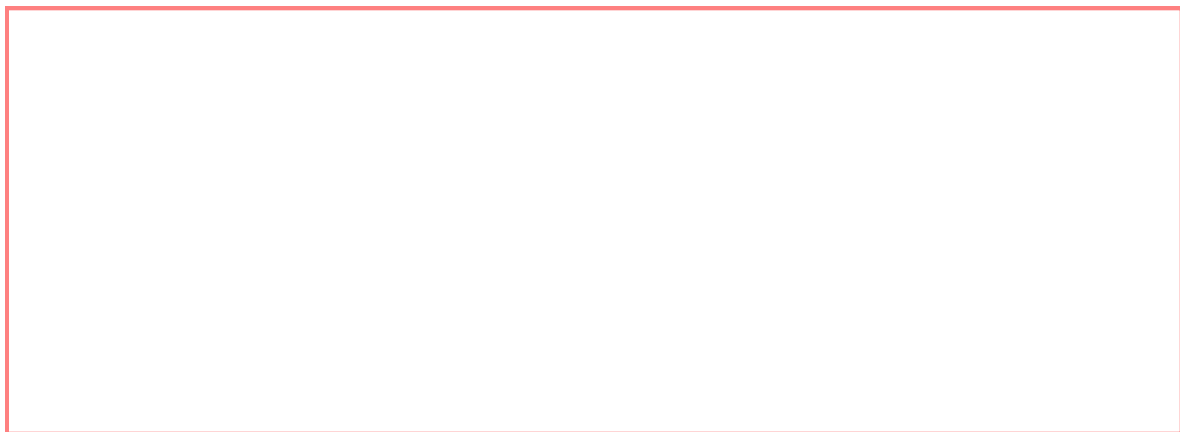
| | | |
|-----------|--|-----------|
| 1. | PROPOSED INDICATIONS FOR USE | 3 |
| 2. | DEVICE DESCRIPTION | 4 |
| 3. | REGULATORY HISTORY | 5 |
| 4. | STUDIES OF THE DRUG SUBSTANCE..... | 7 |
| | a. Safety Pharmacology | 7 |
| | b. Toxicology | 8 |
| | c. Absorption, Distribution, Metabolism, and Excretion (ADME) Studies... 8 | |
| | d. Study M01-336: An Escalating, Intravenous-Dose Study of the Safety and Pharmacokinetics of Zotarolimus (ABT-578) in Healthy Subjects..... 10 | |
| | e. Study M02-501: Clinical Study Report R&D/03/316, “A Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Zotarolimus (ABT-578) in Healthy Subjects” | 13 |
| 5. | PRE-CLINICAL STUDIES | 16 |
| | a. Stent Functional Testing..... | 16 |
| | b. Stent Coating Testing | 16 |
| | c. Stent Delivery System Testing | 17 |
| | d. Animal Studies | 17 |
| | e. Chemistry, Manufacturing, & Controls (CMC) | 18 |
| | f. Sterilization..... | 18 |
| | g. Biocompatibility | 19 |
| | h. Manufacturing..... | 19 |
| 6. | DEFINITIONS & ABBREVIATIONS | 20 |
| 7. | CLINICAL STUDIES | 24 |
| | a. ENDEAVOR I..... | 26 |
| | b. ENDEAVOR II..... | 30 |
| | c. ENDEAVOR II CA..... | 38 |
| | d. ENDEAVOR III..... | 42 |
| | e. ENDEAVOR IV | 47 |
| | f. ENDEAVOR Japan | 52 |
| | g. ENDEAVOR PK..... | 56 |
| | h. Long Term Safety and Effectiveness Outcomes in the Pooled ENDEAVOR Clinical Studies | 60 |
| | i. Stent Thrombosis and Dual Antiplatelet Therapy Use in the Pooled ENDEAVOR Clinical Studies..... | 65 |
| | j. Diabetic Patients in the Pooled ENDEAVOR Clinical Studies..... | 74 |
| | k. Non Cardiac Deaths and Cancer in the Pooled ENDEAVOR Clinical Studies | 82 |
| | l. Summary..... | 83 |
| 8. | POST-APPROVAL STUDY | 89 |
| 9. | REFERENCES..... | 90 |

1. PROPOSED INDICATIONS FOR USE

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 ≥ 2.5 mm to ≤ 3.5 mm.

2. DEVICE DESCRIPTION

The Endeavor Zotarolimus-Eluting Coronary Stent System is a device-drug combination product comprised of a [REDACTED]



[REDACTED] for the following stent diameters and lengths:

| Table 1: Endeavor Coronary Stent System Device Matrix | | | | | | | | |
|---|-------------------|---|----|----|----|----|----|----|
| Diameter (mm) | Stent Length (mm) | | | | | | | |
| | 8 | 9 | 12 | 14 | 15 | 18 | 24 | 30 |
| 2.50 | X | | X | X | | X | X | X |
| 3.0 | | X | X | | X | X | X | X |
| 3.5 | | X | X | | X | X | X | X |

A spray coating of polymer carrier loaded with zotarolimus is applied to the stent at a drug loading [REDACTED] μ length. The maximum nominal drug content on the longest stent [REDACTED] μ

Endeavor stents are supplied pre-mounted on one of three delivery systems: Over-The-Wire (OTW), Rapid Exchange (RX), or Multi Exchange (MX²). All delivery catheters contain a semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. Two radiopaque balloon markers are located on the distal segment of the inner member and are positioned to mark the working length of the balloon. The working lengths of the delivery catheters are [REDACTED]

[REDACTED] The delivery catheter is also designed for post-stent dilation using pressures less than or equal to the rated burst pressure, [REDACTED] All systems are compatible with a [REDACTED] The OTW and RX systems are compatible with a [REDACTED] catheter. The MX system is compatible with a 6F guide catheter.

Please refer to the Product Description section of this panel pack (provided by Medtronic) for further details.

3. **REGULATORY HISTORY**

Medtronic's clinical investigations for the Endeavor Zotarolimus-Eluting Coronary Stent System began in February 2003 with ENDEAVOR I, a single-arm 100 patient feasibility study at 8 sites in Australia and New Zealand. Enrollment was completed in April 2003. The rate of major adverse cardiac events (MACE) at 30 days post-stent implantation, the primary safety endpoint, was 1%.

Medtronic initiated ENDEAVOR II, a 1,197 patient randomized trial of the Endeavor stent versus the Driver bare metal stent at 72 sites in Asia, Australia, Europe, Israel and New Zealand. Enrollment started in July 2003 and was completed in January 2004. Medtronic chose to conduct ENDEAVOR II outside of the United States (OUS) due to their concern that a randomized DES trial with a bare metal stent control group would not be feasible based on the high prevalence of DES use in the US following the approval of the Cypher stent. In ENDEAVOR II, the Endeavor stent met its primary target vessel failure (TVF) endpoint of superiority vs. the bare metal Driver stent at 9 months

[REDACTED]

FDA did not review the ENDEAVOR I or II study protocols prior to their commencement.

In November 2003, Medtronic proposed ENDEAVOR III, a study to be completed in the US; results of Endeavor III were to be used in conjunction with the results of ENDEAVOR II for a US marketing application. ENDEAVOR III was planned to be a 436 patient randomized trial of the Endeavor stent vs. the Cypher stent. An Investigational Device Exemption [REDACTED] was conditionally approved in December 2003 for this trial. In addition, [REDACTED] zotarolimus is an NME, FDA requested a cumulative 2,000 patient exposure to the Endeavor stent for evidence of drug safety. Therefore, Medtronic added the US and OUS Continued Access Registries (referred to as ENDEAVOR IV and ENDEAVOR II CA, respectively). Additionally, Medtronic initiated the Pharmacokinetic (PK) study within the US to gain insights into systemic exposure to zotarolimus following Endeavor stent implantation.

During a review of an FDA requested ENDEAVOR III safety update in May 2004, after 174 patients of the projected 436 had been enrolled, FDA noticed that the sponsor had included the stent treatment assignment for four patients who had experienced adverse events. Because the sponsor had been made aware of the randomization scheme, the integrity of the study was questioned. After careful review, it was concluded that statistical analyses could not fully address potential issues of bias or overcome concerns about study integrity. Therefore, FDA advised Medtronic to immediately stop study enrollment, roll patients who received Endeavor stents into the US Continued Access Registry, and restart the ENDEAVOR III trial after steps were taken to ensure that blinding would not be compromised. Instead, Medtronic continued the ongoing ENDEAVOR III study with a new patient randomization scheme to preserve blinding for the remaining patients. Medtronic assigned a new clinical and regulatory team to the

study, implemented and trained sites to new blinding procedures, and outsourced monitoring and device distribution to two separate clinical research organizations. Enrollment was restarted in May 2004 and completed in September 2004.

In ENDEAVOR III, the Endeavor stent failed to meet its primary angiographic endpoint of noninferiority of in-segment late lumen loss compared to the Cypher stent at 8-months

∞

Due to FDA concerns regarding the unblinding of the original ENDEAVOR III study, but before the results of the re-initiated ENDEAVOR III study were known, Medtronic changed the ENDEAVOR IV study design from a US-based Continued Access Registry to a 1,548 patient randomized trial of the Endeavor stent versus the Taxus stent. Enrollment in ENDEAVOR IV started in April 2005 and was completed in June 2006.

In ENDEAVOR IV, the Endeavor stent met its primary TVF endpoint of noninferiority compared to the Taxus stent at 9 months

In this study, the Endeavor stent failed its secondary angiographic endpoint of noninferiority of 8 month in-segment late lumen loss compared to the Taxus stent

∞

In July 2005 Medtronic initiated the ENDEAVOR Japan study. The objective of this small (n=99), single-arm trial was to evaluate the safety and effectiveness of the Endeavor stent in Japanese patients. Enrollment was completed in February 2007, and clinical follow-up through the nine month primary endpoint (9 month TVF rate) is complete. The TVF rate at 9 months was 5.2%. No hypothesis was pre-specified but descriptive statistics were provided.

FDA received the Endeavor PMA submission on November 20, 2006. Additional information has been requested by FDA over the course of the review. As of August 1st, Medtronic has responded to the vast majority of FDA's questions. The following clinical datasets (with latest available patient follow-up data) were provided for review within the PMA and its amendments: ENDEAVOR I (patient follow-up through 4 years), ENDEAVOR II (3 years), ENDEAVOR II CA (2 years), ENDEAVOR III (2 years), ENDEAVOR IV (9 months), ENDEAVOR PK (9 months), and ENDEAVOR Japan (9 months).

ENDEAVOR FIVE is a European postmarketing surveillance registry that enrolled 8200 patients. Medtronic monitored approximately 800 patients (10% of the patient population). Thirty-day follow-up data for approximately 2000 patients were presented in the original PMA filing. The patients enrolled in this registry reflected real world use of the stent in Europe and included both the CE mark labeled indication and off label usage. These data were not reviewed to support approvability of the PMA because patients were treated for a wide variety of indications, monitoring was limited, and all sites were OUS. However, these data may be useful in the consideration of the design of a post-approval study.

4. STUDIES OF THE DRUG SUBSTANCE

Abbott Laboratories, manufacturer of zotarolimus (ABT-578) conducted a series of pre-clinical and clinical studies of the drug substance and has provided Medtronic with the right to reference this information to support the Endeavor PMA application.

a. Safety Pharmacology

FDA recommends that safety pharmacology studies of the drug substance be conducted using several animal models. The purpose of this testing is to demonstrate that any effects of the drug on organ systems are well tolerated. Test reports for the following safety pharmacology studies have been provided:

- Effects on central nervous system in the rat
- Effects on pulmonary function in the rat
- Cardiovascular effects in conscious primates
- Effects on hemodynamic and electrophysiologic function in the conscious and anesthetized dog
- In vitro effects on canine cardiac Purkinje fibers repolarization assay
- In vitro effects on hERG current
- Antigenicity study in guinea pigs
- Local lymph node assay in mice

In summary, IV administered zotarolimus has no effect on the CNS and respiratory system parameters in the rat at blood concentrations of ~ 30-times the estimated C_{max} from one stent. [REDACTED]

[REDACTED]

μ

[REDACTED]

Zotarolimus caused *in vitro* inhibition of cell proliferation of human T cell, coronary artery smooth muscle and endothelial cells at [REDACTED], respectively. Zotarolimus did not exhibit receptor interaction when tested *in vitro* at a concentration of [REDACTED] μ for binding to [REDACTED]. At levels of [REDACTED] greater than a typical projected [REDACTED], zotarolimus caused no direct aggregation of human platelets in whole blood or did not enhance aggregation to stimulation by platelet agonists.

In guinea pigs sensitized once per week for four weeks by subcutaneous administration of zotarolimus [REDACTED] μ, showed no induced systemic anaphylactic or passive cutaneous anaphylactic reactions indicating that zotarolimus was non-antigenic. Topically applied zotarolimus [REDACTED] on the dorsal surface of both ears of mice showed no increase in

³H-thymidine incorporation in the lymph nodes indicating lack of skin sensitizing activity.

These initial reviews have not indicated any safety concerns and supported initiation of the human clinical studies of the Endeavor DES. Further review of these studies is ongoing.

b. Toxicology

FDA recommends toxicology studies of the drug substance in several animal models. The purpose of this testing is to determine the general toxicological effects in various species and the potential for genetic, reproductive and developmental toxicology. Test reports for the following toxicology studies have been provided:

- Single dose toxicokinetic studies in the rat and cynomolgus monkey following IV infusion
- 28 day repeat dose toxicology studies in the rat and cynomolgus monkey
- Reproductive toxicity:
 - Fertility studies in the male and female rate following IV infusion
 - Teratology studies of embryofetal development in the pregnant rat and rabbit following IV infusion
- Genotoxicity:
 - *In vitro* bacterial and mammalian microsome reverse mutation assay
 - Chromosomal aberrations in human peripheral blood lymphocytes
 - *In vivo* mouse micronucleus assay

Review of the single- and repeat-dose toxicology studies supported the initiation of human clinical studies of the Endeavor DES.

Review of the reproductive toxicology studies indicated that zotarolimus should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

Zotarolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the human peripheral lymphocyte chromosomal aberration assay, or the *in vivo* mouse micronucleus assay.

c. Absorption, Distribution, Metabolism, and Excretion (ADME) Studies

FDA recommends ADME studies of the drug substance in several animal models. The purpose of this testing is to characterize the absorption, distribution, metabolism, and excretion profiles in each species. Test reports for the following ADME studies have been provided:

- Absorption: pharmacokinetic evaluations in the rat, rabbit, mouse, monkey, and pig following single IV or oral drug dosing

- Distribution:
 - *In vitro* distribution in human whole blood
 - *In vitro* binding to plasma proteins in the mouse, rat, rabbit, dog, pig, monkey, and human plasma
 - Tracing of radioactivity-labeled drug in the rat, monkey, and pig following IV dosing
- Metabolism:
 - Metabolites after metabolism by human liver microsomes *in vitro*
 - Metabolites in blood, plasma, feces, and urine in the rat, pig, monkey, and human following IV dosing
 - Metabolism and excretion in rats
 - Metabolism, excretion, and tissue distribution in rabbits
 - Metabolism by hepatocytes from the rat, dog, monkey, and human
 - Effect of ketoconazole on PK profile in the dog following IV dosing
- Excretion: physical and metabolic stability in excreta in male rats

Distribution

The results of the plasma protein binding study suggest that all clinically relevant concentrations, zotarolimus would be extensively protein bound in plasma and would undergo significant degradation. Results from the analysis of radioactive-labeled drug in the blood and plasma are consistent with zotarolimus undergoing rapid degradation within plasma while drug that is sequestered within blood cells is relatively more stable and is released slowly. All concentrations largely decreased in parallel with blood radioactivity with little evidence for accumulation.

Metabolism

Review of studies of the metabolism in the rat, dog, monkey, and human indicated that in all cases the presence of hepatocytes accelerated the loss of parent compound from the incubation mixture. Although no metabolites or breakdown products were formally identified in the present study, it is likely that many routes of metabolism will be shared.

In the studies of metabolites by human liver microsomes, the IC₅₀ for zotarolimus determined as a competitive inhibitor was not significantly different from the potency determined after pre-incubation, suggesting that the compound is not a mechanism-based inhibitor of human CYP3A enzymes. The anticipated clinical plasma levels of zotarolimus are unlikely to exceed the IC₅₀ values determined in this study, which would suggest that the compound is unlikely to be a source of clinical drug–drug interactions through inhibition of CYP3A.

In studies of the effects of zotarolimus on seven cytochrome P450-dependent monooxygenase activities in human liver microsomes, in all cases the extent of inhibition of each enzyme were largely the same, irrespective of the absence or presence of a pre-incubation step, suggesting that the compound is not a mechanism based inhibitor of any of the human P450 enzymes tested. Given the anticipated clinical plasma levels of zotarolimus, the compound is unlikely to be a source of clinical drug- drug interactions through inhibition of CYP3A or the other P450 enzymes tested. In common with other

immunosuppressive macrolides, such as sirolimus, the metabolism of zotarolimus appears to be catalyzed by cytochromes P450 of the CYP3A subfamily, CYP3A4 in particular.

In a study of ketoconazole interaction with zotarolimus in the dog, the results indicated that oxidative metabolism of zotarolimus can be blocked by the CYP3A selective inhibitor ketoconazole. Co-dosing with ketoconazole produced a statistically significant ($p < 0.05$) increase in the zotarolimus area under the curve, with a significant decrease in the clearance values.

These initial reviews have not indicated any safety concerns. Further review of these studies is ongoing.

d. Study M01-336: An Escalating, Intravenous-Dose Study of the Safety and Pharmacokinetics of Zotarolimus (ABT-578) in Healthy Subjects

Objective: To assess the safety, tolerability, and pharmacokinetics of escalating single intravenous doses of zotarolimus in healthy male subjects

Design: This was a Phase I, single-escalating-dose, double-blind, randomized, placebo-controlled, single-center study in 60 subjects.

Procedure: Sixty healthy male subjects from 19 to 44 years of age were enrolled and exposed to doses of zotarolimus ranging from 100-900 µg via IV administration as outlined in Table 2:

| Table 2: Dosing Scheme (Study M01-336) | | |
|--|--------------------|------------------------|
| Treatment Group | Number of Subjects | Double-blind Treatment |
| I | 8 | 100 µg ABT-578 |
| | 4 | Placebo |
| II | 8 | 300 µg ABT-578 |
| | 4 | Placebo |
| III | 8 | 500 µg ABT-578 |
| | 4 | Placebo |
| IV | 8 | 700 µg ABT-578 |
| | 4 | Placebo |
| V | 8 | 900 µg ABT-578 |
| | 4 | Placebo |

The starting dose of 100 µg zotarolimus (approximately 1.4 µg/kg based on a 70 kg man) was 50-fold less than the no adverse effect dose in rat and monkey. The high intravenous dose of 900 µg (12.8 µg/kg) was 6-fold less than the no adverse effect dose in rat and monkey.

Follow up schedule: Blood samples were collected by venipuncture prior to dosing (0 hour) and at 0.083 (5 min), 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing on Study Day 1. Blood concentrations of zotarolimus were determined using a validated liquid/liquid extraction HPLC tandem mass spectrometric

method (LC-MS/MS) with a lower limit of quantification for zotarolimus of 0.20 ng/ml using 0.3 ml blood sample. Safety was evaluated based on adverse events, physical examination, vital signs, ECG, injection site, and laboratory tests assessments.

Results: There were no deaths or serious adverse events reported during the study. Adverse events are summarized in the table below. There was a dose-dependent increase in adverse events in the zotarolimus treatment groups.

Table 3. Overall Summary of Adverse Events Reported by Treatment Group (Study M01-336)

| Group I | | Group II | | Group III | | Group IV | | Group V | | Total | |
|----------------------------|------------------|----------------------------|------------------|----------------------------|------------------|----------------------------|------------------|----------------------------|------------------|-------------------|-------------------|
| ABT-578 100 µg (n=8) | Placebo (n=4) | ABT-578 300 µg (n=8) | Placebo (n=4) | ABT-578 500 µg (n=8) | Placebo (n=4) | ABT-578 700 µg (n=8) | Placebo (n=4) | ABT-578 900 µg (n=8) | Placebo (n=4) | ABT-578 (n=40) | Placebo (n=20) |
| 2 (25%) | 2 (50%) | 5 (63%) | 2 (50%) | 6 (75%) | 4 (100%) | 6 (75%) | 4 (100%) | 7 (88%) | 3 (75%) | 26 (65%) | 15 (75%) |

Treatment-Emergent Adverse Events (TEAEs)

A treatment-emergent adverse event was defined as any adverse event with onset or worsening reported by a subject from the time that the first dose of study drug was administered until 30 days following discontinuation of study drug. The most common TEAEs were injection site reaction, application site reaction, and pain. All of these pain, paresthesia, taste perversion, and edema adverse events appeared to be minor, transient reactions to the IV infusions.

Table 4: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events by Treatment Group and Dose (M01-336)

| | Treatment Group I | | Treatment Group II | | Treatment Group III | | Treatment Group IV | | Treatment Group V | | Total | |
|---------------------------|-------------------|-----------------------|--------------------|-----------------------|---------------------|-----------------------|--------------------|-----------------------|-------------------|-----------------------|----------------|----------------|
| | Placebo (n=4) | ABT-578 100 mcg (n=8) | Placebo (n=4) | ABT-578 300 mcg (n=8) | Placebo (n=4) | ABT-578 500 mcg (n=8) | Placebo (n=4) | ABT-578 700 mcg (n=8) | Placebo (n=4) | ABT-578 900 mcg (n=8) | Placebo (n=20) | ABT-578 (n=40) |
| Any adverse event | 2 (50%) | 2 (25%) | 2 (50%) | 5 (63%) | 4 (100%) | 6 (75%) | 4 (100%) | 6 (75%) | 3 (75%) | 7 (88%) | 15 (75%) | 26 (65%) |
| Headache | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (25%) | 0 (0%) | 2 (50%) | 1 (13%) | 0 (0%) | 0 (0%) | 3 (15%) | 1 (2.5%) |
| Injection Site Reaction | 1 (25%) | 2 (25%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (25%) | 1 (25%) | 0 (0%) | 1 (25%) | 0 (0%) | 3 (15%) | 4 (10%) |
| Pain | 0 (0%) | 1 (13%) | 1 (25%) | 0 (0%) | 3 (75%) | 5 (63%) | 2 (50%) | 5 (63%) | 1 (25%) | 2 (25%) | 7 (35%) | 13 (32.5%) |
| Thrombophlebitis | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (25%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | 0 (0%) |
| Diarrhea | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (25%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (25%) | 0 (0%) | 2 (10%) | 0 (0%) |
| Stomatitis | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (13%) | 0 (0%) | 1 (2.5%) |
| Vomiting | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (25%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (5%) | 0 (0%) |
| Albuminuria | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (25%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (13%) | 1 (5%) | 1 (2.5%) |
| Bilirubinemia | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (13%) | 0 (0%) | 1 (2.5%) |
| Edema | 0 (0%) | 1 (13%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2.5%) |
| Pharyngitis | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (13%) | 0 (0%) | 1 (2.5%) |
| Application Site Reaction | 1 (25%) | 1 (13%) | 2 (50%) | 5 (63%) | 1 (25%) | 2 (25%) | 2 (50%) | 1 (13%) | 2 (50%) | 5 (63%) | 8 (40%) | 14 (35%) |
| Taste Perversion | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (13%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2.5%) |
| Hematuria | 0 (0%) | 0 (0%) | 0 (0%) | 1 (13%) | 1 (25%) | 0 (0%) | 0 (0%) | 1 (13%) | 0 (0%) | 1 (13%) | 1 (5%) | 3 (7.5%) |

Laboratory Results

Subject 512 in the 900 µg ABT-578 treatment group experienced “bilirubinemia.”

Subject 512 was a 38 year-old white male with borderline high indirect bilirubins (1.1 mg/dl) prior to treatment that increased transiently to 1.5 mg/dl on Days 1 and 3 before declining to 1.0 mg/dl by Day 16. The subject’s hemoglobin levels were stable (15.6-15.9 gm/dl) as well as other CBC counts, during the study except for an isolated high reticulocyte count of 1.6% on Day 3. His ALTs (serum glutamic-pyruvic transaminases or serum alanine aminotransaminases) were minimally elevated (23-24) on Day -1 to 2 with normal AST, alkaline phosphatase, and LDH. Minor elevations of indirect bilirubin (to 1.1-1.6) were not uncommon among both placebo and ABT-578 subjects pre- and post-treatment on the lab value listings.

The shift tables did not show any patterns to changes in laboratory values. Lab value tabulations was unremarkable except for the following: in addition to the bilirubin abnormalities previously described, Subject 111 in the 100 µg group had cholesterol of 191 mg/dl and triglycerides of 143 mg/dl on Day -2 that increased to 201 and 190 mg/dl, respectively, on Day -1 and then to 276 and 700 mg/dl, respectively, by Day 8.

Vital signs

With the exception of average Study Day 1 post-dose diastolic blood pressure, there was no statistically significant different drug dose effect seen in any of the vital sign parameters. The least squares means (standard errors) for average Study Day 1 post-dose diastolic blood pressure measurements for placebo was 83.57 (1.18) and for ABT-578 dose levels of 100 µg, 300 µg, 500 µg, 700 µg, and 900 µg were 78.89 (3.13), 79.80 (2.91), 83.23 (2.90), 76.85 (2.93), and 77.23(2.90) mm Hg , respectively (Sponsor's analysis: p-value for ABT-578 vs. placebo: 0.004; p-value for high doses vs. placebo: 0.005). There was no consistent variation in blood pressure.

ECG

Three subjects receiving zotarolimus and five subject receiving placebo experienced a maximum change in QTcF of 30-60 msec from baseline to post-dose values. No subjects experienced increases of QTcF interval values more than 60 msec from baseline, and no subjects in any treatment group had post-dose QTcFs exceeding 450 msec.

Note: Pharmacokinetic parameters were also evaluated in 40 subjects in this study. These results are not discussed here because pharmacokinetics of the finished product were later evaluated in the ENDEAVOR PK study described below.

Summary

1. The bilirubin variations do not appear to be drug-related.
2. The increases in cholesterol and triglycerides may be drug-related, although the changes may also be related to the subject's diet during confinement and whether or not the samples were obtained in a fasting or non-fasting state.

e. Study M02-501: Clinical Study Report R&D/03/316, "A Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Zotarolimus (ABT-578) in Healthy Subjects"

Objective: To evaluate the safety, tolerability, and pharmacokinetics of zotarolimus in healthy subjects following 60-minute once daily intravenous infusions of 200, 400 and 800 µg of zotarolimus administered for 14 consecutive days

The secondary objective was to provide a foundation for the assessment of the potential ECG and immunosuppressant effects of zotarolimus, at systemic exposures that are likely to be approximately 76x those expected in patients with stents.

Design: This was a Phase I, multiple-escalating dose, double-blind, placebo-controlled, randomized study, conducted at two sites in healthy male and female subjects.

Procedure: Seventy-two (72) healthy male and female subjects were enrolled and exposed to doses of zotarolimus ranging from 200-800 µg via IV administration as outlined in Table 5:

| Table 5: Dosing Scheme (Study M02-501) | | |
|--|--------------------|------------------------|
| Treatment Group | Number of Subjects | Double-blind Treatment |
| I | 16 | 200 µg ABT-578 |
| | 8 | Placebo |
| II | 16 | 400 µg ABT-578 |
| | 8 | Placebo |
| III | 16 | 800 µg ABT-578 |
| | 8 | Placebo |

Follow up schedule:

1. **Immunosuppression** monitoring occurred on Study Days -2, 3, 7, 10, 11, 12, 15, 21, and 44 or upon subject discontinuation.
2. **Lymphocyte activity** (inhibition of mitogen stimulated lymphocyte proliferation) was evaluated on Study Days -2, 3, 7, 15, 21, and 44, or upon subject discontinuation.
3. **Hypersensitivity** to zotarolimus was assessed on Study Days 1 through 21 and 44 by checking for local reactions at the injection site. Clinical (e.g., rashes, hypotension, tachycardia, bronchoconstriction, etc) and laboratory (e.g., eosinophilia) markers of hypersensitivity were monitored.
4. **Safety** was evaluated based on adverse events, physical examinations, vital signs, ECGs, injection site evaluations, and laboratory tests.

Results: There were no deaths, serious adverse events, or discontinuations due to adverse events.

Treatment-Emergent Adverse Events (TEAEs)

There did not appear to be any dose-response effect reflected in TEAEs, as shown in Table 6:

| Table 6: Treatment Emergent Adverse Events | | | | |
|--|-------------------|--------------------|--------------------|--------------------|
| | Placebo (N=24) | 200µg QD (N=16) | 400µg QD (N=16) | 800µg QD (N=16) |
| All | 8 (33%) | 6 (38%) | 7 (44%) | 4 (25%) |
| Most Common | | | | |
| Headache | 1 (4%) | 2 (13%) | 2 (13%) | 2 (13%) |
| Pain | 1 (4%) | 2 (13%) | 1 (6%) | 0 (0%) |
| Injection site reaction | 2 (8%) | 0 (0%) | 0 (0%) | 2 (13%) |
| Injection site pain | 2 (8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Abdominal pain | 1 (4%) | 1 (6%) | | 0 (0%) |
| Diarrhea | 1 (4%) | 0 (0%) | 1 (6%) | 0 (0%) |
| Dry skin | 0 (0%) | 0 (0%) | 2 (13%) | 0 (0%) |
| Rash | 0 (0%) | 1 (6%) | 1 (6%) | 0 (0%) |

Laboratory Results

Except for possible inhibition of lymphocyte proliferation, graphs of the mean daily changes from baseline in immunomarkers did not suggest any consistent adverse drug effects. No subject had an absolute CD3+CD4+ count below 200/µl (mm³), a value associated with an increased risk of infection in immunocompromised individuals.

With respect to lymphocyte proliferation inhibition, this effect was observed starting with the 200 µg dose. The effects appeared to persist for several weeks after discontinuation of dosing on Day 14. The sponsor's analysis found only the 400 µg dose to be statistically significantly different from placebo ($p < 0.05$) on Study Day 15. Given the small number of subjects studied, no definitive conclusions can be drawn from the results of this single test of immunosuppression.

Eosinophilia (Abbott Criteria $> 10\%$) was observed in one placebo subject (10.2%) on Day 21. One subject in the 200 µg, one subject in the 400 µg, and one subject in the 800 µg treatment groups experienced elevated eosinophil counts of 13.4%, 10.1%, and 11.6% on Study Days 21, 21, and 7, respectively. All values returned to $< 10\%$ by Day 44, and none of these subjects had concomitant skin rashes. One subject in the 200 µg treatment group had elevated SGPT/ALT levels of 87 IU/L and 74 IU/l on Study Days 15 and 21, respectively; however, this value returned to 59 IU/l by Study Day 44.

Two zotarolimus patients (200 and 400 µg doses) had slightly elevated direct and indirect bilirubin levels. However, both subjects had elevated total bilirubin at baseline and values returned to either baseline or lower at the end of the study.

Although zotarolimus may affect fasting serum cholesterol and triglycerides, the clinical relevance of this effect is uncertain in coronary disease patients, in which hyperlipidemia is highly prevalent at baseline.

Vital Signs

There were no clinically significant changes in vital signs.

ECGs

Based on QTcI and QTcF, zotarolimus did not have any significant effect on repolarization. However, the sponsor did not perform a double delta time-matched comparison ((drug on Day 14 – drug baseline) – (placebo on Day 14 – placebo baseline)).

Note: Pharmacokinetic parameters were also evaluated in this study. These results are not discussed here because pharmacokinetics of the finished product were later evaluated in the ENDEAVOR PK study described below.

Summary: Possible effects from zotarolimus include:

1. Inhibition of lymphocyte proliferation
2. Eosinophilia
3. Increases in fasting serum cholesterol and triglycerides

5. PRE-CLINICAL STUDIES

a. Stent Functional Testing

FDA recommends stent functional testing as outlined in our guidance document “Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.” The purpose of this testing is to ensure that the stent platform (i.e., metal stent) functions as intended. Test reports for the following stent functional tests have been provided:

- Material composition
- Stent pitting, crevice corrosion resistance
- Stent fretting corrosion resistance
- Stent galvanic corrosion resistance
- Dimensional verification
- Percent surface area
- Foreshortening
- Recoil
- Stent integrity
- Radial stiffness and radial strength
- Mechanical properties
- Stress analysis
- Accelerated durability
- MRI safety at 3Tesla
- Radiopacity

FDA has completed its review of the preclinical test reports submitted for stent functional testing; there are no remaining concerns.

b. Stent Coating Testing

For drug-eluting stents, FDA recommends additional testing of the stent coating to ensure that the integrity of the coating will be maintained over the simulated use of the device. Test reports for the following stent functional tests have been provided:

- Chemical characterization
- Coating thickness and uniformity
- Coating integrity
- Coating stress analysis
- Particulate analysis
- Corrosion resistance with scoring of coating
- Coating adhesion

FDA has completed its review of the preclinical reports submitted for stent coating testing. Because optimal test methods were not used for certain coating integrity and

particulate analyses, Medtronic is repeating these specific evaluations using new methods developed with FDA.

c. Stent Delivery System Testing

FDA recommends stent functional testing as outlined in our guidance document “Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.” The purpose of this testing is to ensure that the stent delivery systems function as intended. Test reports for the following stent functional tests have been provided:

- Delivery, Deployment and Retraction
- Balloon Rated Burst Pressure (RBP=16atm)
- Balloon Fatigue
- Stent Diameter vs. Balloon Pressure (Compliance Chart)
- Bond Strength
- Crossing Profile with stent
- Crossing Profile without stent
- Inflation and Deflation Time to RBP
- Deflation Time from Nominal Pressure
- Stent Securement - distal and proximal
- Stent Securement - forward and reverse motion
- Balloon Deflatability

FDA has completed its review of the preclinical test reports submitted for stent delivery system testing; there are no remaining concerns.

d. Animal Studies

Medtronic has provided test reports from 14 animal studies of the Endeavor product. These studies evaluate single and overlapped stents at 7, 28, 90, and 180 days, the deliverability of the product with each of the three delivery systems, and the pharmacokinetics of the drug. FDA has reviewed these data and notes no concerns regarding the deliverability of the product with each delivery system, arterial histologic findings, or in vivo pharmacokinetic data. Examination of myocardial sections showed occasional emboli of foreign material within small arterioles rarely associated with inflammation and small foci of myocardial necrosis or scarring. These lesions were not associated with clinical events. Medtronic conducted additional animal studies which suggest that these intramyocardial emboli could be related to liberation of the coating on guidewires or stent delivery systems. We are working with the Sponsor to elucidate the mechanism of particulate generation during stent delivery.

e. Chemistry, Manufacturing, & Controls (CMC)

The drug substance, zotarolimus, is a new molecular entity, which is a chemically-modified analog of rapamycin. It is a semi-synthetic macrocyclic compound with a mechanism of action similar to sirolimus, as both are immunosuppressants with anti-proliferative properties. The drug substance characterization data, manufacturing and controls information, and stability data are provided in a drug master file (DMF). At this time, some pending drug substance issues remain with the DMF holder.

For the finished product, Medtronic has provided the details of the manufacturing process, the quantitative composition of the product, and controls for each of the components used in the manufacture of the Endeavor stent (i.e., zotarolimus drug substance, PC polymer, and ethanol excipient), including the analytical test methods and supporting validation data. Some minor issues remain with the specifications for the incoming PC polymer.

Medtronic has also proposed complete finished product specifications, including the analytical procedures and supporting validation data. At this time, the specifications have not been finalized and are still under discussion with FDA.

Medtronic proposes a 12 month shelf life for the finished product and has provided functional testing of accelerated-aged devices to 24 months and stability data of aged product to 6 months with a regression analysis to estimate 12 month stability. FDA has found the functional test data acceptable but believes that the 6 month stability data provided are insufficient to reliably apply the statistical methods of shelf-life estimation to support the proposed 12 month shelf-life. Additionally, shelf life can not be determined until the specifications are finalized. In the meantime, Medtronic is collecting additional stability data which will be submitted to FDA for consideration of a 12 month shelf life.

f. Sterilization

The Endeavor drug-eluting stent and delivery systems are provided sterile. After reviewing the information submitted by the sponsor, FDA has concluded that under the stated exposure conditions, the ethylene oxide cycle will render the Endeavor stent and delivery systems sterile at a sterility assurance level of 10^{-6} , or the probability of one survivor in one million products sterilized. Ethylene oxide and ethylene chlorohydrin residual analysis was performed to confirm that residual levels are below those considered tolerable and safe per accepted standards. Likewise, Limulus Amebocyte Lysate analysis was performed to confirm that bacterial endotoxin levels are below stated acceptance criteria. Packaging studies were performed to demonstrate that the current packaging configuration will maintain a sterile barrier to support a one year shelf life claim.

g. Biocompatibility

Medtronic has identified all material components of the stent and delivery systems.

Medtronic has provided data from the following biocompatibility evaluations of the finished drug-eluting stent: cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, *in vitro* hemolysis, *in vivo* mouse bone marrow micronucleus assay, bacterial reverse mutation assay, and chromosomal aberration assay.

Medtronic has provided data from the following biocompatibility evaluations of the finished drug-eluting stent and delivery system: cytotoxicity, pyrogenicity, sensitization, intracutaneous reactivity, acute systemic toxicity, complement activation, plasma recalcification, white blood cell morphology, *in vitro* hemolysis, and *in vivo* thrombogenicity.

FDA has reviewed all biocompatibility test reports and finds them acceptable with one exception; because appropriate test article amounts were not used for *in vitro* genotoxicity testing, Medtronic is repeating these tests per FDA's request.

h. Manufacturing

FDA has reviewed the manufacturing information and facility inspections are pending.

6. DEFINITIONS & ABBREVIATIONS

The following definitions and abbreviations were used by the Sponsor across the Endeavor clinical study program and reproduced here for ease of review.

a. Acute success

- **Device Success:** Attainment of <50% in-stent residual stenosis of the target lesion using only the assigned device
- **Lesion Success:** Attainment of <50% in-stent residual stenosis of the target lesion using any percutaneous method
- **Procedure Success:** Attainment of <50% in-stent residual stenosis of the target lesion and no in-hospital MACE
- **Device-Specific Procedure Success:** Device success and no in-hospital MACE. Device-Specific Procedure Success is utilized to account for procedural successes/failures that are related to the implanted device.

b. Binary restenosis rate: Percent of patients with a follow-up percent diameter stenosis of $\geq 50\%$ determined by QCA.

c. Death (Divided into 2 categories):

- **Cardiac death** is defined as death due to any of the following:
 1. Acute myocardial infarction
 2. Cardiac perforation/pericardial tamponade
 3. Arrhythmia or conduction abnormality
 4. Stroke within 30 days of the procedure or stroke suspected of being related to the procedure
 5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery
 6. Any death in which a cardiac cause cannot be excluded
- **Non-cardiac death** is defined as a death not due to cardiac causes (as defined above).

d. Diabetes: A patient was considered to have a history of diabetes mellitus if he/she was taking insulin or oral antidiabetic agents, or was on a modified diet to control diabetes mellitus. Patients who were taking both oral medications and insulin were considered to be insulin-dependent. Patients with a history of untreated diabetes mellitus (or diabetes mellitus treated with diet only) were classified as having non-insulin-dependent diabetes mellitus.

e. In-Lesion Measurement (Also In-Segment Measurement): Measurements either within the stented segment or within 5 mm proximal or distal to the stent edges

f. In-Stent Measurement: Measurements within the stented segment

g. Late Lumen Loss: Difference between the post-procedure minimal lumen diameter [MLD] and the follow-up angiography MLD

h. Major adverse cardiac events (MACE): Composite of death, MI (Q wave and non-Q wave), emergent bypass surgery, or TLR (repeat PTCA or CABG)

i. Myocardial infarction (MI): A diagnosis of myocardial infarction is made when one of the following criteria is met:

- **Q wave MI:** (QMI) requires one of the following criteria:
 - Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data.
 - New pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data, the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.
- **Non-Q Wave MI (NQWMI):** Elevated CK ≥ 2 X the ULN with the presence of elevated CK-MB (any amount above the ULN) in the absence of new pathological Q waves

j. Stent thrombosis (per protocol): A diagnosis of stent thrombosis is made when one of the following criteria is met:

- Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain and ECG changes)
- Any death not attributed to a non-cardiac cause within the first 30 days
- Late Stent Thrombosis is reported according to the following criteria:
 - **Definite Late Stent Thrombosis:** MI >30 days after index and attributable to the target vessel, angiographic documentation (site reported or by QCA) of thrombus or total occlusion at the target site, and freedom from interim revascularization of the target vessel
 - **Possible Late Stent Thrombosis:** MI >30 days after index and attributable to the target vessel, no identifiable culprit lesion elsewhere, freedom from

interim revascularization of the target lesion, and freedom from interim bypass grafting of the target vessel

k. Stent thrombosis (ARC, Academic Research Consortium):

Timing:

| | |
|-----------------------------|--|
| Acute stent thrombosis* | 0 – 24 hours post stent implantation |
| Subacute stent thrombosis* | > 24 hours – 30 days post stent implantation |
| Late stent thrombosis† | > 30 days – 1 year post stent implantation |
| Very late stent thrombosis† | > 1 year post stent implantation |

* Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 – 30 days) will be used in the remainder of this document.

† Including ‘primary’ as well as ‘secondary’ late stent thrombosis; ‘secondary’ late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Level of Evidence

- ***Definite stent thrombosis:*** Definite stent thrombosis is considered to have occurred by *either* angiographic or pathologic confirmation.
 - Angiographic confirmation of stent thrombosis: The presence of a thrombus originating in the stent or in the segment 5 mm proximal or distal to the stent **AND** at least one of the following criteria has been fulfilled within a 48 hours time window:
 - 1) acute onset of ischemic symptoms at rest
 - 2) new ischemic ECG changes suggestive of acute ischemia
 - 3) typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
 - Pathologic confirmation of stent thrombosis: Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy
- ***Probable stent thrombosis:*** Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
 - Any unexplained death within the first 30 days
 - Irrespective of the time after the index procedure any MI, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
- ***Possible stent thrombosis:*** Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

Stent Thrombosis After TLR: Censored vs. Non-Censored: Censoring stent thrombosis events that occur post-TLR performed for stent restenosis may be appropriate as the thrombosis may be related to the treatment chosen to treat restenosis (e.g., brachytherapy) rather than the type of stent used in the index procedure.

Alternatively, censoring stent thrombosis events that occur after TLR may bias results in favor of devices with higher restenosis risks. Therefore, stent thrombosis data presented in this review will report both TLR-censored and TLR-uncensored rates as follows:

- ***ARC Definite + probable (TLR-censored):*** Adjudicated stent thrombosis meeting the definite or probable ARC definition with censoring of any definite or probable stent thrombosis events that may have occurred after a TLR.
- ***ARC Definite + probable (TLR-uncensored):*** Adjudicated stent thrombosis meeting the definite or probable ARC definition including any definite or probable stent thrombosis events that may have occurred after a TLR.

The ARC definitions are available in the following publication: Cutlip DE, Windecker S, Mehran R, Boam A, et al. Academic Research Consortium. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation*. 2007; 115: 2344-51.

l. Target lesion revascularization (TLR): Any clinically-driven repeat intervention of the target lesion by PCI or CABG of the target vessel. Clinically-driven revascularizations are those in which the subject has a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms. Revascularization of a target lesion with an in-lesion diameter stenosis $\geq 70\%$ (by QCA) in the absence of the above-mentioned ischemic signs or symptoms is also considered clinically-driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization is adjudicated using the presence or absence of ischemic signs and symptoms. Non-clinically driven repeat TLR are those in which the subject undergoes a non-emergent revascularization for a diameter stenosis $< 50\%$ (by QCA). Nonemergent repeat TLR for a diameter stenosis $< 70\%$ (by QCA) in subjects without either a positive functional study or angina are also considered non-clinically driven.

m. Target vessel failure (TVF): Target vessel revascularization (defined below), Q or Non Q-Wave MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel. TVF includes any revascularization or adverse endpoint due to renarrowing of any portion of the target vessel, and assumes that the entire vessel is vulnerable to late failures because of guide catheter or guide wire trauma or progression of disease remote from the treatment site.

n. Target vessel revascularization (TVR): Any clinically driven (as defined for TLR) repeat percutaneous intervention of the target vessel or bypass surgery of the target vessel.

7. CLINICAL STUDIES

Data from seven clinical trials have been provided to support this application. Table 7 provides a brief overview of each study design:

| Table 7: Endeavor Program Trial Designs | | | | | | | |
|---|--|--|--|---|--|--|--|
| | Endeavor I | Endeavor II | Endeavor IICA | Endeavor III | Endeavor IV | Endeavor PK | Endeavor Japan |
| Study Type | Multi-center (n=8), OUS Prospective Non-randomized | Multi-center (n=72), OUS Prospective Randomized | Multi-Center (n=15), OUS Prospective Non-randomized | Multi-center (n=29), US Prospective Randomized | Multi-center (n=80), US Prospective Randomized | Multi-center (n=6), US Prospective Non-randomized | Multi-center (n=11), OUS Prospective Non-randomized |
| # of Patients Enrolled | Endeavor: 100 | Total : 1197 Endeavor: 598 Driver Control: 599 | Endeavor: 296 | Total : 436 (3:1 randomization) Endeavor: 323 Cypher: 113 | Total : 1548 (1:1 randomization) Endeavor: 773 Taxis: 775 | Endeavor: 43 | Endeavor: 99 |
| Lesion Criteria | Single <i>de novo</i> lesion in native coronary artery ≤ 15 mm in length and ≥ 3.0 to ≤ 3.5 mm in diameter and coverable with one stent | Single <i>de novo</i> lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.25 to ≤ 3.5 mm in diameter and coverable with one stent | Single <i>de novo</i> lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.25 to ≤ 3.5 mm in diameter and coverable with one stent | Single <i>de novo</i> lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.5 to ≤ 3.5 mm in diameter and coverable with one stent | Single <i>de novo</i> lesion in native coronary artery ≤ 27 mm in length and ≥ 2.5 to ≤ 3.5 mm in diameter and coverable with one stent | Single <i>de novo</i> lesions in native coronary artery ≤ 27 mm in length and ≥ 2.5 to ≤ 3.5 mm in diameter | Single <i>de novo</i> lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.25 to ≤ 3.5 mm in diameter and coverable with one stent |
| Anti-platelet Therapy | Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks | Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks | Aspirin indefinitely, and Clopidogrel for 12 weeks | Aspirin indefinitely, and Clopidogrel for minimum of 12 weeks | Aspirin indefinitely, and Clopidogrel for minimum of 6 months | Aspirin indefinitely, and Clopidogrel for minimum of 12 weeks | Aspirin indefinitely, Ticlopidine for minimum of 12 weeks |
| Status | 48-month follow up complete. | 36-month follow up is complete. | 24-month follow up is complete. | 24-month follow up is complete. | 9-month follow up is complete. | 9-month follow up is complete. | 9-month follow up is complete. |

All studies utilized core labs for evaluation of angiographic, IVUS, and ECG data. Trials were monitored by Data Safety Monitoring Boards and events were adjudicated by Clinical Events Committees.

Patient inclusion and exclusion criteria were similar across trials. Table 8 outlines the primary and important secondary endpoints for each trial.

| Table 8: Comparison of Endeavor Zotarolimus-Eluting CSS Clinical Study Endpoints | | |
|--|---|---|
| | Primary Endpoint(s) | Secondary Endpoints |
| ENDEAVOR I | <ul style="list-style-type: none"> • 30 day MACE • angiographic late lumen loss at 4 months | <ul style="list-style-type: none"> • TVF • Clinically-driven TLR rate at 9 months • Late lumen loss at 12 months (angio) • Neointimal hyperplastic volume at 4, and 12 months (IVUS) |
| ENDEAVOR II | TVF rate at 9 months | <ul style="list-style-type: none"> • Lesion, procedure, and device success • Late lumen loss at 8 months (QCA) • MACE at 30 days, 6, 9 and 12 months • TLR and TVR at 9 months • Angiographic in-stent and in-segment MLD and BAR at 8 months • Neointimal hyperplastic volume at 8 months by IVUS • PK analyses • Safety and tolerance |
| ENDEAVOR II CA | 30 day MACE | <ul style="list-style-type: none"> • Device, lesion, and procedure success • Late lumen loss at 8 months • MACE at 30 days, 6, 9 and 12 months • TVR and TVF at 9 months • Angiographic in-stent and in-segment or lesion MLD and BAR at 8 months • Neointimal hyperplastic volume at 8 months by IVUS • In-stent and in-lesions binary restenosis rate at 8 months |
| ENDEAVOR III | In-segment late lumen loss at 8 months | <ul style="list-style-type: none"> • Device, lesion, and procedure success • In-stent late lumen loss • TLR, TVR, and TVF at 9 months • MACE at 30 days, 6, 9 and 12 months • Angiographic binary restenosis at 8 months • Neointimal hyperplastic volume at 8 months by IVUS • In-stent and in-segment minimum lumen diameter at 8 months |
| ENDEAVOR IV | TVF rate at 9 months | <ul style="list-style-type: none"> • Device, lesion, and procedure success • Angiographic in-stent and in-segment percent diameter stenosis at 8 months • Late lumen loss and late loss index at 8 months • Angiographic binary restenosis rate at 8 months • Neointimal hyperplastic volume and percent volume obstruction at 8 months by IVUS • Minimum luminal diameter at 8 months • TLR and TVR at 9 months |
| ENDEAVOR PK | Pharmacokinetic parameters at 30 days | <ul style="list-style-type: none"> • Device, lesion, and procedure success • MACE at 30 days, 6, 9 and 12 months <p>For patients receiving overlapping stents:</p> <ul style="list-style-type: none"> • In-stent and in-segment percent diameter stenosis • Late lumen loss and late loss index • Angiographic binary restenosis rate • Minimum luminal diameter • Neointimal hyperplastic volume and percent volume obstruction at 8 months by IVUS • Target site revascularization (TSR) • TVF, TVR, and at 9 months |
| ENDEAVOR Japan | TVF rate at 9 months | <ul style="list-style-type: none"> • Device, lesion, and procedure success • Clinically-driven TLR and TVR at nine months post-procedure • MACE at 30 days, 6 months, and 9 months • Late lumen loss at 8 months • In-stent and in-segment MLD and BAR at 8 month |

a. ENDEAVOR I

Objective: To demonstrate the feasibility of the Endeavor Zotarolimus-Eluting CSS for the treatment of single *de novo* lesions in native coronary arteries.

Primary endpoints:

1. MACE at 30 days
2. In-segment late lumen loss at 4 months

Important secondary endpoints

1. TVF at 9 months
2. Clinically-driven TLR at 9 months
3. In-segment late loss at 12 months

Design: Non-randomized, prospective, multi-center, single arm trial. Endeavor stent sizes evaluated in this study are identified in Table 9.

| Table 9: ENDEAVOR I Device Matrix | | | | | | | | |
|-----------------------------------|-------------------|---|----|----|----|----|----|----|
| Diameter (mm) | Stent Length (mm) | | | | | | | |
| | 8 | 9 | 12 | 14 | 15 | 18 | 24 | 30 |
| 3.0 | | | | | | X | | |
| 3.5 | | | | | | X | | |

Randomization: none

Key Inclusion Criteria:

1. Evidence of ischemic heart disease or a positive functional study
2. The target lesion was a single *de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$.
3. The target lesion was ≤ 15 mm in length with a target vessel reference diameter of ≥ 3.0 mm and ≤ 3.5 mm.

Key Exclusion Criteria:

1. Left ventricular ejection fraction $< 30\%$
2. Acute MI within 72 hours
3. Creatinine > 2.0 mg/dl
4. Left main, ostial lesion, or bifurcation lesion

Stent procedure: Predilatation of target lesion with standard PTCA (no direct stenting).

Antiplatelet therapy: At least 75 mg aspirin indefinitely and clopidogrel 75 mg daily for at least 12 weeks

Study site and dates of enrollment: ENDEAVOR I enrolled 100 patients at 8 clinical research sites in Australia and New Zealand from January 7, 2003 through April 29, 2003.

Follow up schedule:

1. Clinical follow-up at 30 days, 4 months, 9 months, and 12 months; telephone follow-up annually through 5 years
2. Angiographic and IVUS follow-up at 4 and 12 months

Statistical Analyses (primary endpoint): No statistical hypothesis were pre-specified for this feasibility study.

Results

Enrollment: The total enrollment in Endeavor I was 100 patients all of whom received the Endeavor stent. Clinical follow-up for the primary endpoint at 30 days was 100%. Angiographic follow-up at the primary endpoint at 4 months was 99%. IVUS follow-up at 4 months was 97%. The baseline demographics, clinical characteristics, lesion characteristics, and vessel characteristics are outlined in Tables 10 and 11.

| Table 10: ENDEAVOR I Baseline Demographics and Clinical Characteristics | | |
|--|-----------------|----------|
| | Endeavor | |
| | N (100) | % |
| Age (years) | | |
| Mean (SD) | 58.7 ± 10.08 | |
| Gender | 100 | |
| Male | 79 | (79.0%) |
| Female | 21 | (21.0%) |
| Prior MI | 47/100 | (47.0%) |
| Prior CABG | 2/100 | (2.0%) |
| Diabetes mellitus | 16/100 | (16.0%) |
| Insulin Dependent Diabetes | 6/100 | (6.0%) |
| Smoking | 34/100 | (34.0%) |
| HTN | 52/98 | (53.1%) |
| Hyperlipidemia | 90/98 | (91.8%) |
| Prior PCI | 19/100 | (19.0%) |
| Major coronary stenosis (>50%) | 100 | |
| Single | 65 | (65.0%) |
| Double | 29 | (29.0%) |
| Triple | 6 | (6.0%) |
| PCI for angina or MI | 94/100 | (94.0%) |
| Stable | 29/94 | (30.9%) |
| Unstable | 39/94 | (41.5%) |
| MI | 26/94 | (27.7%) |
| IIb /IIIa inhibitor | 0/100 | (0.0%) |

| Table 11: ENDEAVOR I Baseline Lesion and Vessel Characteristics | |
|--|------------------|
| | Endeavor |
| Reference vessel diameter, mm* (n) | 2.96±0.47 (100) |
| Lesion length, mm* | 10.94±3.13 (100) |
| Pre-procedure % Stenosis* (n) | 70.32±9.80 (100) |
| Vessel Location | |
| LAD | 43/100 (43.0%) |
| LCX | 23/100 (23.0%) |
| RCA | 34/100 (34.0%) |
| LMCA | 0/100 (0.0%) |
| Post-procedure % Stenosis* (n) | |
| In-Stent | 5.37±7.51 (100) |
| In-Segment | 16.54±8.40 (100) |

*Mean±SD

Primary endpoints (Table 12):

| Table 12: ENDEAVOR I Primary Endpoint Results | |
|---|-------------------|
| | Endeavor |
| MACE at 30 days | 1.0% (1/100) |
| In-segment late lumen loss at 4 months (n) | 0.22±0.43 mm (98) |

Secondary endpoints (Tables 13 and 14):

| Table 13: ENDEAVOR I Major Clinical Endpoint Results at 9 months | |
|--|--------------|
| | Endeavor |
| TVF | 2.0% (2/100) |
| Death | 0.0% (0/100) |
| Cardiac Death | 0.0% (0/100) |
| MI | 1.0% (1/100) |
| Q-wave MI | 0.0% (0/100) |
| Non Q-wave MI | 1.0% (1/100) |
| TLR | 2.0% (2/100) |
| TVR | 2.0% (2/100) |
| Stent thrombosis | |
| Protocol | 1.0% (1/100) |
| ARC definite + probable (TLR-censored) | 1.0% (1/100) |
| ARC definite + probable (TLR-uncensored) | 1.0% (1/100) |

| Table 14: ENDEAVOR I Angiographic Results at 12 months | |
|--|---------------------|
| | Endeavor |
| In-segment late loss, mm (n) | 0.43±0.44 (92) |
| % diameter stenosis (n) | 28.00 ± 13.41% (92) |
| Binary in-segment restenosis (n) | 5.4% (5/92) |

Latest available clinical follow-up (Table 15):

| Table 15: ENDEAVOR I Major Clinical Endpoint Results at 48 months | |
|--|-----------------|
| | Endeavor |
| TVF | 5.2% (5/97) |
| Death | 4.1% (4/97) |
| Cardiac Death | 0.0% (0/97) |
| MI | 1.0% (1/97) |
| Q-wave MI | 0.0% (0/97) |
| Non Q-wave MI | 1.0% (1/97) |
| TLR | 3.1% (3/97) |
| TVR | 5.2% (5/97) |
| Stent thrombosis | |
| Protocol | 1.0% (1/97) |
| ARC definite + probable (TLR-censored) | 1.0% (1/97) |
| ARC definite + probable (TLR-uncensored) | 1.0% (1/97) |

Summary of Results: A low (1%) 30-day MACE rate was observed in this single arm feasibility study. There were no unanticipated adverse events.

b. ENDEAVOR II

Objective: To demonstrate the safety and efficacy of the Endeavor Zotarolimus-Eluting CSS compared to 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 (composite of TVR, Q or Non Q-Wave MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel) at 9 months post-procedure

Important secondary endpoints

1. Device Success, lesion success, procedure success, and device specific procedure success
2. Total MACE and individual rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually out to five years
3. In-segment late lumen loss at 8 months. *Late loss was assessed as a powered secondary endpoint.*

Design: Prospective, multicenter, double-blind; randomized controlled trial. The stent sizes were used in the Endeavor and Driver arms are outlined in Tables 16 and 17, respectively.

| Table 16: ENDEAVOR II Device Matrix | | | | | | | | |
|-------------------------------------|-------------------|----|----|----|----|----|----|----|
| Diameter (mm) | Stent Length (mm) | | | | | | | |
| | 8* | 9* | 12 | 14 | 15 | 18 | 24 | 30 |
| 2.25 | X | | | | | X | X | X |
| 2.50 | X | | | | | X | X | X |
| 3.0 | | X | | | | X | X | X |
| 3.5 | | X | | | | X | X | X |

*Used only in cases of insufficient lesion coverage or bailout.

Randomization: 1:1 randomization to either Endeavor Stent or Driver bare metal stent

Key Inclusion Criteria:

1. Evidence of ischemic heart disease or a positive functional study
2. Single vessel disease or multi-vessel disease with only moderate stenosis (max 50-60%) or total occlusion of non-target lesions for which no interventions planned
3. The target lesion was a single *de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$.
4. The target lesion was ≥ 14 mm and ≤ 27 mm in length with a target vessel reference diameter of ≥ 2.25 mm and ≤ 3.5 mm

Key Exclusion Criteria:

1. Left ventricular ejection fraction <30%
2. Acute MI within 72 hours
3. Creatinine >2.0 mg/dl
4. Thrombus in target vessel
5. Left main, ostial lesion, or bifurcation lesion

Stent procedure: Predilatation of target lesion with standard PTCA (no direct stenting).

Antiplatelet therapy: At least 75 mg aspirin indefinitely and clopidogrel 75 mg daily for at least 12 weeks

Study site and dates of enrollment: ENDEAVOR II enrolled a total of 1,197 patients at 72 clinical sites in Europe, Asia Pacific, Israel, Australia, and New Zealand from July 14, 2003 through January 13, 2004.

Follow up schedule:

1. Clinical follow-up at 30 days and at 9 months; telephone follow-up at 6 and 12 months, and annually through 5 years
2. Angiographic follow-up at 8 months for the first 600 consecutive patients and IVUS follow-up at 8 months for the first approximately 300 patients

Statistical Analyses (primary endpoint): The null hypothesis was that the Endeavor stent would have a TVF rate equal to that of the control Driver Stent. The alternative hypothesis was that the Endeavor Stent would have a TVF rate less than, or greater than, the control stent. The parameters/assumptions for this analysis were:

- The 9-month TVF rate in control subjects was assumed to be 16.0%, and the TVF rate in Endeavor subjects was assumed to be 9.5% (which corresponds to a treatment effect of approximately 40%).
- The power of the study was 90%, and the two-sided alpha error was 5%.

The calculated sample size for two-sided significance testing was 1104; a total of 1197 patients were enrolled to account for those lost to follow-up.

Statistical Analyses (secondary endpoint): The null hypothesis that the mean in-segment late lumen loss at 8 months in patients treated with the Endeavor stent is equal to the mean late loss at 8 months in patients treated with the control Driver stent. The alternative hypothesis was that the mean late lumen loss at 8 months in patients treated with the Endeavor stent was not equal to that in patients treated with the Driver stent.

The parameters/assumptions for this analysis were:

- The mean late loss at eight months in the Endeavor stent arm would be 0.21 mm smaller than the mean late loss at eight months in the control arm.
- The standard deviation of the late loss would be 0.70 mm in both arms.
- The power was 90%, and the two-sided alpha error was 5%
- The loss to follow up would be approximately 20%.

The calculated sample size under these assumptions was 234 per arm (total 468). The number was increased to 600 in order to account for those lost to follow-up.

Results

Enrollment: Endeavor II enrolled 1197 patients with 598 randomized to the Endeavor stent and 599 randomized to the Driver control group. Clinical follow-up for the primary endpoint at 9 months was 98.8%. Angiographic follow-up at the powered secondary endpoint at 8 months was 90.3%. The baseline demographics, clinical characteristics, lesion characteristics, and vessel characteristics are outlined in Tables 17 and 18. The treatment groups appear to be appropriately balanced with respect to their clinical and angiographic features except for a higher rate of individuals with insulin-dependent diabetes in the Driver group (7.4%) compared to the Endeavor group (4.5%, p=0.05).

| Table 17: ENDEAVOR II Baseline Demographics and Clinical Characteristics | | | | |
|---|--------------------|----------|--------------------|----------|
| | Endeavor | | Driver | |
| | N | % | N | % |
| Age (years) | | | | |
| Mean (SD) | 61.58 ± 10.53(597) | | 61.89 ± 10.45(596) | |
| Gender | 597 | | 596 | |
| Male | 461 | (77.2%) | 449 | (75.3%) |
| Female | 136 | (22.8%) | 147 | (24.7%) |
| Prior MI | 236/594 | (39.7%) | 247/595 | (41.5%) |
| Prior CABG | 28/597 | (4.7%) | 29/596 | (4.9%) |
| Diabetes mellitus | 108/595 | (18.2%) | 132/595 | (22.2%) |
| Insulin Dependent Diabetes | 27/594 | (4.5%) | 44/595 | (7.4%) |
| Smoking | 207/587 | (35.3%) | 207/588 | (35.2%) |
| HTN | 378/596 | (63.4%) | 403/591 | (68.2%) |
| Hyperlipidemia | 476/591 | (80.5%) | 455/592 | (76.9%) |
| Prior PCI | 129/595 | (21.7%) | 107/594 | (18.0%) |
| Major coronary stenosis (>50%) | 597 | | 596 | |
| Single | 387 | (64.8%) | 375 | (62.9%) |
| Double | 140 | (23.5%) | 157 | (26.3%) |
| Triple | 70 | (11.7%) | 64 | (10.7%) |
| PCI for angina or MI | 545/597 | (91.3%) | 543/596 | (91.1%) |
| Stable | 268/545 | (49.2%) | 276/543 | (50.8%) |
| Unstable | 181/545 | (33.2%) | 181/543 | (33.3%) |
| MI | 96/545 | (17.6%) | 86/543 | (15.8%) |
| IIb /IIIa inhibitor | 79/597 | (13.2%) | 62/594 | (10.4%) |

| Table 18: ENDEAVOR II Baseline Lesion and Vessel Characteristics | | |
|---|-------------------|------------------|
| | Endeavor | Driver |
| Reference vessel diameter (mm) | 2.73±0.48 (590) | 2.76±0.49 (591) |
| Lesion length, mm* | 14.04±5.56 (582) | 14.38±5.73 (588) |
| Pre-procedure % Stenosis* (n) | 69.74±10.89(590) | 69.58±11.00(591) |
| Vessel Location | | |
| LAD | 255/590 (43.2%) | 281/591 (47.5%) |
| LCX | 132/590 (22.4%) | 125/591 (21.2%) |
| RCA | 203/590 (34.4%) | 185/591 (31.3%) |
| LMCA | 0/590 (0.0%) | 0/591 (0.0%) |
| Post-procedure % Stenosis* (n) | | |
| In-Stent | 6.04±10.43 (588) | 6.23±10.03 (589) |
| In-Segment | 20.39±10.26 (589) | 20.11±9.38 (590) |

*Mean±SD

Primary endpoint: Endeavor II met its primary target vessel failure endpoint (Table 19).

| Table 19: ENDEAVOR II Primary Endpoint Results at 9 months | | | | |
|--|---------------|----------------|-----------------------|---------|
| | Endeavor | Driver Control | Difference [95% CI] | P value |
| TVF Rate | 7.9% (47/592) | 15.1% (89/591) | -7.1% [-10.7%, -3.5%] | <0.001 |

Secondary endpoints:

- Device Success, lesion success, procedure success, and device specific procedure success in Endeavor stent-treated patients was 98.8%, 99.7%, 97.3%, and 96.5%, respectively.
- Thirty-day MACE was 2.9% for the Endeavor stent and 3.7% for the Driver stent, Difference -0.9% (95% CI -2.9%, 1.2%)
- Major secondary endpoint outcomes at 9 months are shown in Tables 20 and 21.

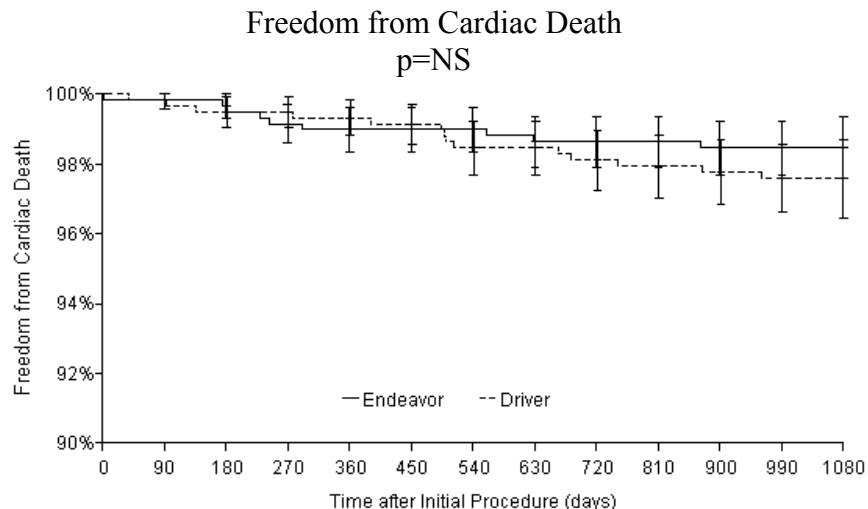
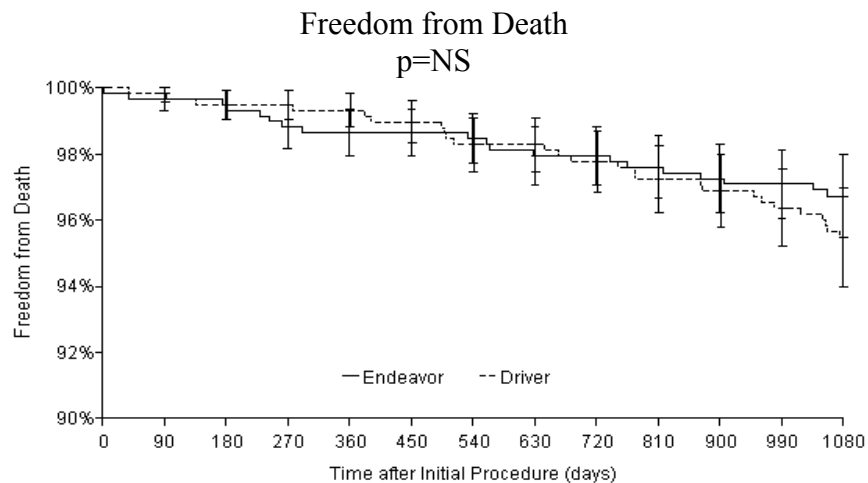
| Table 20: Endeavor II Major Clinical Endpoint Results at 9 months | | | |
|---|--------------|---------------|-----------------------|
| | Endeavor | Driver | Difference [95% CI] |
| Death | 1.2%(7/592) | 0.5%(3/591) | 0.7% [-0.4%,1.7%] |
| Cardiac Death | 0.8%(5/592) | 0.5%(3/591) | 0.3% [-0.6%,1.3%] |
| MI | 2.7%(16/592) | 3.9%(23/591) | -1.2% [-3.2%,0.8%] |
| Q-wave MI | 0.3%(2/592) | 0.8%(5/591) | -0.5% [-1.4%,0.4%] |
| Non Q-wave MI | 2.4%(14/592) | 3.0%(18/591) | -0.7% [-2.5%,1.2%] |
| TLR | 4.6%(27/592) | 11.8%(70/591) | -7.3% [-10.4%, -4.2%] |
| TVR | 5.6%(33/592) | 12.5%(74/591) | -6.9% [-10.2%, -3.7%] |
| Stent thrombosis | | | |
| Protocol | 0.5%(3/592) | 1.2%(7/591) | -0.7% [-1.7%,0.4%] |
| ARC definite + probable (TLR-censored) | 0.5%(3/592) | 1.4%(8/591) | -0.8% [-1.9%,0.2%] |
| ARC definite + probable (TLR-uncensored) | 0.5%(3/592) | 1.4%(8/591) | -0.8% [-1.9%,0.2%] |

| Table 21: Endeavor II Angiographic Results at 8 months | | | | |
|--|-------------------|-------------------|------------------------|---------|
| | Endeavor | Driver Control | Difference [95% CI] | P value |
| In-segment late loss, mm (n) | 0.36±0.46 (264) | 0.72±0.61 (263) | -0.36 [-0.45,-0.27] | <0.001 |
| % diameter stenosis, (n) | 32.67±16.27 (264) | 44.33±20.45 (265) | -11.66 [-14.82,-8.50] | - |
| Binary in-segment restenosis, (n) | 13.3% (35/264) | 34.7% (92/265) | -21.5% [-28.5%,-14.4%] | - |
| IVUS Volume Obstruction, % (n) | 17.34±10.27 (90) | 29.55±17.58 (81) | -12.22 [-16.51,-7.92] | - |

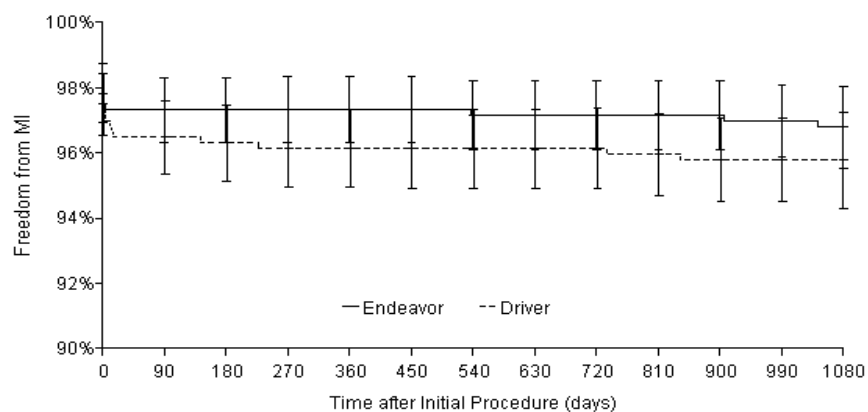
Latest available clinical follow-up (Table 22):

| Table 22: Endeavor II Major Clinical Endpoint Results at 36 months | | | |
|--|----------------|-----------------|-----------------------|
| | Endeavor | Driver | Difference [95% CI] |
| TVF | 12.8% (74/577) | 21.4% (124/579) | -8.6% [-12.9%, -4.3%] |
| Death | 3.3% (19/577) | 4.5% (26/579) | -1.2% [-3.4%, 1.0%] |
| Cardiac Death | 1.6% (9/577) | 2.4% (14/579) | -0.9% [-2.5%, 0.8%] |
| MI | 3.3% (19/577) | 4.3% (25/579) | -1.0% [-3.2%, 1.2%] |
| Q-wave MI | 0.3% (2/577) | 1.0% (6/579) | -0.7% [-1.6%, 0.3%] |
| Non Q-wave MI | 2.9% (17/577) | 3.3% (19/579) | -0.3% [-2.3%, 1.7%] |
| TLR | 7.3% (42/577) | 14.7% (85/579) | -7.4% [-11.0%, -3.8%] |
| TVR | 9.5% (55/577) | 17.6% (102/579) | -8.1% [-12.0%, -4.2%] |
| Stent thrombosis | | | |
| Protocol | 0.5% (3/577) | 1.2% (7/579) | -0.7% [-1.8%, 0.4%] |
| ARC definite + probable (TLR-censored) | 0.9% (5/577) | 1.4% (8/579) | -0.5% [-1.7%, 0.7%] |
| ARC definite + probable (TLR-uncensored) | 0.9% (5/577) | 1.6% (9/579) | -0.7% [-1.9%, 0.6%] |

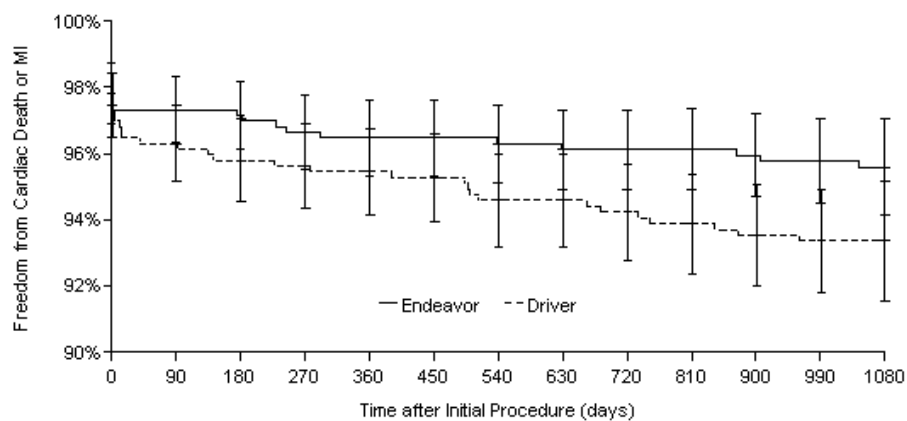
The following Kaplan Meier Curves depict the safety and effectiveness profile of the Endeavor stent as compared to the Driver control through 3 years follow-up. Error bars represent ± 1.5 standard error.



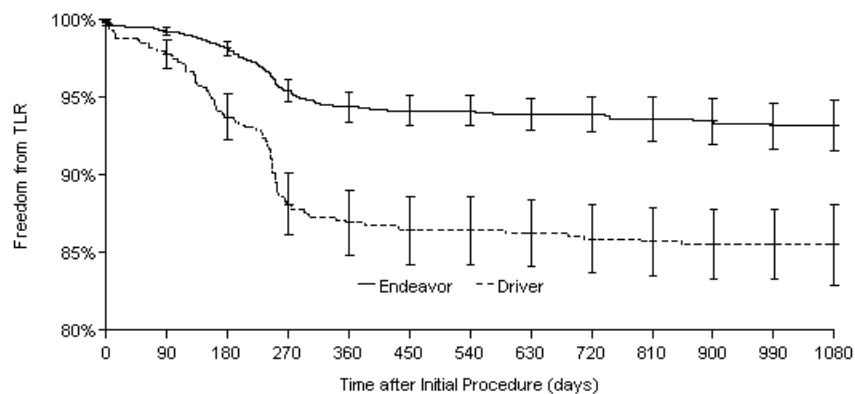
Freedom from MI p=NS

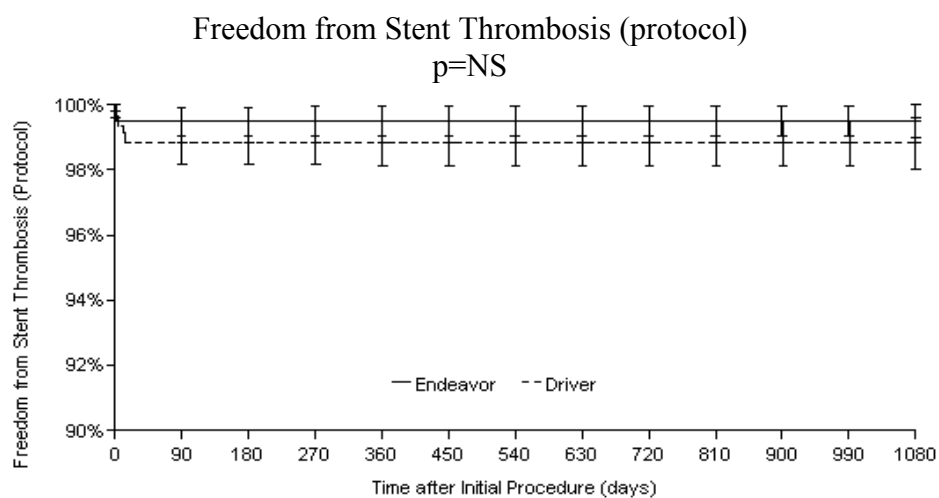
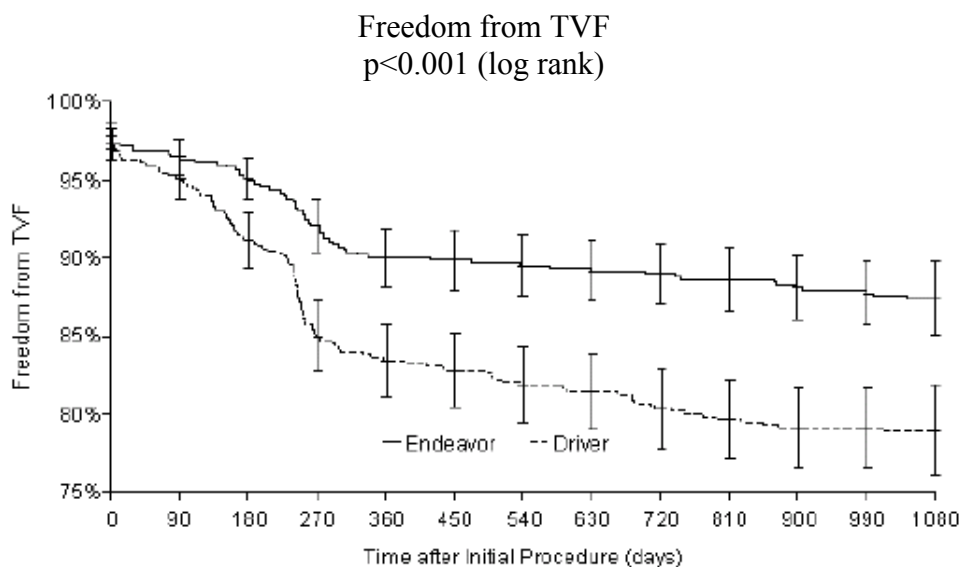
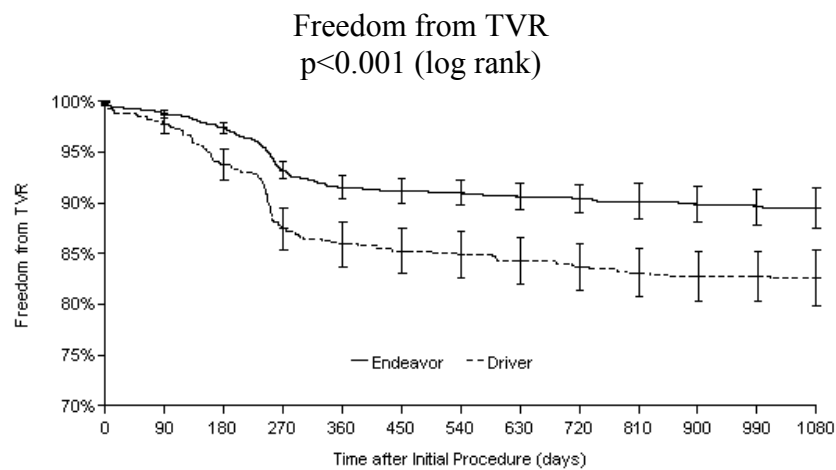


Freedom from Cardiac Death + MI p=NS

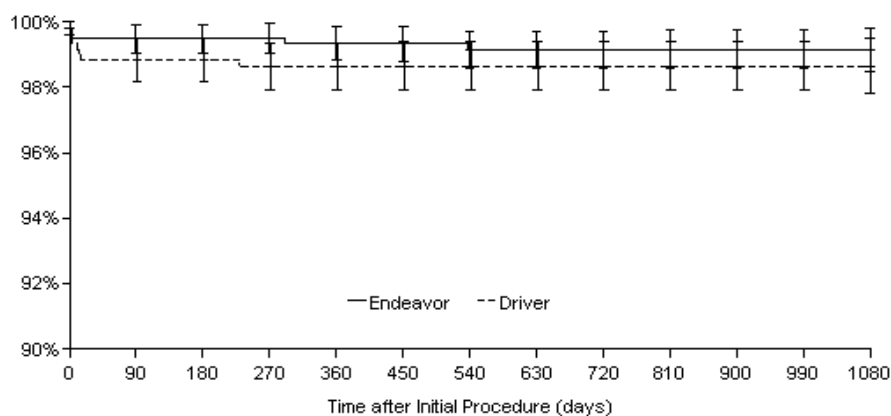


Freedom from TLR p<0.001 (log rank)

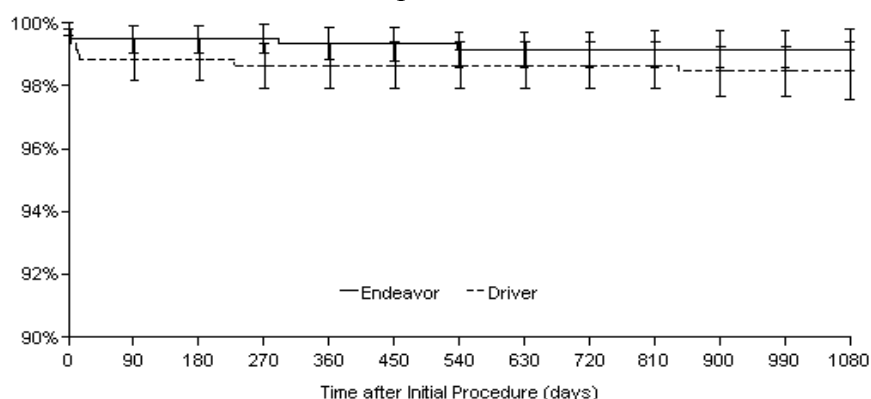




Freedom from Stent Thrombosis (ARC definite + probable, TLR-censored)
p=NS



Freedom from Stent Thrombosis (ARC definite + probable, uncensored)
p=NS



Summary of Results: Endeavor II was a large randomized trial comparing the Endeavor stent to an approved bare metal stent (the Driver stent) in the treatment of de novo coronary lesions. Clinical outcomes for patients treated with the Driver stent were typical of bare metal stent trials. The Endeavor stent met its primary TVF clinical endpoint. The reduced rates of TLR/TVR in patients treated with the Endeavor stent compared to the control Driver stent were consistent with coronary imaging results, which showed a reduction in in-stent neointimal growth. Reduced repeat revascularization rates were maintained through 3 years in Endeavor patients. There were no signals increased rates of death, MI, or stent thrombosis or unexpected adverse events associated with the Endeavor stent.

Limitations: Like other pivotal trials of other DES, Endeavor II included clinically stable patients with relatively non-complex de novo single coronary lesions. In addition, Endeavor II was conducted entirely outside of the US.

c. ENDEAVOR II CA

Objective: To expand the acute safety information and performance data of the Endeavor Zotarolimus-Eluting CSS for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter

Primary endpoint: MACE rate at 30 days post procedure

Important secondary endpoints

1. Device Success, lesion success, procedure success, and device specific procedure success
2. TLR, TVR and TVF at 9 months post-procedure
3. Total MACE and individual rates of death, MI, and stent thrombosis at 30 days, 6, 9, and 12-months and annually through five years
4. In-segment late lumen loss at 8 months

Design: Prospective, multicenter, single-arm, open-label substudy. The Endeavor stent sizes used are identified in Table 23.

| Table 23: ENDEAVOR II CA Device Matrix | | | | | | | | |
|--|-------------------|----|----|----|----|----|----|----|
| Diameter (mm) | Stent Length (mm) | | | | | | | |
| | 8* | 9* | 12 | 14 | 15 | 18 | 24 | 30 |
| 2.25 | X | | | | | X | X | X |
| 2.50 | X | | | | | X | X | X |
| 3.0 | | X | | | | X | X | X |
| 3.5 | | X | | | | X | X | X |

*Used only in cases of insufficient lesion coverage or bailout

Key Inclusion Criteria:

1. Evidence of ischemic heart disease or a positive functional study
2. Single vessel disease or multi-vessel disease with only moderate stenosis (max 50-60%) or total occlusion of non-target lesions for which no interventions planned
3. The target lesion was a single *de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$.
4. The target lesion was ≥ 14 mm and ≤ 27 mm in length with a target vessel reference diameter of ≥ 2.25 mm and ≤ 3.5 mm.

Key Exclusion Criteria:

1. Left ventricular ejection fraction $< 30\%$
2. Acute MI within 72 hours
3. Creatinine > 2.0 mg/dl
4. Thrombus within the target
5. Left main, ostial lesion, or bifurcation lesion

Stent procedure: Pre-dilatation was performed at the physician's discretion for lesions that were readily accessible and < 20 mm in length.

Antiplatelet therapy: At least 75 mg aspirin indefinitely and clopidogrel 75 mg daily for at least 12 weeks

Study site and dates of enrollment: The ENDEAVOR II Continued Access substudy enrolled 296 patients at 15 clinical research sites in Germany and the Netherlands from March 18, 2004 to June 21, 2004.

Follow up schedule:

1. Clinical follow-up at 30 days and at 9 months; telephone follow-up at 6 and 12 months, and annually through 5 years
2. Angiographic follow-up at 8 months for the first 150 consecutive patients and IVUS follow-up at 8 months for 100 patients

Statistical Analyses (primary endpoint): No statistical hypothesis were pre-specified for this registry study.

Results

Enrollment: Endeavor II CA enrolled 296 patients all of whom received the Endeavor stent. There were 170 patients with pre-dilatation and 126 patients with direct stenting. Clinical follow-up for the primary endpoint at 30 days was 100%. The baseline demographics, clinical characteristics, lesion characteristics, and vessel characteristics are outlined in the Tables 24 and 25.

| Table 24: ENDEAVOR II CA Baseline Demographics and Clinical Characteristics | | |
|--|--------------------|---------|
| | Endeavor | |
| | N | % |
| Age (years) | | |
| Mean (SD) | 64.25 ± 9.69 (296) | |
| Gender | 296 | |
| Male | 222 | (75%) |
| Female | 74 | (25%) |
| Prior MI | 86/295 | (29.2%) |
| Prior CABG | 15/296 | (5.1%) |
| Diabetes mellitus | 76/295 | (25.8%) |
| Insulin Dependent Diabetes | 20/295 | (6.8%) |
| Smoking | 79/291 | (27.1%) |
| HTN | 241/295 | (81.7%) |
| Hyperlipidemia | 220/292 | (75.3%) |
| Prior PCI | 97/296 | (32.8%) |
| Major coronary stenosis (>50%) | 296 | |
| Single | 160 | (54.1%) |
| Double | 78 | (26.4%) |
| Triple | 58 | (19.6%) |
| PCI for angina or MI | 278/296 | (93.9%) |
| Stable | 197/278 | (70.9%) |
| Unstable | 54/278 | (19.4%) |
| MI | 27/278 | (9.7%) |
| IIb /IIIa inhibitor | 21/296 | (7.1%) |

| Table 25: ENDEAVOR II CA Baseline Lesion and Vessel Characteristics | |
|--|-------------------|
| | Endeavor |
| Reference vessel diameter, mm* (n) | 2.63 ± 0.45 (297) |
| Lesion length, mm* | 16.49±7.86 (293) |
| Pre-procedure % Stenosis* (n) | 70.03±11.83 (297) |
| Vessel Location | |
| LAD | 150/297 (50.5%) |
| LCX | 67/297 (22.6%) |
| RCA | 80/297 (26.9%) |
| LMCA | 0/297 (0%) |
| Post-procedure % Stenosis* (n) | |
| In-Stent | 5.27±9.45 (296) |
| In-Segment | 17.76±9.57 (296) |

*Mean±SD

Primary endpoint (Table 26):

| Table 26: ENDEAVOR II CA Primary Endpoint Results | |
|---|---------------|
| | Endeavor |
| MACE at 30 days | 5.4% (16/296) |

Secondary endpoints:

- Device Success, lesion success, procedure success, and device specific procedure success in Endeavor stent-treated patients was 98.3%, 99.7%, 94.9%, and 93.6%, respectively.
- Major secondary endpoint outcomes at 9 months are shown in Tables 27 and 28.

| Table 27: ENDEAVOR II CA Major Clinical Endpoint Results at 9 months | |
|--|----------------|
| | Endeavor |
| TVF | 13.0% (38/293) |
| Death | 0.7% (2/293) |
| Cardiac Death | 0.7% (2/293) |
| MI | 5.1% (15/293) |
| Q-wave MI | 0.3% (1/293) |
| Non Q-wave MI | 4.8% (14/293) |
| TLR | 5.1% (15/293) |
| TVR | 8.9% (26/293) |
| Stent thrombosis | |
| Protocol | 0.0% (0/293) |
| ARC definite + probable (TLR-censored) | 0.0% (0/293) |
| ARC definite + probable (TLR-uncensored) | 0.0% (0/293) |

| Table 28: ENDEAVOR II CA Angiographic Results at 8 months | |
|---|--------------------|
| | Endeavor |
| In-segment late loss, mm (n) | 0.39±0.56 (117) |
| % diameter stenosis (n) | 31.93± 20.54 (117) |
| Binary in-segment restenosis | 17.1% (20/117) |

Latest available clinical follow-up (Table 29):

| Table 29: ENDEAVOR II CA Major Clinical Endpoint Results at 24 months | |
|--|-----------------|
| | Endeavor |
| TVF | 16.3% (47/288) |
| Death | 1.4% (4/288) |
| Cardiac Death | 0.7% (2/288) |
| MI | 5.9% (17/288) |
| Q-wave MI | 0.3% (1/288) |
| Non Q-wave MI | 5.6% (16/288) |
| TLR | 7.3% (21/288) |
| TVR | 12.5% (36/288) |
| Stent thrombosis | |
| Protocol | 0.0% (0/288) |
| ARC definite + probable (TLR-censored) | 0.0% (0/288) |
| ARC definite + probable (TLR-uncensored) | 0.0% (0/288) |

Summary of Results: ENDEAVOR II CA provides additional Endeavor stent safety and effectiveness data that are generally consistent with results observed in the randomized trials, recognizing that the patients enrolled in this all-comers registry reflect greater lesion complexity than those enrolled in the randomized trials. There were no unexpected adverse events associated with the Endeavor stent.

d. ENDEAVOR III

Objectives:

1. To demonstrate the equivalency in in-segment late lumen loss at 8 months between the Endeavor and the Cypher stent for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter
2. To provide data on Endeavor stent performance in a US patient population.

Primary endpoint: In-segment late lumen loss at 8 months post-procedure

Important secondary endpoints

1. Device Success, lesion success, procedure success, and device specific procedure success
2. Total MACE and individual rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually through five years
3. Clinically-driven TLR, clinically-driven TVR, and TVF at nine months

Design: Prospective, multicenter, single-blind; randomized controlled non-inferiority trial. The Endeavor and Cypher stent sizes used are identified in Tables 30 and 31, respectively.

| Table 30: ENDEAVOR III Device Matrix – Endeavor | | | | | |
|---|-------------------|----|----|----|----|
| | Stent Length (mm) | | | | |
| Diameter (mm) | 8* | 9* | 18 | 24 | 30 |
| 2.50 | X | | X | X | X |
| 3.0 | | X | X | X | X |
| 3.5 | | X | X | X | X |

*Used only in cases of insufficient lesion coverage or bailout

| Table 31: ENDEAVOR III Device Matrix – Cypher | | | | | |
|---|-------------------|----|----|----|----|
| | Stent Length (mm) | | | | |
| Diameter (mm) | 8* | 18 | 23 | 28 | 33 |
| 2.50 | X | X | X | X | |
| 3.0 | X | X | X | | X |
| 3.5 | X | X | X | | X |

*Used only in cases of insufficient lesion coverage or bailout

Randomization: 3:1 randomization to either Endeavor stent or CYPHER stent (control), respectively

Key Inclusion Criteria:

1. Evidence of ischemic heart disease, stable or unstable angina, silent ischemia, or a positive functional study
2. The target lesion was a single *de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$
3. The target lesion ≥ 14 mm and ≤ 27 mm in length with a target vessel reference diameter of ≥ 2.5 mm and ≤ 3.5 mm

Key Exclusion Criteria:

1. Left ventricular ejection fraction <30%
2. Acute MI within 72 hours
3. Creatinine >2.0 mg/dl
4. Left main, ostial lesion, or bifurcation lesion

Stent procedure: Predilatation of target lesion with standard PTCA (no direct stenting)

Antiplatelet therapy: At least 75 mg aspirin indefinitely and clopidogrel 75 mg daily for at least 12 weeks

Study site and dates of enrollment: Endeavor III enrolled 436 patients at 29 clinical research sites in the US from February 19, 2004 to September 18, 2004 under IDE

**Follow up schedule:**

1. Clinical follow-up at 30 days and at 8 months; telephone follow-up at 6, 9, and 12 months, and annually through 5 years
2. Angiographic and IVUS follow-up at 8 months

Statistical Analyses: This study evaluated equivalency of 8-month in-segment late lumen loss between Endeavor and Cypher stents with an equivalency margin (delta) of late lumen loss set at 0.2 mm. The null hypothesis was that the Endeavor stent would have a mean in-segment late lumen loss equal to or exceeding that of the Cypher stent by 0.2 mm or more. The alternative hypothesis was that the Endeavor would have a mean in-segment late lumen loss less than the control Cypher stent mean plus 0.2 mm. The power of the study was 90%, and the one-sided alpha error was 5%. The calculated sample size for one-sided significance testing was 348; a total of 436 patients were enrolled to account for those lost to follow-up.

Results

Enrollment: The total enrollment in Endeavor III was 436 with 323 randomized to the Endeavor stent and 113 randomized to the Cypher stent. Angiographic follow-up at the primary endpoint at 8 months was 89.4% for angiography and 70.4% for IVUS. The baseline demographics, clinical characteristics, lesion characteristics, and vessel characteristics are outlined in Tables 32 and 33. The treatment groups appear to be appropriately balanced with respect to their clinical and angiographic features except for a higher percentage of women in the Endeavor stent treatment group (p=0.001).

| Table 32: ENDEAVOR III Baseline Demographics and Clinical Characteristics | | | | |
|--|--------------------|---------|---------------------|---------|
| | Endeavor | | Cypher | |
| | N | % | N | % |
| Age (years) | | | | |
| Mean (SD) | 61.4 ± 10.58 (323) | | 61.73 ± 11.59 (113) | |
| Gender | 323 | | 113 | |
| Male | 211 | (65.3%) | 92 | (81.4%) |
| Female | 112 | (34.7%) | 21 | (18.6%) |
| Prior MI | 64/321 | (19.9%) | 23/111 | (20.7%) |
| Prior CABG | 17/323 | (5.3%) | 9/113 | (8.0%) |
| Diabetes mellitus | 96/323 | (29.7%) | 32/113 | (28.3%) |
| Insulin Dependent Diabetes | 21/322 | (6.5%) | 10/113 | (8.8%) |
| Smoking | 212/319 | 66.5% | 85/113 | 75.2% |
| HTN | 227/321 | (70.7%) | 84/113 | (74.3%) |
| Hyperlipidemia | 268/321 | (83.5%) | 98/113 | (86.7%) |
| Prior PCI | 73/323 | (22.6%) | 19/113 | (16.8%) |
| Major coronary stenosis (>50%) | 323 | | 113 | |
| Single | 201 | (62.2%) | 66 | (58.4%) |
| Double | 94 | (29.1%) | 34 | (30.1%) |
| Triple | 28 | (8.7%) | 13 | (11.5%) |
| PCI for angina or MI | 274/323 | (84.8%) | 97/113 | (85.8%) |
| Stable | 118/274 | (43.1%) | 39/97 | (40.2%) |
| Unstable | 140/274 | (51.1%) | 54/97 | (55.7%) |
| MI | 16/274 | (5.8%) | 4/97 | (4.1%) |
| IIb /IIIa inhibitor | 142/323 | (44.0%) | 50/112 | (44.6%) |

| Table 33: ENDEAVOR III Baseline Lesion and Vessel Characteristics | | |
|--|-------------------|-------------------|
| | Endeavor | Cypher |
| Reference vessel diameter (mm) | 2.75 ± 0.46 (323) | 2.79 ± 0.46 (113) |
| Lesion length, mm* | 14.96±6.20 (321) | 14.95±7.28 (112) |
| Pre-procedure % Stenosis* (n) | 66.81±12.40 (323) | 67.91±12.42 (113) |
| Vessel Location | | |
| LAD | 41.2% (133/323) | 39.8% (45/113) |
| LCX | 23.2% (75/323) | 28.3% (32/113) |
| RCA | 35.6% (115/323) | 31.9% (36/113) |
| LMCA | 0.0% (0/323) | 0.0% (0/113) |
| Post-procedure % Stenosis* (n) | | |
| In-Stent | 4.33±9.77 (323) | 5.92±9.07 (112) |
| In-Segment | 19.38±9.25 (323) | 20.17±11.74 (113) |

*Mean±SD

Primary endpoint: The Endeavor stent failed to meet its late loss primary non-inferiority endpoint vs. the Cypher stent (Table 34).

| Table 34: ENDEAVOR III Primary Endpoint Results at 8 months | | | | |
|---|-------------------|-----------------|----------------------------------|-------------|
| | Endeavor n=323 | Cypher n=113 | Difference [One-sided 95% CI] | P value* |
| In-segment late loss, mm (n) | 0.36 ±0.46 (277) | 0.13 ±0.33 (94) | 0.24 [-∞, 0.32] | 0.791 |

*test for non-inferiority

Statistical test for non-inferiority: The mean late loss treatment difference (Endeavor minus Cypher) was 0.24 mm. The upper bound of the one-sided 95% confidence interval was 0.32 mm, which was greater than 0.20 mm. The p-value was >0.05. Therefore at a one-sided 0.05 significance level, the criterion for non-inferiority was not met for the Endeavor stent with regard to 8-month in-segment late lumen loss compared to the Cypher stent, and the null hypothesis of non-inferiority could not be rejected. The treatment difference significantly favors Cypher.

Secondary endpoints:

- Device Success, lesion success, procedure success, and device specific procedure success in Endeavor stent-treated patients was 98.8%, 100%, 99.4%, 98.1%, respectively.
- Thirty-day MACE was 0.6% for the Endeavor patients and 3.5% for the Cypher patients, Difference -2.9% (95% CI -6.4%, 0.6%), driven by a difference in rates of peri-procedural non-Q wave MI [0.6% (2/323) in Endeavor and 3.5% (4/113) in Cypher].
- Major secondary endpoint outcomes at 9 months are shown in Tables 35 and 36.

Table 35: ENDEAVOR III Major Clinical Endpoint Results at 9 months

| | Endeavor | Cypher | Difference [95% CI] |
|---|-----------------|----------------|----------------------------|
| TVF | 11.8% (38/321) | 11.5% (13/113) | 0.3% [-6.5%, 7.2%] |
| Death | 0.6% (2/321) | 0.0% (0/113) | 0.6% [-0.2%, 1.5%] |
| Cardiac Death | 0.0% (0/321) | 0.0% (0/113) | 0.0% [--,--] |
| MI | 0.6% (2/321) | 3.5% (4/113) | -2.9%[-6.4%,0.6%] |
| Q-wave MI | 0.0% (0/321) | 0.0% (0/113) | 0.0% [--,--] |
| Non Q-wave MI | 0.6% (2/321) | 3.5% (4/113) | -2.9%[-6.4%,0.6%] |
| TLR | 6.2% (20/321) | 3.5% (4/113) | 2.7% [-1.6%, 7.0%] |
| TVR | 11.2% (36/321) | 8.0% (9/113) | 3.3% [-2.8%, 9.3%] |
| Stent thrombosis | | | |
| Protocol | 0.0% (0/321) | 0.0% (0/113) | 0.0% [--,--] |
| ARC definite + probable (TLR-censored) | 0.0% (0/321) | 0.0% (0/113) | 0.0% [--,--] |
| ARC definite + probable (TLR-uncensored) | 0.0% (0/321) | 0.0% (0/113) | 0.0% [--,--] |

Table 36: Other ENDEAVOR III Angiographic and IVUS Results at 8 months

| | Endeavor | Cypher | Difference [95% CI] |
|---------------------------------------|-------------------|------------------|----------------------------|
| % diameter stenosis (n) | 30.42±15.57 (277) | 23.86±13.87 (94) | 6.56 [3.01,10.12] |
| Binary in-segment restenosis | 12.3% (34/277) | 4.3% (4/94) | 8.0% [2.4%,13.6%] |
| IVUS Volume Obstruction, % (n) | 15.94±10.94 (187) | 2.66±3.11 (61) | 13.27 [10.48,16.07] |

Latest available clinical follow-up (Table 37):

| Table 37: ENDEAVOR III Major Clinical Endpoint Results at 24 months | | | |
|--|-----------------|----------------|----------------------------|
| | Endeavor | Cypher | Difference [95% CI] |
| TVF | 14.4% (45/313) | 13.4% (15/112) | 1.0% [-6.4%,8.4%] |
| Death | 1.6% (5/313) | 4.5% (5/112) | -2.9% [-6.9%,1.2%] |
| Cardiac Death | 0.0% (0/313) | 0.9% (1/112) | -0.9% [-2.6%,0.8%] |
| MI | 0.6% (2/313) | 3.6% (4/112) | -2.9% [-6.5%,0.6%] |
| Q-wave MI | 0.0% (0/313) | 0.0% (0/112) | 0.0% [--,--] |
| Non Q-wave MI | 0.6% (2/313) | 3.6% (4/112) | -2.9% [-6.5%,0.6%] |
| TLR | 7.0% (22/313) | 4.5% (5/112) | 2.6% [-2.2%,7.3%] |
| TVR | 13.7% (43/313) | 9.8% (11/112) | 3.9% [-2.8%,10.6%] |
| Stent thrombosis | | | |
| Protocol | 0.0% (0/313) | 0.0% (0/112) | 0.0% [--,--] |
| ARC definite + probable (TLR-censored) | 0.0% (0/313) | 0.0% (0/112) | 0.0% [--,--] |
| ARC definite + probable (TLR-uncensored) | 0.3% (1/313) | 0% (0/112) | 0.3% [-0.3%,0.9%] |

Summary of Results: ENDEAVOR III was a randomized trial designed to compare angiographic outcomes of the Endeavor stent to an approved DES (the Cypher stent) in non-complex de novo coronary lesions. The Endeavor stent failed to meet its primary late lumen loss angiographic endpoint, a surrogate measure of clinical effectiveness. The Cypher stent appeared to be significantly more effective in inhibiting neointimal growth compared to the Endeavor stent. There were no significant differences in clinical safety and effectiveness endpoints (TVF composite or individual components such as cardiac death, MI, and TVR) between Endeavor and Cypher-treated patients; however ENDEAVOR III was under-powered for these clinical outcomes. The observed rates for safety outcomes (death, cardiac death, MI, and stent thrombosis) were low in both stent treatment groups. Repeat revascularization rates in Endeavor stent patients were higher than those seen in the other Endeavor trials; PCI trials with angiographic endpoints have higher repeat revascularization rates compared to trials without angiographic follow-up due to the “oculostenotic reflex.” There were no unexpected adverse events in the trial.

e. ENDEAVOR IV

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. Endeavor stent sizes evaluated in the study were 2.5, 3.0 and 3.5 mm in diameter and 8 or 9, 18, 24, and 30 mm in length.

Primary endpoint: TVF rate at 9 months post-procedure

Important secondary endpoints

1. Device Success, lesion success, procedure success, and device specific procedure success
2. Total MACE and individual rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually through five years
3. In-segment late lumen loss at eight months. *Late loss assessment was a powered secondary endpoint.*

Design: Prospective, multi-center, randomized, two-arm, single-blind trial. The Endeavor and Taxus stent sizes used are identified in Tables 38 and 39, respectively.

| Table 38: ENDEAVOR IV Device Matrix – Endeavor | | | | | |
|--|-------------------|----|----|----|----|
| | Stent Length (mm) | | | | |
| Diameter (mm) | 8* | 9* | 18 | 24 | 30 |
| 2.50 | X | | X | X | X |
| 3.0 | | X | X | X | X |
| 3.5 | | X | X | X | X |

*Used only in cases of insufficient lesion coverage or bailout

| Table 39: ENDEAVOR IV Device Matrix – Taxus | | | | | |
|---|-------------------|----|----|----|----|
| | Stent Length (mm) | | | | |
| Diameter (mm) | 8* | 12 | 20 | 24 | 32 |
| 2.50 | X | X | X | X | |
| 3.0 | | X | X | X | X |
| 3.5 | | X | X | X | X |

*Used only in cases of insufficient lesion coverage or bailout

Randomization: Patients were stratified by diabetic status and subsequently randomized in a 1:1 ratio to receive either the Endeavor or Taxus stent. This stratification was introduced to ensure a balanced study population and was not intended to support a diabetic indication. Diabetes was defined as an individual who is taking insulin, oral antidiabetic agents, or on a modified diet to treat diabetes mellitus.

Key Inclusion Criteria:

1. Evidence of ischemic heart disease, stable or unstable angina, silent ischemia, or a positive functional study
2. The target lesion was a single *de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$.

3. The target lesion was ≤ 27 mm in length with a target vessel reference diameter of ≥ 2.5 mm and ≤ 3.5 mm.

Key Exclusion Criteria:

1. Left ventricular ejection fraction $< 30\%$
2. Acute MI within 72 hours
3. Creatinine > 2.0 mg/dl
4. Thrombus within the target vessel
5. Left main, ostial lesion, or bifurcation lesion

Stent procedure: Predilatation of target lesion with standard PTCA (no direct stenting); GP IIb/IIIa receptor blocker use optional

Antiplatelet therapy: At least 75 mg aspirin indefinitely and clopidogrel 75 mg daily for at least 6 months

Study site and dates of enrollment: Endeavor IV enrolled 1548 patients at 80 clinical research sites in the US from April 11, 2005 to June 27, 2006 under IDE .

Follow up schedule:

1. Clinical follow-up at 30 days and at 9 months; telephone follow-up at 6 and 12 months, and annually through 5 years
2. Angiographic and IVUS follow-up at 8 months for the first 328 consecutive patients

Statistical Analyses (primary endpoint): The null hypothesis was that the Endeavor stent would have a 9 month TVF rate that exceeds that of the control Taxus stent arm by at least a pre-specified margin of δ (delta). The alternative hypothesis is that the Endeavor stent would have a 9-month TVF rate that is no more than that of the control stent, or exceeds that of the control stent by less than δ . The parameters/assumptions for this analysis were:

- The 9-month TVF rate in Taxus subjects was assumed to be 7.6%, and the 9-month TVF failure rate in Endeavor subjects was assumed to be 7.6% with a non-inferiority margin set at 3.8%
- The power of the study was 84%, and the one-sided alpha error was 5%.

The calculated sample size for one-sided significance testing was 1,394; a total of 1,548 patients were enrolled to account for those lost to follow-up.

Statistical Analyses (secondary endpoint): This randomized study evaluated the non-inferiority of 8-month in-segment late lumen loss of the Endeavor stent compared to the Taxus stent, using a non-inferiority margin (delta) set at 0.2 mm. The null hypothesis for the secondary endpoint was that the Endeavor stent would have a mean in-segment late lumen loss equal to or exceeding that of the control by 0.2 mm or more. The alternative hypothesis was that the Endeavor stent would have a mean in-segment late lumen loss less than the Taxus stent mean plus 0.2 mm. The power of the study was 90%, and the one-sided alpha error was 5%. The calculated sample size for one-sided significance

testing was 262; a total of 328 patients were scheduled for angiography to account for those lost to follow-up.

Results

Enrollment: The total enrollment in Endeavor IV was 1,548 with 773 randomized to the Endeavor stent and 775 randomized to the TAXUS Control group. Clinical follow-up for the primary endpoint at 9 months was 95.2%. Angiographic follow-up at 8 months was 87.2%. The baseline demographics, clinical characteristics, lesion characteristics, and vessel characteristics are outlined in Tables 40 and 41. The treatment groups appear to be appropriately balanced with respect to their clinical and angiographic features.

| Table 40: ENDEAVOR IV Baseline Demographics and Clinical Characteristics | | | | |
|---|-----------------|----------|-----------------|----------|
| | Endeavor | | Taxus | |
| | N | % | N | % |
| Age (years) | | | | |
| Mean (SD) | 63.5±11.1 (773) | | 63.6±11.0 (775) | |
| Gender | 773 | | 775 | |
| Male | 517 | 66.9% | 531 | 68.5% |
| Female | 256 | 33.1 | 244 | 31.5 |
| Prior MI | 161/764 | 21.1% | 176/759 | 23.2% |
| Prior CABG | 76/773 | 9.8% | 65/775 | 8.4% |
| Diabetes mellitus | 241/773 | 31.2% | 236/775 | 30.5% |
| Insulin Dependent Diabetes | 80/773 | 10.3% | 64/775 | 8.3% |
| Smoking | 479/765 | 62.6% | 462/765 | 60.4% |
| HTN | 614/773 | 79.4% | 640/775 | 82.6% |
| Hyperlipidemia | 629/773 | 81.4% | 657/775 | 84.8% |
| Prior PCI | 218/773 | 28.2% | 229/775 | 29.5% |
| Major coronary stenosis (>50%) | 772 | | 774 | |
| Single | 424 | 54.9% | 443 | 57.2% |
| Double | 221 | 28.6% | 202 | 26.1% |
| Triple | 127 | 16.5% | 129 | 16.7% |
| PCI for angina or MI | 617/773 | 79.8% | 610/775 | 78.7% |
| Stable | 281/616 | 45.6% | 292/609 | 47.9% |
| Unstable | 318/616 | 51.6% | 304/609 | 49.9% |
| MI | 17/616 | 2.8% | 13/609 | 2.1% |
| IIb /IIIa inhibitor | | | | |
| Pre-Procedure | 50/209 | 23.9% | 45/209 | 21.5% |
| During Procedure | 195/209 | 93.3% | 194/209 | 92.8% |
| Post-Procedure | 154/209 | 73.7% | 159/209 | 76.1% |

| Table 41: ENDEAVOR IV Baseline Lesion and Vessel Characteristics | | |
|---|-------------------|-------------------|
| | Endeavor | Taxus |
| Reference vessel diameter (mm) | 2.73±0.47 (772) | 2.70±0.46 (774) |
| Lesion length, mm* | 13.41±5.67 (771) | 13.80±6.09 (773) |
| Pre-procedure % Stenosis* (n) | 64.83±13.29 (772) | 65.68±13.10 (774) |
| Vessel Location | | |
| LAD | 42.2% (326/772) | 41.5% (321/774) |
| LCX | 26.9% (208/772) | 26.1% (202/774) |
| RCA | 30.8% (238/772) | 32.4% (251/774) |
| LMCA | 0.0% (0/772) | 0.0% (0/774) |
| Post-procedure % Stenosis* (n) | | |
| In-Stent | 5.50±9.61 (763) | 5.01±10.49 (763) |
| In-Segment | 20.47±9.54 (770) | 20.97±11.12 (772) |

*Mean±SD

Primary endpoint: Endeavor IV met its target vessel failure non-inferiority primary endpoint (Table 42).

| Table 42: Endeavor IV Primary Endpoint Results at 9 months | | | | |
|--|---------------|---------------|----------------------------------|----------|
| | Endeavor | Taxus | Difference [One-sided 95% CI] | P value* |
| TVF | 6.8% (50/740) | 7.4% (54/734) | -0.6% [-100%, 1.6%] | <0.001 |

*test for non-inferiority

Statistical test for non-inferiority: The mean TVF rate difference (Endeavor minus Taxus) was -0.6% mm. The upper bound of the one-sided 95% confidence interval for the difference was 1.6%, meeting the 3.8% specified non-inferiority margin ($p < 0.001$). Therefore at a one-sided 0.05 significance level, the criterion for non-inferiority was met for the Endeavor stent with regard to 9 month TVF rate compared to the Taxus stent.

Secondary endpoints:

- Device Success, lesion success, procedure success, and device specific procedure success in Endeavor stent-treated patients was 97.3%, 99.6%, 98.7%, and 96.5%, respectively.
- The 30-day MACE rate was 1.2% for the Endeavor patients and 3.0% for the Taxus patients, Difference -1.8% (95% CI -3.2%, -0.4%), driven by a difference in rates of peri-procedural non-Q wave MI [0.5% (4/770) in Endeavor and 2.2% (17/771) in Taxus].
- The Endeavor stent failed to meet its powered non-inferiority late loss secondary endpoint vs. the Taxus stent (Table 43).

| Table 43: ENDEAVOR IV Powered Secondary Endpoint Results at 8 months | | | | |
|--|-------------------|-----------------|----------------------------------|----------|
| | Endeavor N=164 | Taxus n=164 | Difference [One-sided 95% CI] | P value* |
| In-segment late loss (n) | 0.36±0.47 (143) | 0.23±0.45 (135) | 0.13 [-∞, 0.22] | 0.089 |

*test for non-inferiority

Statistical test for non-inferiority: The mean late loss treatment difference (Endeavor minus Taxus) was 0.13 mm. The upper bound of the one-sided 95% confidence interval for the difference was 0.22, exceeding the 0.2 mm specified non-inferiority margin (p=0.089). Therefore at a one-sided 0.05 significance level, the criterion for non-inferiority was not met for the Endeavor stent with regard to 8-month in-segment late lumen loss compared to the Taxus stent.

- Major secondary endpoint outcomes at 9 months are shown in Tables 44 and 45.

| Table 44: ENDEAVOR IV Major Clinical Endpoint Results at 9 months | | | |
|--|-----------------|---------------|----------------------------|
| | Endeavor | Taxus | Difference [95% CI] |
| Death | 0.7% (5/740) | 0.8% (6/734) | -0.1% [-1.0%, 0.7%] |
| Cardiac Death | 0.4% (3/740) | 0.3% (2/734) | 0.1% [-0.5%, 0.7%] |
| MI | 1.5% (11/740) | 2.5% (18/734) | -1.0% [-2.4%, 0.5%] |
| Q-wave MI | 0.3% (2/740) | 0.1% (1/734) | 0.1% [-0.3%, 0.6%] |
| Non Q-wave MI | 1.2% (9/740) | 2.3% (17/734) | -1.1% [-2.4%, 0.2%] |
| TLR | 4.2% (31/740) | 2.7% (20/734) | 1.5% [-0.4%, 3.3%] |
| TVR | 5.5% (41/740) | 5.0% (37/734) | 0.5% [-1.8%, 2.8%] |
| Stent thrombosis | | | |
| Protocol | 0.8% (6/740) | 0.1% (1/734) | 0.7% [-0.0%, 1.4%] |
| ARC definite + probable (TLR-censored) | 0.9% (7/740) | 0.1% (1/734) | 0.8% [0.1%, 1.6%] |
| ARC definite + probable (TLR-uncensored) | 0.9% (7/740) | 0.1% (1/734) | 0.8% [0.1%, 1.6%] |

| Table 45: Other ENDEAVOR IV Angiographic and IVUS Results at 8 months | | | |
|--|------------------|-------------------|----------------------------|
| | Endeavor | Taxus | Difference [95% CI] |
| % diameter stenosis (n) | 32.28±17.02(144) | 26.61±15.52 (135) | 5.68 [1.83, 9.52] |
| Binary in-segment restenosis | 15.3% (22/144) | 10.4% (14/135) | 4.9% [-2.9%, 12.7%] |
| IVUS Volume Obstruction, % (n) | 15.72±10.40 (74) | 9.88±9.24 (77) | 5.84 [2.68, 9.00] |

Summary of Results: ENDEAVOR IV was a large randomized trial designed to compare clinical and angiographic outcomes of the Endeavor stent to an approved DES (the Taxus stent) in non-complex denovo coronary lesions. The Endeavor stent met its primary non-inferiority TVF endpoint, a composite of clinical safety and effectiveness, despite failing to meet its secondary late lumen loss angiographic endpoint vs. the Taxus stent. These discordant results are discussed in detail in Section 7l (page 82) of this review. The observed rates for safety outcomes (death, cardiac death, MI, and stent thrombosis) and clinical effectiveness were low in Endeavor patients and generally consistent with those observed in the other Endeavor studies. There were no unexpected adverse events in the trial.

f. ENDEAVOR Japan

Objectives:

1. To evaluate the Endeavor Stent in Japanese patients for the treatment of stenotic lesions of native coronary arteries with reference vessel diameters ≥ 2.25 mm and ≤ 3.5 mm.
2. To meet requirements for regulatory approval in Japan.

Primary endpoint: TVF rate at 9 months post-procedure

Important secondary endpoints

1. Device Success, lesion success, procedure success, and device specific procedure success
2. Clinically-driven TVR at nine months post-procedure
3. Total MACE and individual rates of death, MI, and stent thrombosis at 30 days, 6 months, and 9 months
4. Late lumen loss at 8 months

Design: non-randomized, prospective, multicenter, single arm trial. The Endeavor stent sizes used are identified in Table 46.

| Table 46: ENNDEAVOR Japan Device Matrix | | | | | | | | |
|---|-------------------|----|----|----|----|----|----|----|
| Diameter (mm) | Stent Length (mm) | | | | | | | |
| | 8* | 9* | 12 | 14 | 15 | 18 | 24 | 30 |
| 2.25 | X | | | | | X | X | X |
| 2.50 | X | | | | | X | X | X |
| 3.0 | | X | | | | X | X | X |
| 3.5 | | X | | | | X | X | X |

*Used only in cases of insufficient lesion coverage or bailout.

Randomization: none

Key Inclusion Criteria:

1. Evidence of ischemic heart disease or a positive functional study
2. The target lesion was a single *de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$.
3. The target lesion was ≥ 14 mm and ≤ 27 mm in length with a target vessel reference diameter of ≥ 2.25 mm and ≤ 3.5 mm.

Key Exclusion Criteria:

1. Left ventricular ejection fraction $< 30\%$
2. Acute MI within 72 hours
3. Creatinine > 2.0 mg/dl
4. Thrombus within the target vessel
5. Left main, ostial lesion, or bifurcation lesion

Stent procedure: Predilatation of target lesion with standard PTCA (no direct stenting)

Antiplatelet therapy: All subjects were to have received 200 mg aspirin daily from at least 24 hours pre-procedure through 12 weeks post-procedure followed by a 100 mg/day indefinitely. All subjects were to have received 200 mg ticlopidine from two weeks pre-procedure through 12 weeks post-procedure. FDA believes that ticlopidine is an acceptable alternative to clopidogrel.

Study site and dates of enrollment: Endeavor Japan enrolled a total of 99 patients at 11 clinical research sites in Japan from July 6th, 2005 to February 19th, 2007.

Follow up schedule:

1. Clinical follow-up at 30 days, 6 months, and 9 months
2. Angiographic follow-up at 8 months

Statistical Analyses (primary endpoint): No statistical hypothesis were pre-specified for this registry study.

Results

Enrollment: The total enrollment in Endeavor Japan was 99 patients, all of whom received an Endeavor stent. Clinical follow-up at the primary endpoint (9 months) was 98%. Angiographic follow-up at the secondary endpoint (8 months) was 99%. The baseline demographics, clinical characteristics, lesion characteristics, and vessel characteristics are outlined in Tables 47 and 48.

| Table 47: ENDEAVOR Japan Baseline Demographics and Clinical Characteristics | | |
|--|-----------------|----------|
| | Endeavor | |
| | N | % |
| Age (years) | | |
| Mean (SD) | 67.7 ± 10.3 | |
| Gender | 99 | |
| Male | 67 | 67.7% |
| Female | 32 | 32.3% |
| Prior MI | 24 | 24.2% |
| Prior CABG | 1 | 1.0% |
| Diabetes mellitus | 38 | 38.4% |
| Insulin Dependent Diabetes | 10 | 10.1% |
| Smoking | 27 | 27.3% |
| HTN | 78 | 78.8% |
| Hyperlipidemia | 76 | 76.8% |
| Prior PCI | 31 | 31.3% |
| Major coronary stenosis (>50%) | | |
| Single | 75 | 75.8% |
| Double | 15 | 15.2% |
| Triple | 9 | 9.1% |
| Revascularization Reason | | |
| Stable | 83 | 83.8% |
| Unstable | 4 | 4.0% |
| Abnormal functional test | 7 | 7.1% |
| Other | 9 | 9.1% |
| IIb /IIIa inhibitor | N/A | |

| Table 48: ENDEAVOR Japan Baseline Lesion and Vessel Characteristics | |
|--|------------------|
| | Endeavor |
| Reference vessel diameter (mm) | 2.78±0.52 (99) |
| Lesion length, mm* | 13.90±6.05 (99) |
| Pre-procedure % Stenosis* (n) | 70.01±11.18 (99) |
| Vessel Location | |
| LAD | 39.4% (39/99) |
| LCX | 24.2% (24/99) |
| RCA | 36.4% (36/99) |
| LMCA | 0.0% (0/99) |
| Post-procedure % Stenosis* (n) | |
| In-Stent | 3.05±11.37 (99) |
| In-Segment | 20.15±9.37 (99) |

*Mean±SD

Primary endpoint (Table 49):

| Table 49: ENDEAVOR Japan Primary Endpoint Results | |
|---|-------------|
| | Endeavor |
| TVF rate at 9 months | 5.2% (5/97) |

Secondary endpoints:

- Device Success, lesion success, procedure success, and device specific procedure success in Endeavor stent-treated patients was 97.0%, 100%, 98%, and 94.9%, respectively
- 30 day MACE was 2.0%.
- Major secondary endpoint outcomes at 9 months are shown in Tables 50 and 51.

| Table 50: ENDEAVOR Japan Major Clinical Endpoint Results at 9 months | |
|---|-------------|
| | Endeavor |
| Death | 0.0% (0/97) |
| Cardiac Death | 0.0% (0/97) |
| MI | 2.1% (2/97) |
| Q-wave MI | 0.0% (0/97) |
| Non Q-wave MI | 2.1% (2/97) |
| TLR | 3.1% (3/97) |
| TVR | 3.1% (3/97) |
| Stent thrombosis | |
| Protocol | 0.0% (0/97) |
| ARC definite + probable (TLR-censored) | N/A |
| ARC definite + probable (TLR-uncensored) | N/A |

| Table 51: ENDEAVOR Japan Angiographic Results at 8 months | |
|--|--------------------|
| | Endeavor |
| In-segment late loss (n) | 0.23±0.42 mm (98) |
| % diameter stenosis (n) | 29.19 ± 15.27 (98) |
| Binary in-segment restenosis | 8.2% (8/98) |

Summary of Results: Safety and effectiveness clinical and angiographic outcomes in this small single arm study of Endeavor stent implantation in Japanese patients are consistent with other Endeavor trial results.

g. ENDEAVOR PK

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 in 43 patients (6 with overlapped stents).

Primary endpoint: The following pharmacokinetic parameters were evaluated:

1. Maximum blood concentration
2. Time to maximum blood concentration
3. Area under the blood concentration-time curve from time 0 to time of last measurable concentration and to infinity
4. Harmonic mean half-life
5. Apparent volume of distribution
6. Mean apparent clearance

Important secondary endpoints

1. Device Success, lesion success, procedure success, and device specific procedure success
2. Total MACE and individual rates of death, MI, and stent thrombosis at 30 days and 6, 9, and 12-months and annually through five years
3. Clinically-driven TLR, clinically-driven TVR, and TVF at nine months
4. In-segment late lumen loss at eight months

Design: Prospective, multi-center, single-arm, open-label, US registry. The Endeavor stent sizes used are identified in Table 52.

| Table 52: ENDEAVOR PK Device Matrix | | | | | | | | |
|-------------------------------------|-------------------|----|----|----|----|----|----|----|
| Diameter (mm) | Stent Length (mm) | | | | | | | |
| | 8* | 9* | 12 | 14 | 15 | 18 | 24 | 30 |
| 2.50 | X | | | | | X | X | X |
| 3.0 | | X | | | | X | X | X |
| 3.5 | | X | | | | X | X | X |

*Used only in cases of insufficient lesion coverage or bailout.

Randomization: none

Key Inclusion Criteria:

1. Evidence of ischemic heart disease, stable or unstable angina, silent ischemia, or a positive functional study
2. The target lesion was a single *de novo* lesion in a native coronary artery with a stenosis of $\geq 50\%$ and $< 100\%$.
3. The target lesion was ≤ 27 mm in length with a target vessel reference diameter of ≥ 2.5 mm and ≤ 3.5 mm

Key Exclusion Criteria:

1. Left ventricular ejection fraction $< 30\%$
2. Acute MI within 72 hours
3. Creatinine > 2.0 mg/dl

4. Left main, ostial lesion, or bifurcation lesion

Stent procedure: Predilatation of target lesion with standard PTCA (no direct stenting)

Antiplatelet therapy: At least 75 mg aspirin indefinitely and clopidogrel 75 mg daily for at least 12 weeks

Study site and dates of enrollment: Endeavor PK enrolled 43 patients at 6 clinical research sites in the US from January 24, 2006 through April 14, 2006 under IDE



Follow up schedule:

1. Blood samples (5 mL) for zotarolimus assay were collected at 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 48, 72, 168, 336 and 720 hours after the procedure.
2. Clinical follow-up at 30 days and at 8 months; telephone follow-up at 6, 9 and 12 months, and annually through 5 years
3. Angiographic and IVUS follow-up at 8 months

Statistical Analyses: none

Results:

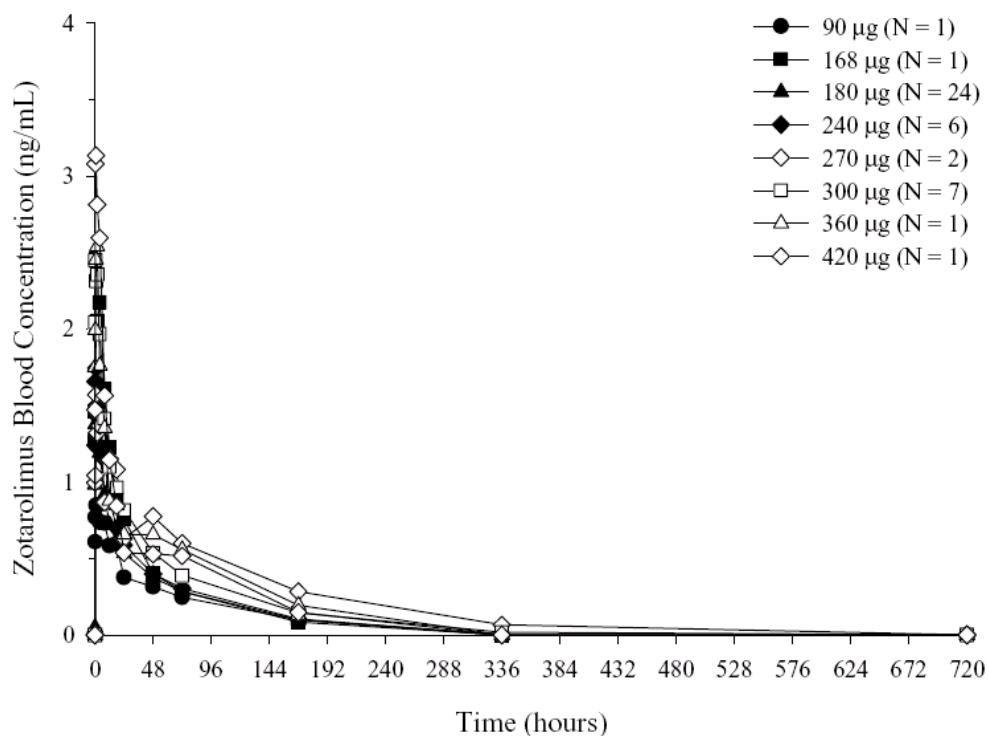
Enrollment: The baseline demographics, clinical characteristics, lesion characteristics, and vessel characteristics are outlined in Tables 53 and 54.

| Table 53: ENDEAVOR PK Baseline Demographics and Clinical Characteristics | | |
|---|---------------|-------|
| | Endeavor | |
| | N | % |
| Age (years) | | |
| Mean (SD*) | 64.74 ± 11.06 | |
| Gender | 43 | |
| Male | 34 | 79.1% |
| Female | 9 | 20.9% |
| Prior MI | 10/43 | 23.3% |
| Prior CABG | 5/43 | 11.6% |
| Diabetes mellitus | 18/43 | 41.9% |
| Insulin Dependent Diabetes | 4/43 | 9.3% |
| Smoking | 24/43 | 55.8% |
| HTN | 39/43 | 90.7% |
| Hyperlipidemia | 37/43 | 86.0% |
| Prior PCI | 18/43 | 41.9% |
| Major coronary stenosis (>50%) | 43 | |
| Single | 16 | 37.2% |
| Double | 7 | 16.3% |
| Triple | 20 | 46.5% |
| PCI for angina or MI | 36/43 | 83.7% |
| Stable | 16/36 | 44.4% |
| Unstable | 20/36 | 55.6% |
| MI | 0/36 | 0.0% |
| IIb /IIIa inhibitor | 16/43 | 37.2% |

| Table 54: ENDEAVOR PK Baseline Lesion and Vessel Characteristics | |
|---|------------------|
| | Endeavor |
| Reference vessel diameter (mm) | 2.54 ± 0.45 (43) |
| Lesion length, mm* | 15.02±5.62 (43) |
| Pre-procedure % Stenosis* (n) | 62.92±12.69 (43) |
| Vessel Location | |
| LAD | 55.8% (24/43) |
| LCX | 30.2% (13/43) |
| RCA | 14.0% (6/43) |
| LMCA | 0.0% (0/43) |
| Post-procedure % Stenosis* (n) | |
| In-Stent | 5.38±8.55 (43) |
| In-Segment | 17.56±6.88 (43) |

*Mean±SD

Primary endpoint: The pharmacokinetic parameters of zotarolimus were estimated using noncompartmental methods. The mean zotarolimus blood concentration over time for the Endeavor stent are depicted below based on the total zotarolimus dose.



The following pharmacokinetic parameters were observed:

| PK Parameter | Units | Group I (90 µg) N = 1 [†] | Group II (168 µg) N = 1 [†] | Group III ^a (180 µg) N = 24 | Group IV ^a (240 µg) N = 6 | Group V (270 µg) N = 2 [†] | Group VI ^a (300 µg) N = 7 | Group VII (360 µg) N = 1 [†] | Group VIII (420 µg) N = 1 [†] |
|-----------------------|--|--|--|--|--|---|--|---|--|
| C _{max} | (ng/mL) | 0.847 | 2.176 | 1.513 ± 0.616 | 1.83 ± 0.210 | 1.564 | 2.658 ± 0.998 | 2.539 | 3.133 |
| T _{max} | (h) | 1.00 | 4.00 | 1.2 ± 0.6 | 1.4 ± 1.3 | 1.5 | 1.5 ± 1.3 | 2.00 | 1.3 |
| AUC _{0-last} | (ng•h/mL) | 46.51 | 71.73 | 57.02 ± 13.46 | 63.83 ± 15.27 | 125.18 | 90.77 ± 19.51 [#] | 95.21 | 87.45 |
| AUC _{0-inf} | (ng•h/mL) | 56.57 | 78.28 | 66.61 ± 14.86 | 72.84 ± 19.96 | 136.65 | 101.45 ± 23.48 [#] | 113.85 | 99.82 |
| β | (1/h) | 0.010 | 0.013 | 0.012 ± 0.003 | 0.012 ± 0.002 | 0.010 | 0.012 ± 0.003 | 0.010 | 0.012 |
| t _{1/2} | (h) | 71.5 [§] | 53.7 [§] | 59.7 ± 14.4 | 57.5 ± 7.6 | 68.3 | 59.5 ± 16.1 [#] | 66.67 [§] | 58.4 [§] |
| Vd _β /F | (L) | 164.1 | 166.3 | 254.7 ± 74.5 | 288.5 ± 53.6 | 261.6 | 291.6 ± 113.7 [#] | 304.2 | 354.6 |
| CL/F | (L/h) | 1.6 | 2.1 | 2.8 ± 0.7 | 3.5 ± 1.0 | 2.9 | 3.1 ± 0.8 [#] | 3.2 | 4.2 |
| Vdβ/F | Apparent volume of distribution | | | CL/F Mean apparent clearance | | | | | |
| C _{max} | Maximum blood concentration | | | a. Primary dose groups | | | | | |
| T _{max} | Time to C _{max} | | | ± Harmonic mean ± pseudo-standard deviation | | | | | |
| AUC _{0-last} | Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration | | | † No SD was reported when N ≤ 2 | | | | | |
| AUC _{0-inf} | AUC from time 0 to infinity (AUC _{0-inf}). | | | § Mean only | | | | | |
| t _{1/2} | Harmonic mean half-life | | | # N = 6 | | | | | |

Secondary endpoints (Tables 55 and 56):

| Table 55: ENDEAVOR PK Major Clinical Endpoint Results at 9 months | |
|---|--------------|
| | Endeavor |
| TVF | 11.9% (5/42) |
| Death | 4.8% (2/42) |
| Cardiac Death | 4.8% (2/42) |
| MI | 2.4% (1/42) |
| Q-wave MI | 0.0% (0/42) |
| Non Q-wave MI | 2.4% (1/42) |
| TLR | 2.4% (1/42) |
| TVR | 7.1% (3/42) |
| Stent thrombosis | |
| Protocol | 0.0% (0/42) |
| ARC definite + probable (TLR-censored) | 0.0% (0/42) |
| ARC definite + probable (TLR-uncensored) | 0.0% (0/42) |

| Table 56: ENDEAVOR PK Angiographic Results at 8 months | |
|--|-----------------|
| | Endeavor |
| In-segment late loss, mm (n) | 0.70±0.72 (6) |
| % diameter stenosis (n) | 36.34±20.85 (6) |
| Binary in-segment restenosis | 16.7% (1/6) |

Summary of Results: Based on the overall results, it can be concluded that safety has been established for zotarolimus at multiples of clinically relevant drug exposure.

h. Long Term Safety and Effectiveness Outcomes in the Pooled ENDEAVOR Clinical Studies

The major clinical and angiographic endpoint results in the Endeavor stent trials are shown in Table 57. The Endeavor stent performance assessed by rates of TVR, TLR, and angiographic binary restenosis, was generally consistent across the Endeavor program.

| Table 57: Summary of Results at 9 months | | | | | | | | | |
|---|-------------------|--------------------|-----------------|-----------------------|---------------------|-----------------|--------------------|-----------------|--------------------|
| | ENDEAVOR I | ENDEAVOR II | | ENDEAVOR II CA | ENDEAVOR III | | ENDEAVOR IV | | ENDEAVOR PK |
| | | Endeavor | Driver | | Endeavor | Cypher | Endeavor | Taxus | |
| TVF | 2.0% | 7.9% | 15.1% | 13.0% | 11.8% | 11.5% | 6.8% | 7.4% | 11.9% |
| Death | 0.0% | 1.2% | 0.5% | 0.7% | 0.6% | 0.0% | 0.7% | 0.8% | 4.8% |
| Cardiac Death | 0.0% | 0.8% | 0.5% | 0.7% | 0.0% | 0.0% | 0.4% | 0.3% | 4.8% |
| MI | 1.0% | 2.7% | 3.9% | 5.1% | 0.6% | 3.5% | 1.5% | 2.5% | 2.4% |
| Cardiac Death + MI | 1.0% | 3.4% | 4.4% | 5.5% | 0.6% | 3.5% | 1.9% | 2.7% | 7.1% |
| TVR | 2.0% | 5.6% | 12.5% | 8.9% | 11.2% | 8.0% | 5.5% | 5.0% | 7.1% |
| TLR | 2.0% | 4.6% | 11.8% | 5.1% | 6.2% | 3.5% | 4.2% | 2.7% | 2.4% |
| In-segment Late Loss* | 0.43± 0.44mm** | 0.36± 0.46mm | 0.72± 0.61mm | 0.39± 0.56mm | 0.36± 0.46mm | 0.13± 0.33mm | 0.36± 0.47mm | 0.23± 0.45mm | 0.70± 0.72mm |
| Restenosis Rate* | 5.4%** | 13.3% | 34.7% | 17.1% | 12.3% | 4.3% | 15.3% | 10.4% | 16.7% |

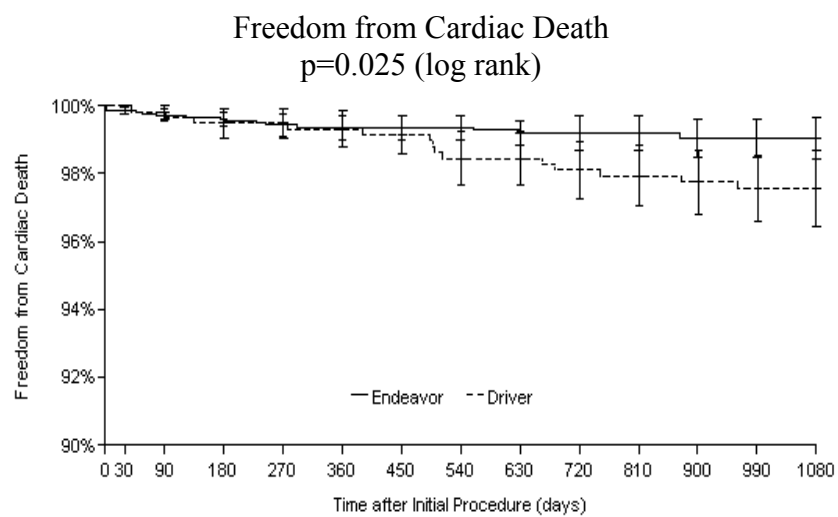
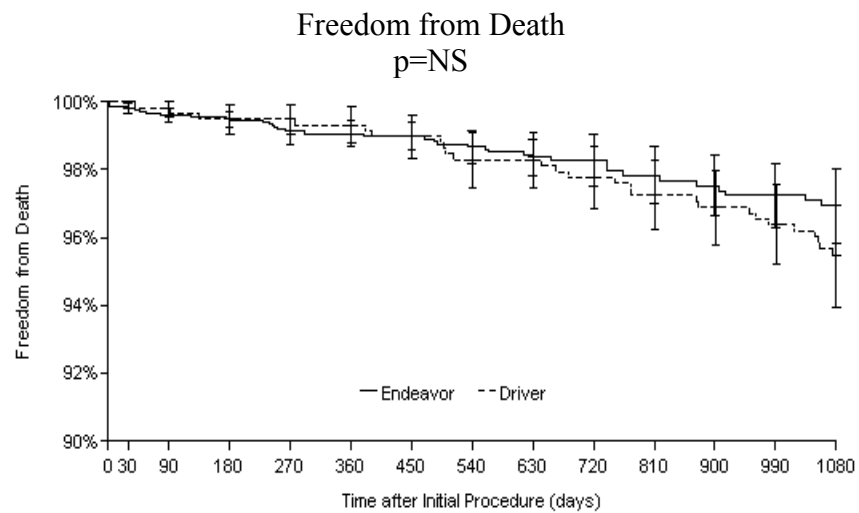
*In-segment late loss and binary angiographic in-segment restenosis at 8 months. **12 months for ENDEAVOR I

For New Molecular Entities (NMEs) such as zotarolimus, FDA requires a minimum 2,000 patient exposure for demonstration of drug safety. Across the ENDEAVOR program, 2,133 patients were assigned to receive the Endeavor stent, of which 1287 have been followed through 2 years. Table 58 indicates the number of patients for each study in which follow-up data are available for the pooled analyses.

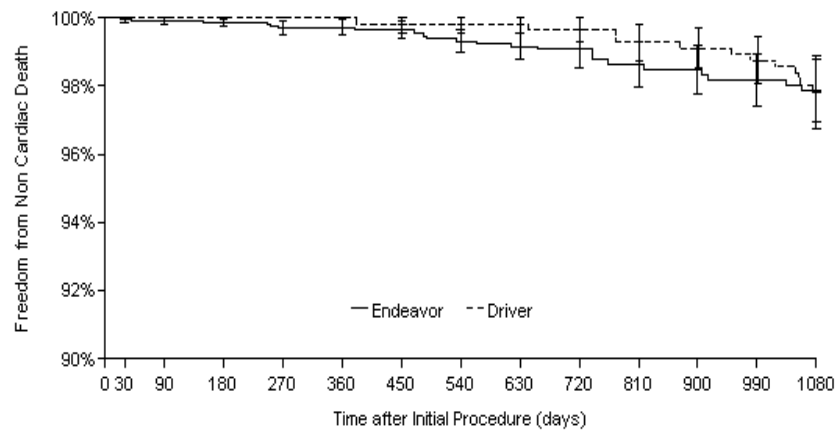
| Table 58: Patient Follow-Up | | | | | | | |
|------------------------------------|-------------|-------------|-------------|-------------|-------------|------------|-----------|
| | 30d | 6m | 9m | 12m | 2y | 3y | 4y |
| ENDEAVOR I | 100 | 100 | 100 | 99 | 99 | 98 | 97 |
| ENDEAVOR II | 596 | 593 | 592 | 590 | 587 | 577 | - |
| ENDEAVOR II CA | 296 | 295 | 293 | 292 | 288 | - | - |
| ENDEAVOR III | 323 | 321 | 321 | 320 | 313 | - | - |
| ENDEAVOR IV | 770 | 766 | 740 | - | - | - | - |
| ENDEAVOR PK | 43 | 43 | 42 | - | - | - | - |
| Total | 2128 | 2118 | 2088 | 1301 | 1287 | 675 | 97 |

At FDA's request, Medtronic submitted post-hoc analyses, in which data from patients receiving Endeavor stents in each trial have been pooled and compared to patients treated with bare metal Driver stents in ENDEAVOR II through 3-years follow-up. These analyses are consistent with the analyses requested of approved DES products and presented at the December 2006 Circulatory System Advisory Panel Meeting on DES Thrombosis. The following Kaplan-Meier

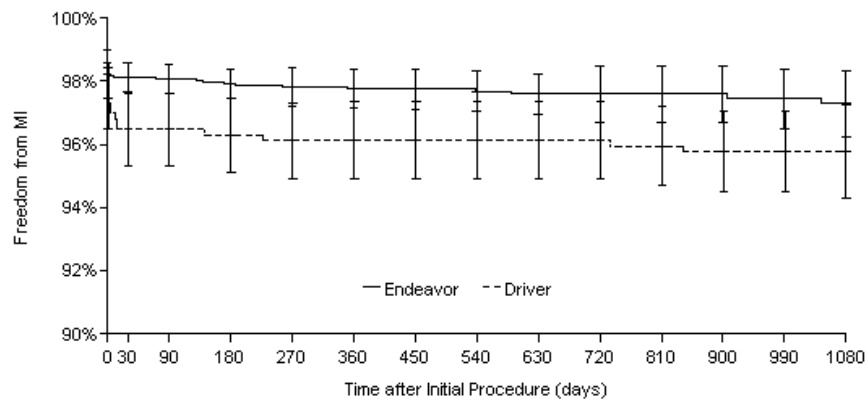
curves from the Endeavor stent trials show the clinically important safety and effectiveness outcomes.



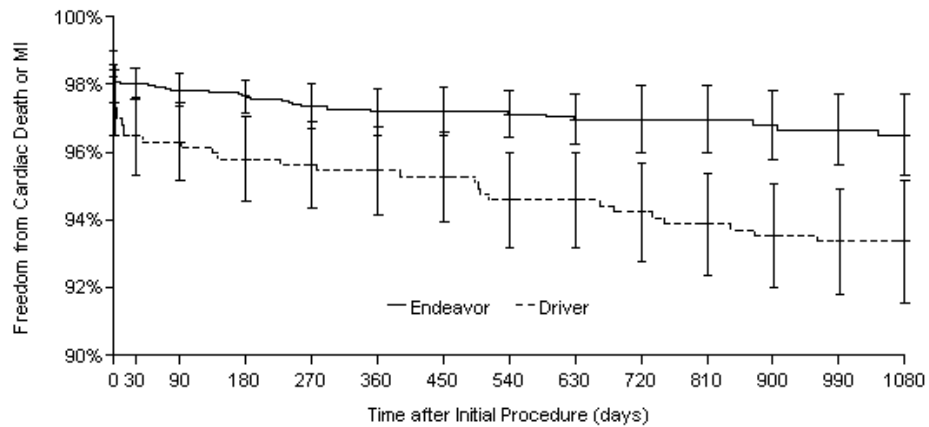
Freedom from Non Cardiac Death p=NS

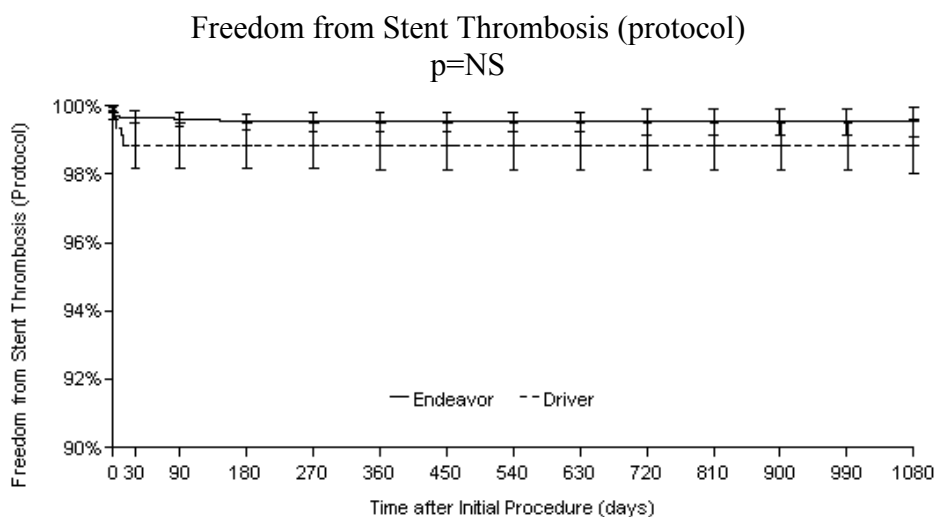
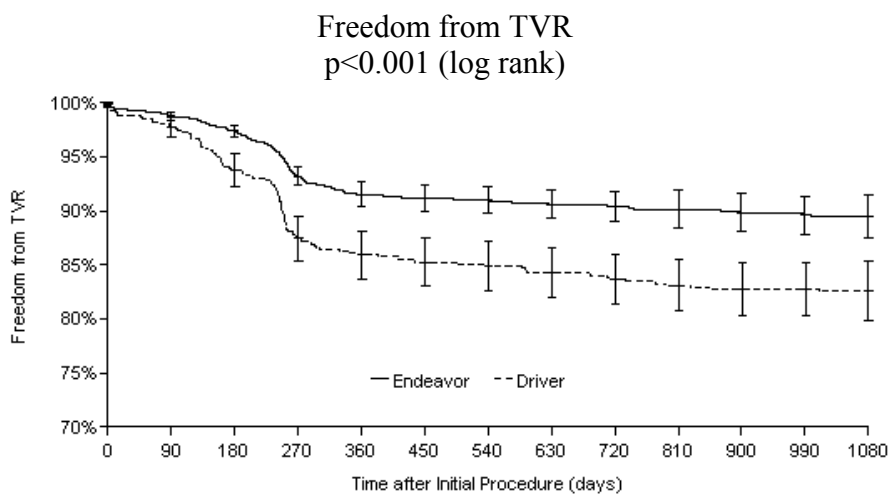
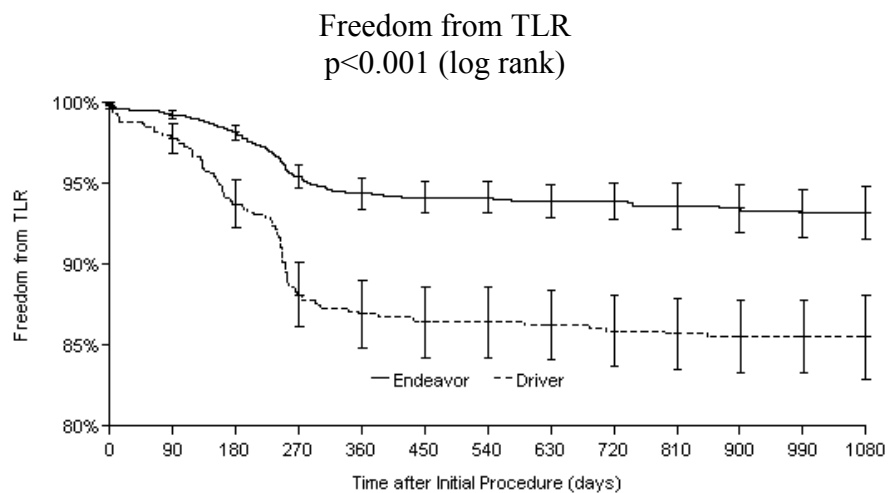


Freedom from MI p=0.047 (log rank)

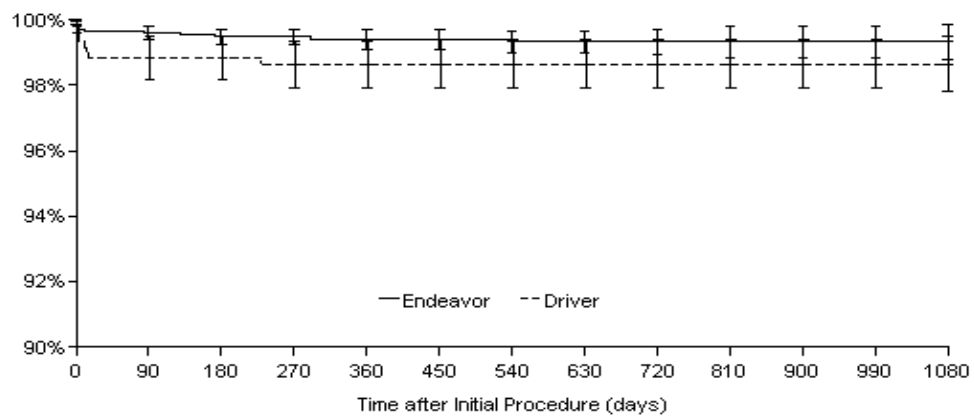


Freedom from Cardiac Death + MI p=0.002 (log rank)

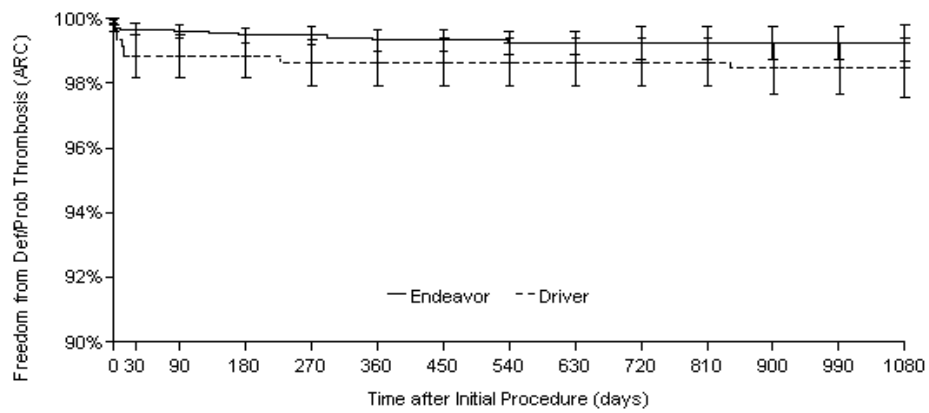




Freedom from Stent Thrombosis (ARC definite + probable, TLR-censored)
p=NS



Freedom from Stent Thrombosis (ARC definite + probable, uncensored)
p=NS



i. Stent Thrombosis and Dual Antiplatelet Therapy Use in the Pooled ENDEAVOR Clinical Studies

Background

Drugs that interrupt the cell cycle such as paclitaxel and sirolimus (and its analogs including zotarolimus) have potent antiproliferative and anti-inflammatory properties. Fundamentally, local delivery of these agents via DES prevent restenosis by inhibiting: (1) vascular smooth muscle cell migration and proliferation and synthesis of extracellular matrix, and (2) inflammatory cell production of growth factors and cytokines. Effective suppression of in-stent neointimal growth, however, can result in delayed or incomplete coverage of stent struts by endothelialized neointimal tissue. Autopsy studies suggest that impaired neointimal healing extends the window of thrombotic risk for DES vs. bare metal stents and is an important mechanism of DES thrombosis. Stent thrombosis, although rare, is often associated with death or MI.

Concurrent with the presentation and publications of reports of DES thrombosis in 2005-6, it became apparent that uniform definitions of stent thrombosis across study protocols were lacking. Reported rates of stent thrombosis are clearly influenced if unequivocal evidence is required (e.g., by angiography or at autopsy) or if any unexplained death is ascribed to stent thrombosis. As part of an effort to devise common clinical outcomes that might be used in DES trials, FDA participated in the Academic Research Consortium (ARC), which produced suggested uniform definitions of stent thrombosis based on the timing of the event post-stent implantation (early, late, and very late) and the level of evidence available (definite, probable, and possible) supporting the diagnosis of stent thrombosis. While recognizing that all proposed stent thrombosis definitions are imperfect, FDA believes the ARC definite + probable category of stent thrombosis provides the optimal balance between clinical sensitivity and specificity. FDA has requested that all DES sponsors apply the ARC stent thrombosis definitions to their datasets for adjudication to supplement stent thrombosis rates per the study protocol definitions.

Concerns regarding DES thrombosis, particularly late stent thrombosis, lead to the convening of an FDA Circulatory Systems Advisory Panel Meeting On December 7 – 8, 2006. Data presented at this meeting and subsequent publications supported the conclusion that compared to bare metal stents, the approved DES are associated with a numerically increased rate of stent thrombosis that emerges after one year post-DES implantation. However, an analysis of pooled DES trials showed no increase in the rates of death or MI in DES-treated patients compared to those receiving bare metal stents. The reasons for discordance between a numerical increase in DES thrombosis and no increase in the rates of death or MI stent are uncertain. It is possible that the sample sizes in the pooled studies were not large enough to permit the detection of a difference between treatment groups. Alternatively, increases in the rate of death or MI among DES patients might have been offset by a reduction in events associated with in-stent restenosis and repeated revascularization. The optimal duration of dual antiplatelet therapy has remained an important area of uncertainty. Early discontinuation or

interruption of dual antiplatelet therapy is associated with DES thrombosis, death and MI, and data from some non-randomized studies suggest that more prolonged dual antiplatelet therapy may be beneficial in DES patients. Addressing this issue, the ACC/AHA/SCAI released a consensus statement recommending extending the use of dual antiplatelet therapy to 12 months post-DES implantation in patients who are not at high risk for bleeding.

Stent thrombosis in the Endeavor program

Late or very late stent thrombosis data may be difficult to interpret when events occur secondary to an intervening TLR or TVR. However censorship of such events may bias reporting in favor of devices with higher restenosis risk. Therefore, ARC definite + probable stent thrombosis is reported both as TLR-censored and uncensored. Stent thrombosis rates were <1% at all time points. There were 2 cases of ARC definite+probable stent thrombosis that occurred post-TLR (late stent thrombosis in 1 Driver patient and very late stent thrombosis in 1 Driver patient, both in ENDEAVOR II). There was 1 case of ARC definite+probable stent thrombosis that occurred post-TVR of a non-target lesion in one Endeavor patient in ENDEAVOR III (stent thrombosis event considered as censored).

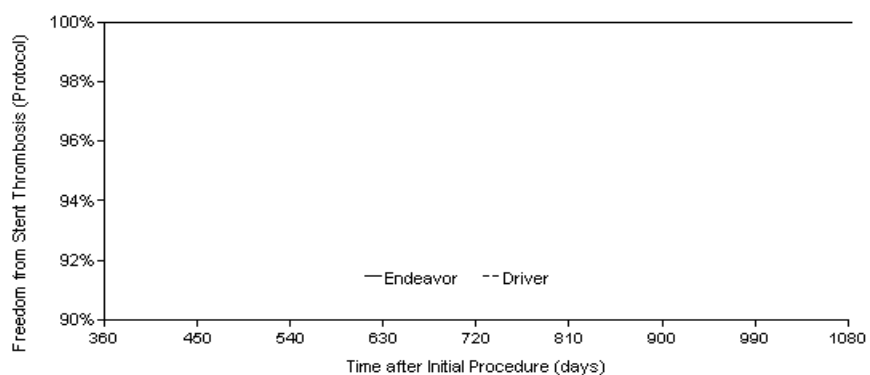
The cumulative rates of stent thrombosis (per protocol and per the ARC definite + probable definitions) in patients treated with Endeavor stents from the pooled Endeavor trials are shown in Table 59. Stent thrombosis rates observed in patients treated with Driver stents in ENDEAVOR II are shown for reference.

| Table 59: Stent Thrombosis (Protocol) and Definite + Probable Stent Thrombosis (ARC) | | | | |
|---|------------------------------|---------------|---------------------------|---------------|
| | Endeavor (N=2132) | 95% CI | Driver (N=596) | 95% CI |
| Thrombosis (0-30 days) | | | | |
| Stent Thrombosis (Protocol) | 0.3% (7/2128) | [0.1%,0.7%] | 1.2% (7/594) | [0.5%,2.4%] |
| ARC definite + probable (TLR-censored) | 0.3% (7/2128) | [0.1%,0.7%] | 1.2% (7/594) | [0.5%,2.4%] |
| ARC definite + probable (TLR-uncensored) | 0.3% (7/2128) | [0.1%,0.7%] | 1.2% (7/594) | [0.5%,2.4%] |
| Thrombosis (0-180 days) | | | | |
| Stent Thrombosis (Protocol) | 0.5% (10/2118) | [0.2%,0.9%] | 1.2% (7/593) | [0.5%,2.4%] |
| ARC definite + probable (TLR-censored) | 0.5% (11/2118) | [0.3%,0.9%] | 1.2% (7/593) | [0.5%,2.4%] |
| ARC definite + probable (TLR-uncensored) | 0.5% (11/2118) | [0.3%,0.9%] | 1.2% (7/593) | [0.5%,2.4%] |
| Thrombosis (0-360 days) | | | | |
| Stent Thrombosis (Protocol) | 0.3%(4/1301) | [0.1%,0.8%] | 1.2% (7/589) | [0.5%,2.4%] |
| ARC definite + probable (TLR-censored) | 0.4% (5/1301) | [0.1%,0.9%] | 1.4% (8/589) | [0.6%,2.7%] |
| ARC definite + probable (TLR-uncensored) | 0.5% (6/1301) | [0.2%,1.0%] | 1.4% (8/589) | [0.6%,2.7%] |
| Thrombosis (0-720 days) | | | | |
| Stent Thrombosis (Protocol) | 0.3%(4/1287) | [0.1%,0.8%] | 1.2% (7/586) | [0.5%,2.4%] |
| ARC definite + probable (TLR-censored) | 0.5% (6/1287) | [0.2%,1.0%] | 1.4% (8/586) | [0.6%,2.7%] |
| ARC definite + probable (TLR-uncensored) | 0.5% (7/1287) | [0.2%,1.1%] | 1.4% (8/586) | [0.6%,2.7%] |
| Thrombosis (0-1080 days) | | | | |
| Stent Thrombosis (Protocol) | 0.6%(4/675) | [0.2%,1.5%] | 1.2% (7/579) | [0.5%,2.5%] |
| ARC definite + probable (TLR-censored) | 0.9% (6/675) | [0.3%,1.9%] | 1.4% (8/579) | [0.6%,2.7%] |
| ARC definite + probable (TLR-uncensored) | 0.9% (6/675) | [0.3%,1.9%] | 1.6% (9/579) | [0.7%,2.9%] |

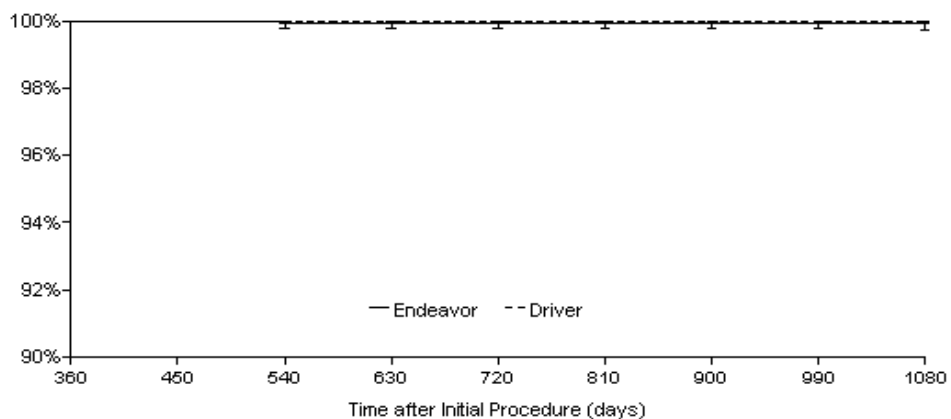
Late stent thrombosis, death and MI.

Based on the mechanism of action of DES in reducing the incidence of restenosis and the potential for delayed neointimal strut coverage and endothelialization, it is important to analyze whether late safety signals (stent thrombosis, death, or MI) might emerge in patients treated with Endeavor stents. Kaplan-Meier curves of the rates of stent thrombosis (per protocol and per the ARC definite + probable definitions), death, cardiac and non-cardiac death, and MI beyond the one year landmark in patients treated with Endeavor stents from the pooled Endeavor trials are shown below. Stent thrombosis rates observed in patients treated with Driver stents in ENDAVOR II is shown for comparison. A safety signal emerging beyond one year post-Endeavor stent implant was not observed.

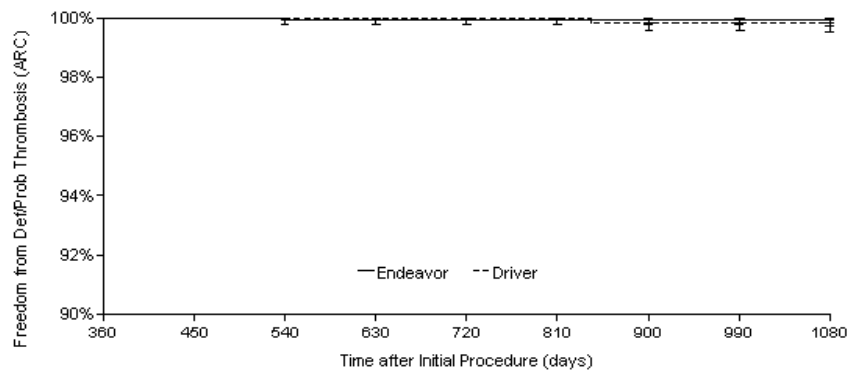
Freedom from Stent Thrombosis (protocol)

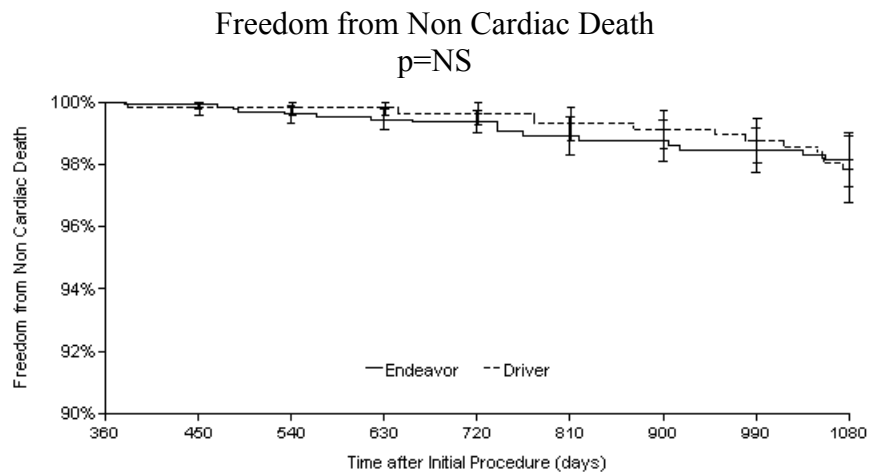
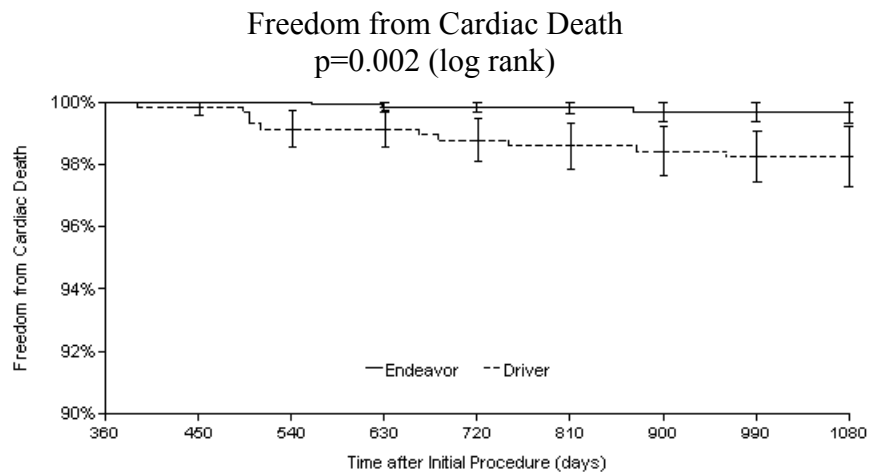
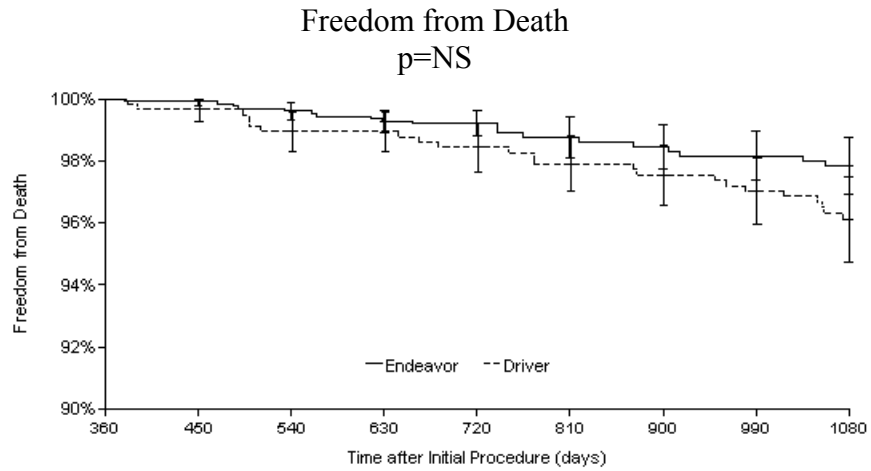


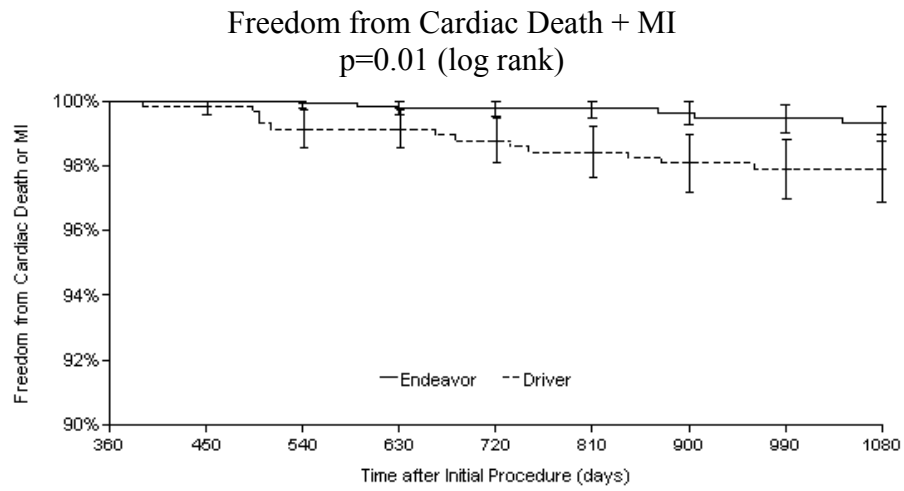
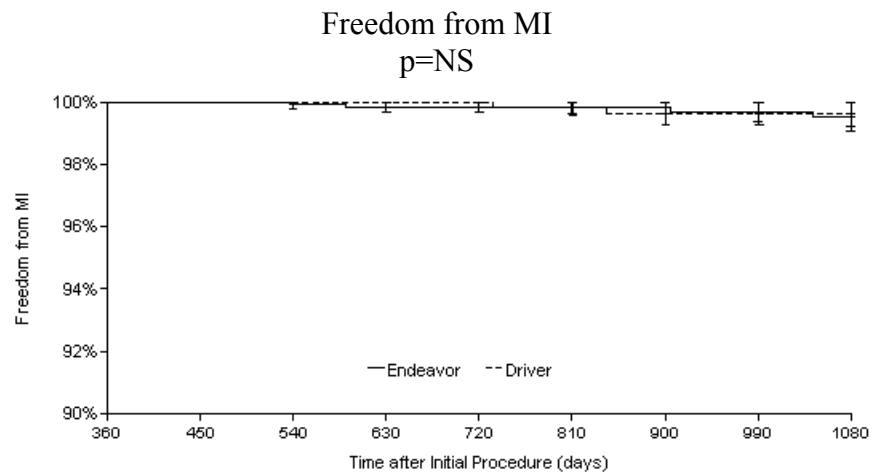
Freedom from Stent Thrombosis (ARC definite + probable, TLR-censored) p=NS



Freedom from Stent Thrombosis (ARC definite + probable, uncensored) p=NS







Incomplete stent apposition

Stent thrombosis is a rare, albeit clinically important, event following DES implantation. DES use in more complex patient and lesion subsets than those in the pivotal trials submitted for PMA approval is associated with an increased risk of stent thrombosis. Additionally, investigations are ongoing that seek to identify imaging markers of increased thrombosis risk. A possible marker is incomplete stent apposition (ISA), which is assessed by IVUS. In the Endeavor studies, ISA was defined as one or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut. ISA may be categorized as early (observed at the time of stent implantation) persistent (ISA present early and at follow-up), or late acquired (ISA absent early and present at late follow-up). Late ISA occurs as a result of the vessel dilatation (positive remodelling) creating a space between the luminal surface of the artery and the overlying stent. Of three types of ISA, late acquired ISA is likely to be more clinically relevant to DES use, as it has been postulated that positive remodeling may occur secondary to inflammatory responses to the DES.

In the Endeavor stent-treated patients, the frequency of all types of ISA is shown in Table 60.

| Table 60: Incomplete Stent Apposition | | | | |
|--|--------------------|--------------------|---------------------|--------------------|
| Difference | ENDEAVOR I* | ENDEAVOR II | ENDEAVOR III | ENDEAVOR IV |
| ISA at Post-Procedure | 12.6% (12/95) | 24.8% (36/145) | 12.4% (31/251) | 12.5% (17/136) |
| ISA at 8 Month Follow- | 4.7% (4/86) | 16.8% (21/125) | 7.5% (17/226) | 10.0% (12/120) |
| Resolved | 8.1% (7/86) | 7.0% (8/114) | 5.8% (11/189) | 3.8% (4/106) |
| Persistent | 4.7% (4/86) | 17.5% (20/114) | 7.9% (15/189) | 8.5% (9/106) |
| Late Acquired | 0.0% (0/86) | 0.0% (0/114) | 0.5% (1/189) | 0.9% (1/106) |

* ENDEAVOR I values are based on 12 month follow up.

The overall rate of late acquired ISA at 8-months follow-up was 0.4% in the Endeavor program.

Although ISA (either persistent or late acquired) is relatively common after DES implantation (observed in 10 – 20% of cases), some observational studies suggest an association of persisted or late acquired ISA with late DES thrombosis. In a recent IVUS study, 10 of 13 (77%) patients with DES thrombosis beyond one year post-implantation had persistent or late acquired ISA vs. 21 of 144 (12%) patients in a control group of patients without late DES thrombosis undergoing routine IVUS follow-up at 8 months (Cook S., et al. Circ 2007; 115: 2426-34). In patients treated with Endeavor stents in the Endeavor clinical trials, there were no apparent safety signals through 270 days post-stent implantation in patients with persistent or late ISA compared to those without persistent or late ISA (see Table 61).

| Table 61: Comparison of Endeavor Patients with vs. without Persistent or Late Acquired ISA | | |
|---|--------------------------|-------------------------------|
| Clinical Events to 270 days | ISA Group, N = 53 | Non-ISA Group, N = 488 |
| Death | 0.0% (0/53) | 0.2% (1/488) |
| Cardiac Death | 0.0% (0/53) | 0.0% (0/488) |
| MI | 1.9% (1/53) | 0.8% (4/488) |
| Cardiac Death or MI | 1.9% (1/53) | 0.8% (4/488) |
| Protocol ST | 0.0% (0/53) | 0.0% (0/488) |
| ARC Definite and Probable ST (TLR-censored) | 0.0% (0/53) | 0.0% (0/488) |
| ARC Definite and Probable ST (TLR-uncensored) | 0.0% (0/53) | 0.0% (0/488) |
| TLR | 3.8% (2/53) | 3.7% (18/488) |
| TVR | 9.4% (5/53) | 5.5% (27/488) |

The event rates in the patients with persistent or late acquired ISA are low. However, considering the DES field as a whole, the limitations on the ability to predict low frequency events like stent thrombosis from relatively small datasets of paired high quality IVUS images should be recognized. FDA anticipates continued interest in imaging markers such as late acquired ISA (with refined quantitative assessment) and positive remodelling that might identify patients at increased risk for adverse, particularly those occurring late, outcomes.

Dual antiplatelet therapy

In the Endeavor clinical studies, the recommended duration of dual antiplatelet therapy was 3 months except for Endeavor IV, where 6 months was recommended in accordance with the label for the Taxus stent to maintain patient level blinding. The actual use of dual antiplatelet therapy may be informative in considering the clinical outcomes in the Endeavor stent program (including stent thrombosis rates of <1%) and recommendations regarding antiplatelet therapy in the Endeavor stent label. The Endeavor case report forms captured antiplatelet therapy use through 6 months. An analysis of the actual use of dual antiplatelet therapy through 6 months among patients treated with Endeavor stents demonstrated that most were still taking a thienopyridine through 6 months (see Table 62).

| Table 62: Antiplatelet Therapy Use at 6 months in Patients Treated With Endeavor Stents | | | | |
|--|--------------------------------|-----------------------------------|----------------------------------|--------------------------------|
| | ENDEAVOR II (N=598) | ENDEAVOR II CA (N=296) | ENDEAVOR III (N= 323) | ENDEAVOR IV (N=773) |
| Aspirin | 96.9% (561/579) | 95.1% (272/286) | 95.9% (303/316) | 95.8% (713/744) |
| Clopidogrel | 65.5% (377/576) | 59.4% (170/286) | 90.1% (264/293) | 94.8% (697/735) |
| Ticlopidine | 2.1% (12/569) | 0% (0/287) | 6.1% (2/33) | 29.4% (5/17) |
| Aspirin + Clopidogrel or Ticlopidine | 64.8% (375/579) | 55.9% (161/288) | 81.6% (258/316) | 92.3% (687/744) |

In the pooled Endeavor studies, there were 14 Endeavor patients with ARC definite or probable stent thrombosis (11 events occurred prior to 180 days post-Endeavor stent implantation and 3 after 180 days). The clinical presentation was death in 3 patients and non-fatal MI in 8 (one of whom died 22 days later). The remaining 3 (of 14) patients had ischemic symptoms, ECG changes, and/or abnormal serum cardiac biomarkers that did not meet criteria for an acute MI. Of the total 14, 8 were taking dual antiplatelet therapy at the time of the stent thrombosis event; 4 were not taking dual antiplatelet therapy for the following reasons: completed ENDEAVOR II 12-week protocol recommendation (n=2), stopped for planned carotid artery procedure (n=1), and stopped due to medication cost (n=1); and definitive information on dual antiplatelet therapy was lacking in 2 subjects. Of the 3 patients who had their stent thrombosis event beyond 180 days post-Endeavor stent implantation, 2 patients were known not to be taking dual antiplatelet therapy (ENDEAVOR II subjects), and antiplatelet therapy information was lacking in the other individual. Independent DSMB and FDA review of all these cases did not reveal other clinically relevant findings.

j. Diabetic Patients in the Pooled ENDEAVOR Clinical Studies

Diabetic patients comprise an important patient subgroup that is at increased risk for cardiovascular morbidity and mortality. Like previous PCI applications for PMA approval, including the currently approved DES, 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 diabetic individuals, FDA believes that clinical outcomes in diabetics should be considered in the review of the Endeavor stent program. Therefore FDA requested that Medtronic conduct a post-hoc pooled analysis of outcomes in diabetics from all ENDEAVOR trials.

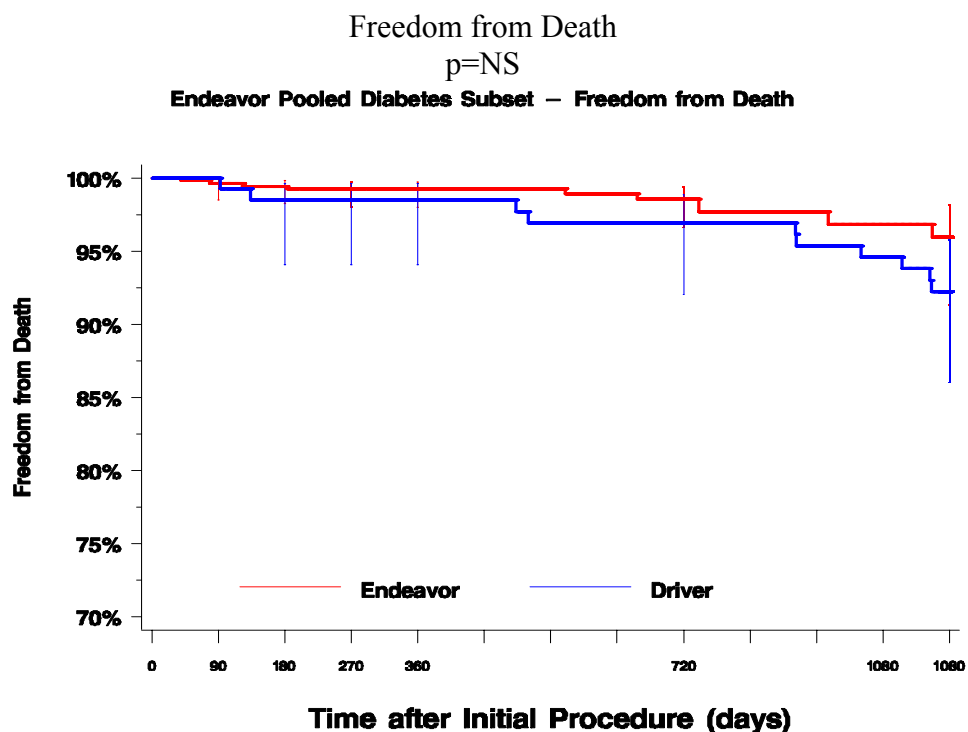
Table 63 shows clinical outcomes through 270 days in patients pooled from the Endeavor trials stratified by non-diabetics, all diabetics, insulin-dependent diabetics, and non-insulin dependent diabetics. As expected, TLR and TVR rates were numerically increased in diabetics vs. non-diabetics with no numerical increase in the rates of death, cardiac death, MI, or stent thrombosis.

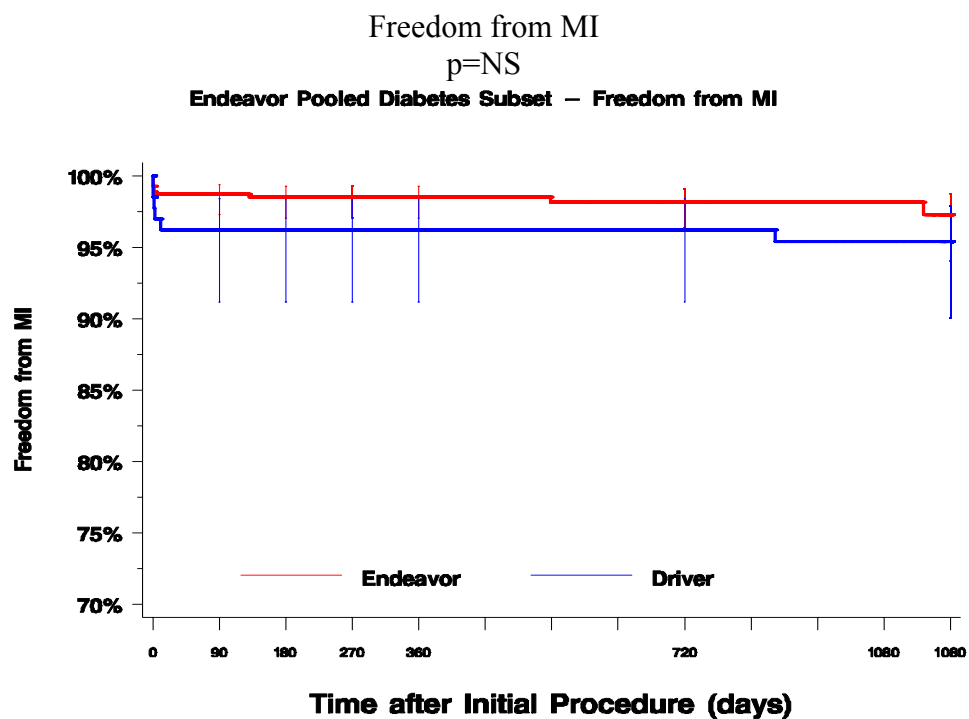
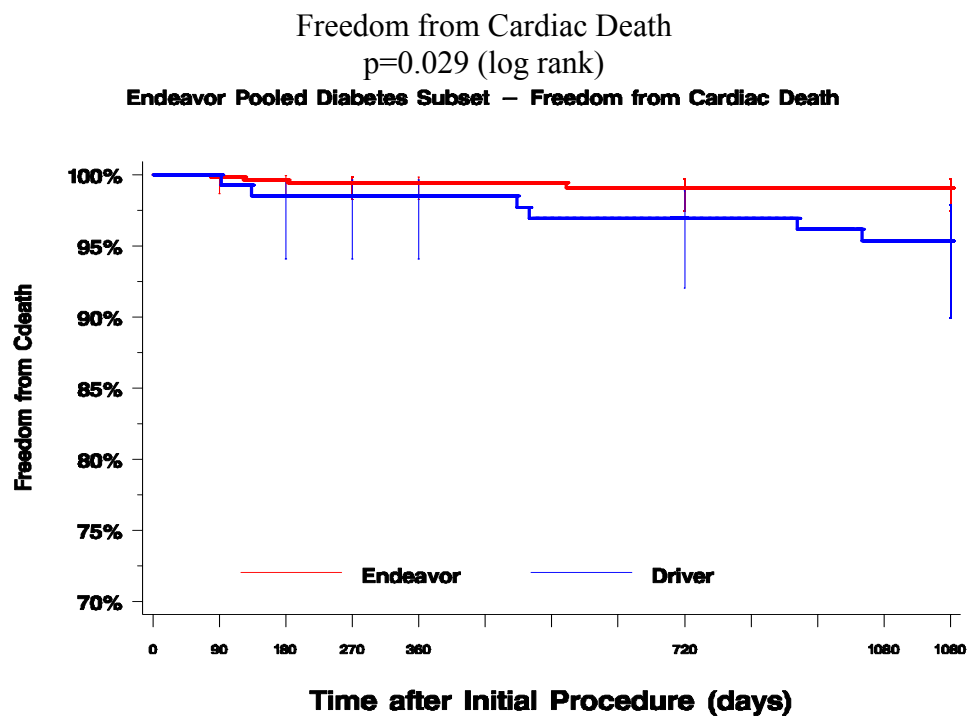
| Table 63: Clinical Events through 270 Days | | | | |
|--|---------------------------------|--------------------------------|------------------------------------|--|
| | Non-Diabetics N=1549 | All Diabetics N=537 | Insulin-Dependent N=154 | Non-Insulin-Dependent N=381 |
| Death | 0.8% | 0.8% | 0.7% | 0.8% |
| Cardiac Death | 0.5% | 0.6% | 0.0% | 0.8% |
| MI | 2.4% | 1.5% | 2.0% | 1.4% |
| Cardiac Death or MI | 2.8% | 1.9% | 2.0% | 1.9% |
| Protocol ST | 0.5% | 0.6% | 0.7% | 0.5% |
| Definite and Probable ST ARC (TLR-censored) | 0.5% | 0.8% | 1.3% | 0.5% |
| Definite and Probable ST ARC (TLR-uncensored) | 0.5% | 0.8% | 1.3% | 0.5% |
| TLR | 4.1% | 6.3% | 6.0% | 6.5% |
| TVR | 5.8% | 9.4% | 8.0% | 9.8% |

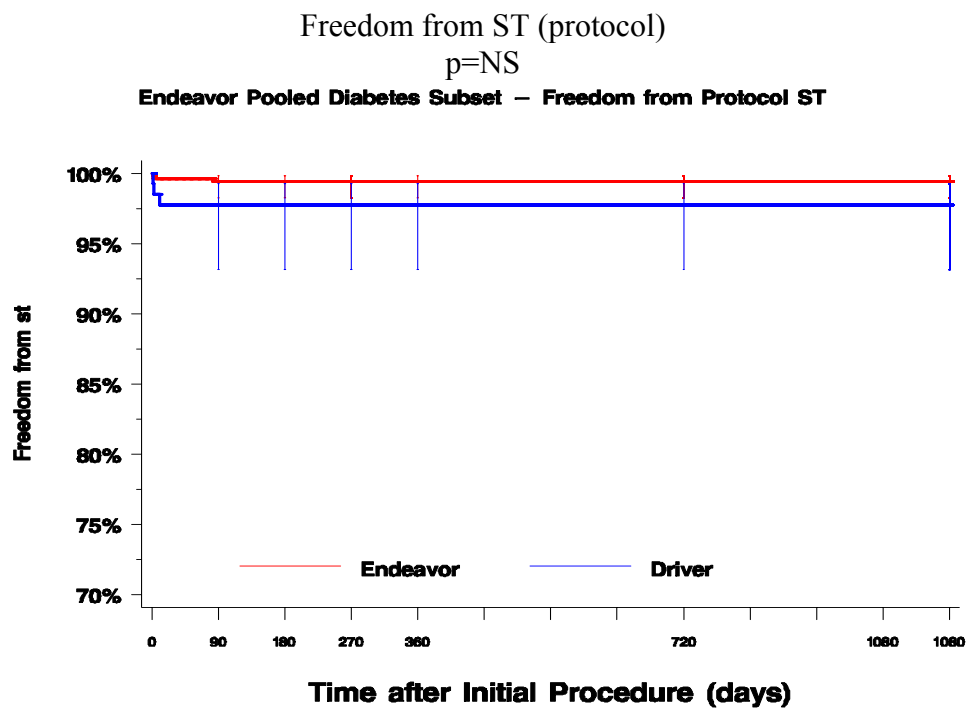
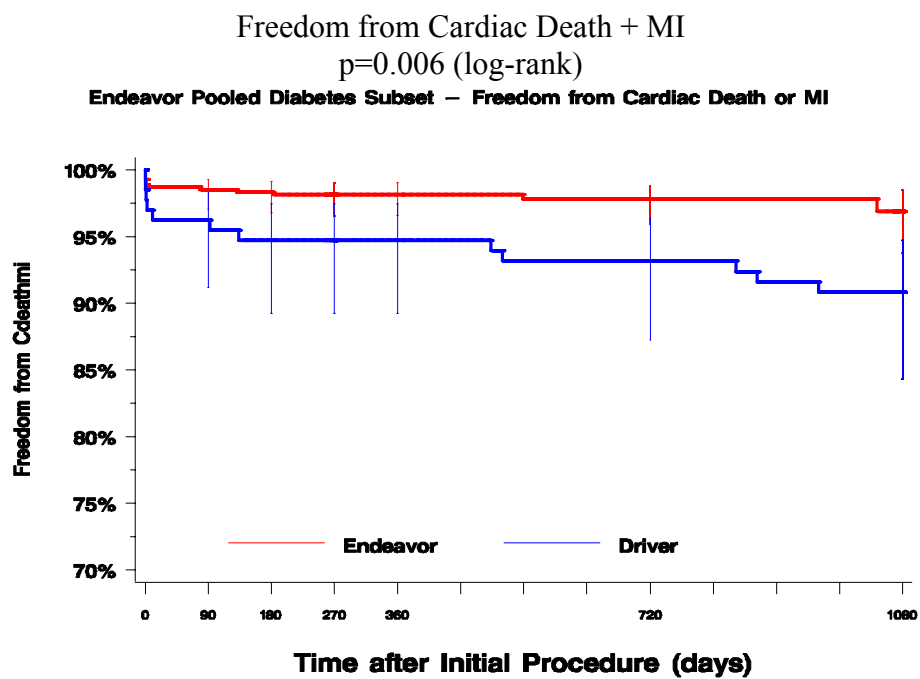
From the pooled Endeavor stent studies, clinical outcomes through 270 days are shown in Table 64 stratified by all diabetics, insulin-dependent diabetics, and non-insulin dependent diabetics. Event rates for the Driver stent patients in the ENDEAVOR II study are shown for reference.

| Table 64: Clinical Events in Diabetics through 270 Days | | | | | | |
|---|-------------------|-----------------|-------------------|----------------|-----------------------|----------------|
| | All Diabetics | | Insulin-Dependent | | Non-Insulin-Dependent | |
| | Endeavor N=537 | Driver N=132 | Endeavor N=154 | Driver N=44 | Endeavor N=381 | Driver N=88 |
| Death | 0.8% | 1.5% | 0.7% | 2.3% | 0.8% | 1.1% |
| Cardiac Death | 0.6% | 1.5% | 0% | 2.3% | 0.8% | 1.1% |
| MI | 1.5% | 3.8% | 2% | 2.3% | 1.4% | 4.5% |
| Cardiac Death or MI | 1.9% | 5.3% | 2% | 4.5% | 1.9% | 5.7% |
| Protocol ST | 0.6% | 2.3% | 0.7% | 0% | 0.5% | 3.4% |
| Definite and Probable ST ARC (TLR-censored) | 0.8% | 2.3% | 1.3% | 0% | 0.5% | 3.4% |
| Definite and Probable ST ARC (TLR-uncensored) | 0.8% | 2.3% | 1.3% | 0% | 0.5% | 3.4% |
| TLR | 6.3% | 15.2% | 6% | 13.6% | 6.5% | 15.9% |
| TVR | 9.4% | 15.9% | 8% | 13.6% | 9.8% | 17% |

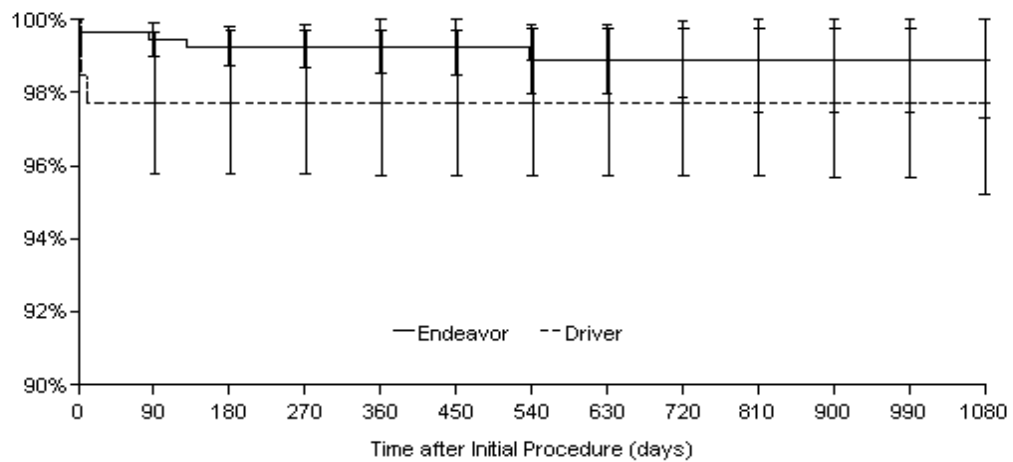
The Kaplan-Meier curves below were derived from diabetic patients treated with Endeavor stents in the pooled Endeavor clinical studies with comparison to patients treated with the Driver stent in ENDEAVOR II.





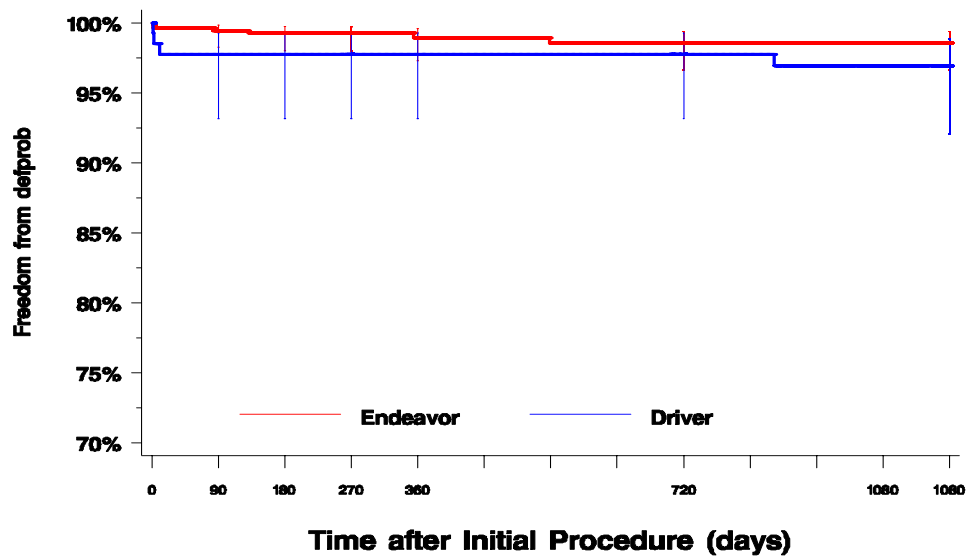


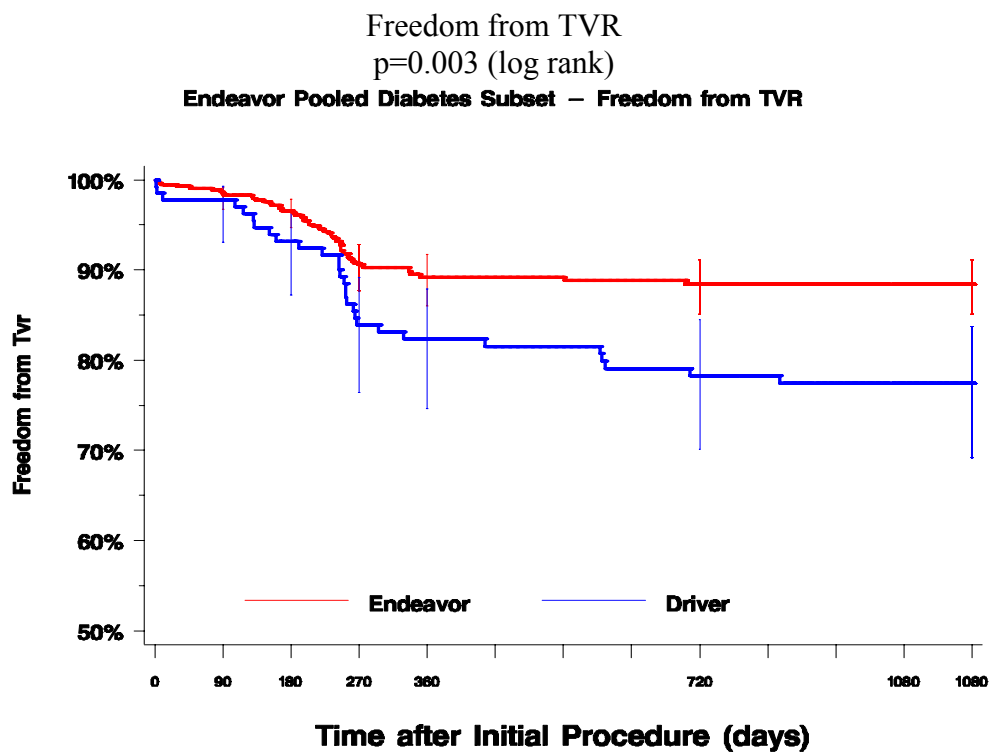
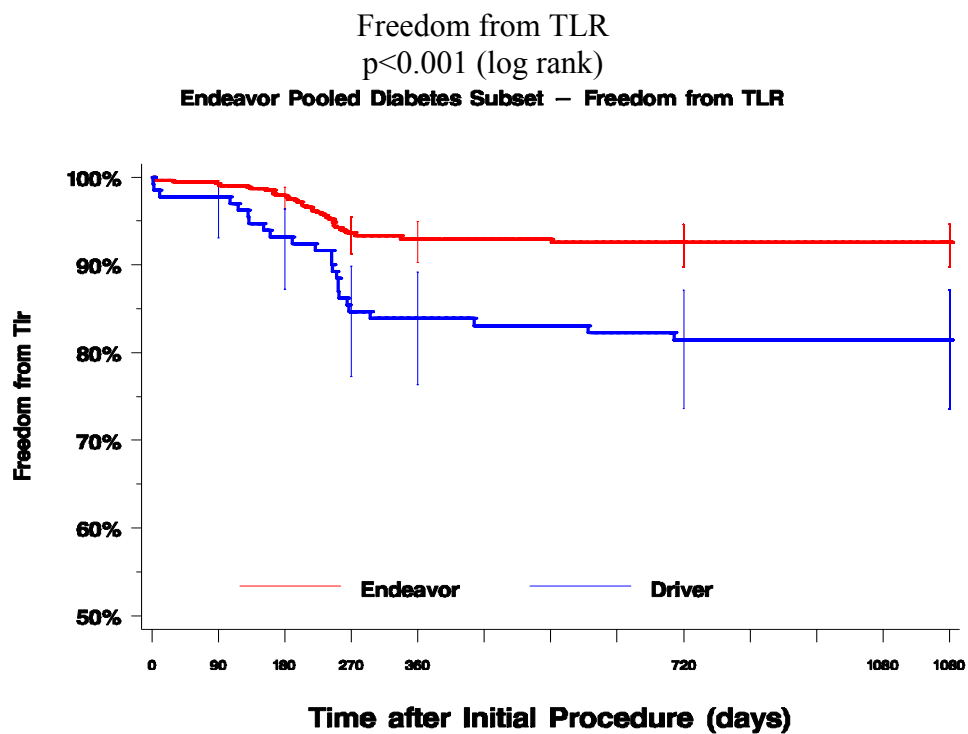
Freedom from Stent Thrombosis (ARC definite + probable, TLR-censored)
p=NS



Freedom from ST (ARC definite + probable, uncensored)
p=NS

Endeavor Pooled Diabetes Subset – Freedom from Definite and Probable ST





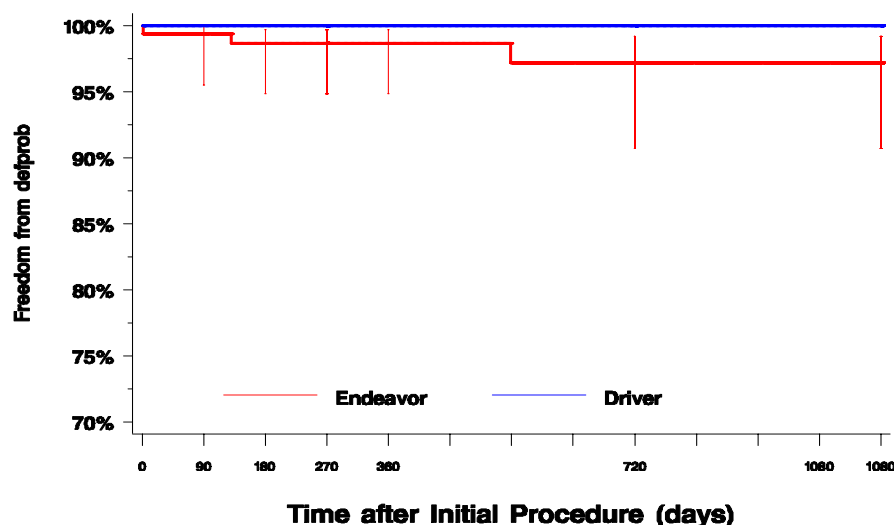
For all diabetics, clinical outcome rates through 270 days (Table 64) and the Kaplan-Meier curves (above) favored patients treated with the Endeavor stent compared with the Driver stent. Clinical outcomes through 270 days (Table 64) in both insulin-dependent and non-insulin dependent diabetics showed a similar pattern favoring Endeavor with the exception of stent thrombosis in insulin-dependent diabetics (1.3% in Endeavor vs. 0% in Driver, see below).

For non-insulin dependent diabetes, Kaplan-Meier analysis (curves not shown) of clinical outcomes demonstrated no significant differences between Endeavor and Driver patients for death, cardiac death (log rank $p=0.086$ favoring Endeavor), or MI (log rank $p=0.084$ favoring Endeavor). A Kaplan-Meier analysis (curves not shown) of cardiac death or MI (log rank $p=0.009$), protocol stent thrombosis (log rank $p=0.017$), ARC definite + probable stent thrombosis (log rank $p=0.036$), TLR (log rank $p=0.001$), and TVR (log rank $p=0.005$) favored Endeavor.

For insulin dependent diabetes, Kaplan-Meier analysis (curves not shown) of clinical outcomes demonstrated no significant differences between Endeavor and Driver patients for death, cardiac death, MI, cardiac death or MI, TLR (log rank $p=0.091$ favoring Endeavor), or TVR.

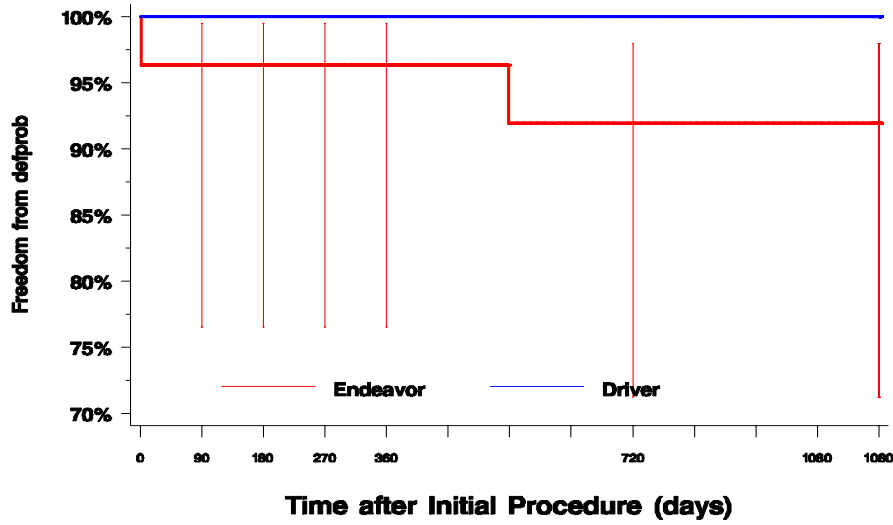
For insulin-dependent patients, the Kaplan-Meier ARC definite + probable stent thrombosis curve for the pooled Endeavor patients compared with Driver patients (ENDEAVOR II) is shown below (log rank $p=0.28$):

Endeavor Pooled Insulin-dependent Subset – Freedom from Definite and Probable ST



A Kaplan-Meier curve of only patients in the ENDEAVOR II study (the randomized trial with the longest available follow-up: 3 years) is shown below (log rank $p=0.062$):

Endeavor II Insulin-dependent Subset – Freedom from Definite and Probable ST



While these stent thrombosis data are of interest and hypothesis-generating, it should be noted that the number of insulin-dependent patients studied is limited (ENDEAVOR II: Endeavor n=27, Driver n=44), the rate was zero in Driver patients, and the total number of stent thrombosis events in Endeavor patients beyond 180 days was 1.

k. Non Cardiac Deaths and Cancer in the Pooled ENDEAVOR Clinical Studies

Listed below are the non cardiac deaths from the Endeavor and Driver patients for which cancer was designated as the likely cause of death in the study documentation that was received from the participating sites and independently reviewed by both the Clinical Events Committee and FDA (see Table 65).

| Table 65: Non Cardiac Deaths and Cancer in the ENDEAVOR Program | | | | | | | | | | |
|--|------------------------|-------------------|--------------------|---------------------|-----------------------|---------------------|---------------|--------------------|--------------------|--------------|
| | Endeavor Pooled | ENDEAVOR I | ENDEAVOR II | | ENDEAVOR II CA | ENDEAVOR III | | ENDEAVOR PK | ENDEAVOR IV | |
| | | | Endeavor | Driver | | Endeavor | Cypher | | Endeavor | Taxus |
| Total Non-Cardiac deaths | | | | | | | | | | |
| 30 Days | 0.04% | 0.0% | 0% | 0% | 0.0% | 0% | 0% | 0.0% | 0.1% | 0% |
| 9 months | 0.3% | 0.0% | 0.3% | 0% | 0.0% | 0.6% | 0% | 0.0% | 0.3% | 0.5% |
| 12 months | 0.3% | 0.0% | 0.3% | 0% | 0.0% | 0.6% | 0.9% | | | |
| 24 months | 0.9% | 1.0% | 0.7% | 0.3% | 0.7% | 1.6% | 3.6% | | | |
| 36 months | 1.9% | 3.1% | 1.7% | 2.1% | | | | | | |
| 48 months | 4.1% | 4.1% | | | | | | | | |
| Subset of patients for which Cancer was designated as the likely cause of death | | | | | | | | | | |
| 30 Days | 0.04% | 0.0% | 0% | 0% | 0% | 0 | ND | 0 | 0.129% | ND |
| 9 months | 0.09% | 0.0% | 0.16% | 0% | 0% | 0.31% | ND | 0 | 0 | ND |
| 12 months | 0% | 0.0% | 0% | 0.169% | 0% | 0% | ND | NA | NA | NA |
| 24 months | 0.2% | 1.01% | 0.17% | 0.17% | 0% | 0.319% | ND | NA | NA | NA |
| 36 months | 1.03% | 2.04% | 0.866% | 0.863% | NA | NA | NA | NA | NA | NA |
| 48 months | 1.03% | 1.03% | NA | NA | NA | NA | NA | NA | NA | NA |
| Rates | 14/2057= 0.65% | | | 7/594= 1.17% | | | NA | | | NA |

The time intervals in the table above reflect the follow-up interval post-stent implantation until death from cancer and are not related to the time at which cancer was diagnosed. The overall rate of cancer deaths among all non-cardiac deaths subset was 0.65% (14/2057) for pooled Endeavor patients and 1.17% (7/594) for Driver patients.

I. Summary

The Endeavor stent was tested in two large randomized clinical trials that compared it to an approved bare metal stent control (Driver stent) in the ENDEAVOR II study and to an approved DES (Taxus stent) in the ENDEAVOR IV study. Experience with the Endeavor stent was supplemented by the ENDEAVOR II-CA registry, the ENDEAVOR III randomized trial (angiographic endpoint study vs. Cypher), and the Endeavor PK registry. The Endeavor stent is the third DES PMA to be brought before an Advisory Panel and the first to elute a new molecular entity. Additionally, this application is the first since concerns regarding the safety of DES were discussed at the FDA Advisory Panel meeting in December 2006.

In pivotal DES trials to date, composite primary study endpoints that combine safety and effectiveness factors, such as TVF and MACE, have been utilized. The overall benefit (superiority) of these DES vs. bare metal stent trials was driven by the significant reduction on TLR/TVR (effectiveness), as there were no differences in the rates of death or MI (safety) between treatment groups.

Over the past 12 to 18 months, concerns about late DES thrombosis have emerged that have raised questions about their long-term safety. Although pivotal DES trials have been large by historical standards for cardiac devices, they have been underpowered to detect significant differences in low frequency (but clinically important) events between treatment groups. Composite endpoints such as TVF and MACE remain acceptable as primary endpoints, but DES safety (rates of death, MI, and stent thrombosis) continue to warrant close scrutiny in all DES submissions and will likely involve data pooling of pre-market trials and post-market studies.

Primary TVF endpoint of Endeavor RCTs: Clinical composites, clinical effectiveness, and angiographic effectiveness

The Endeavor stent met its primary composite clinical endpoint (48% reduction in 9-month TVF vs. the Driver stent) in ENDEAVOR II. The clinical effectiveness superiority of the Endeavor stent was maintained in extended follow-up as evidenced by a 50% reduction in TLR and a 46% reduction in TVR vs. control through 36 months. In patients that underwent follow-up imaging, all angiographic effectiveness parameters (in-segment and in-stent minimum lumen diameter, percent stenosis, late loss, and neointimal hyperplastic volume) favored the Endeavor stent group. It is notable that the effectiveness performance of the control Driver stent was found acceptable for a bare metal stent, so that it is *not* the case that the Endeavor stent is superior to an inferior control device. The effectiveness results of ENDEAVOR II, a large pivotal randomized trial versus a bare metal stent control, are important for establishing the added benefit of the NME.

The high penetrance of the approved DES by interventional cardiologists into routine clinical practice altered clinical trial design for the next generation of DES. It has been argued that in the US it would not be feasible to conduct a randomized trial to test superiority of a new DES to a bare metal stent. Instead, manufacturers have adopted non-

inferiority designs comparing the new DES to one of the approved DES. These studies have otherwise used the same endpoints as were used in the DES vs. bare metal stent trials. ENDEAVOR III and ENDEAVOR IV were structured as DES vs. DES studies. ENDEAVOR III was underpowered for clinical endpoints (TVF or MACE). The Endeavor stent failed to meet its primary angiographic endpoint (8-month in-segment late lumen loss vs. the Cypher stent) in ENDEAVOR III. To place the results of ENDEAVOR III in context of the entire Endeavor program, particularly the substantially larger ENDEAVOR IV study, see the discussion below regarding angiographic endpoints in DES vs. DES trials.

The primary endpoint of the ENDEAVOR IV pivotal study was the clinical endpoint TVF (a composite of TVR, MI or cardiac death) at 9 months post-procedure. This endpoint was chosen because the number of additional patients needed to meet the 2,000 patient exposure requirement for an NME was also sufficient to power the trial for this clinical composite. In the equivalence study design, it was expected that the TVF rates of the Endeavor and Taxus arms would both be equal to 7.6%, and the non-inferiority margin was set at 3.8%. The observed TVF rates in ENDEAVOR IV are shown in Table 66.

| Table 66: TVF rates in ENDEAVOR IV | | | | |
|---|--------------------------------------|-----------------------------------|--|-----------------|
| | Endeavor (N=773 Patients) | Taxus (N=775 Patients) | Difference [One-sided 95% CI] | P-Value* |
| Target Vessel Failure | 6.8% (50/740) | 7.4% (54/734) | 0.6% [-100%, 1.6%] | <0.001 |

*test for non-inferiority

In the Endeavor arm, the TVF rate was 6.8% (50/740) compared with 7.4% (54/734) in the Taxus arm. Non-inferiority of Endeavor to Taxus with respect to TVF rate was demonstrated in this study. Rates of the individual components of the TVF composite in ENDEAVOR IV are shown in Table 67.

| Table 67: Components of TVF in ENDEAVOR IV | | | |
|---|--------------------------------------|-----------------------------------|--|
| Complications to 270 Days | Endeavor (N=773 Patients) | Taxus (N=775 Patients) | Difference [Two-sided 95% CI] |
| Cardiac Death | 0.4% (3/740) | 0.3% (2/734) | 0.1% [-0.5%, 0.7%] |
| MI (Q Wave or Non-Q Wave) | 1.5% (11/740) | 2.5% (18/734) | -1.0% [-2.4%, 0.5%] |
| TVR | 5.5% (41/740) | 5.0% (37/734) | 0.5% [-1.8%, 2.8%] |

In-segment or in-stent late lumen loss and percent diameter stenosis at angiographic follow-up provide a direct measure of in-stent neointimal proliferation, which is pathophysiologically linked to restenosis. Multiple studies have suggested that late lumen loss and percent diameter stenosis at follow-up are useful surrogate markers for TLR and thus provide valuable tools to assess relative effectiveness of coronary stents. Within ENDEAVOR IV, there was an important angiographic substudy to test the effectiveness of the Endeavor stent to reduce neointimal growth compared to the Taxus stent. For this substudy (an adequately powered prespecified secondary endpoint), a non-inferiority hypothesis of 8-month in-segment late lumen loss of the Endeavor arm

compared to the Taxus arm (with a non-inferiority margin set at 0.2 mm) was proposed. The protocol-required 8-month follow-up angiography was to be completed in the first 328 patients and for all patients who received greater than one stent. The results of this analysis are shown in Table 68.

| Table 68: In-Segment Late Lumen Loss (mm) in ENDEAVOR IV | | | | |
|---|--------------------------------------|-----------------------------------|--|-----------------|
| | Endeavor (N=164 Patients) | Taxus (N=164 Patients) | Difference [One-sided 95% CI] | P-Value* |
| Mean±SD (n) | 0.36±0.47 (143) | 0.23±0.45 (135) | 0.13 [-∞, 0.22] | 0.089 |
| Range (Min,Max) | (-0.48,1.90) | (-0.78,2.45) | | |

*test for non-inferiority

The p-value for testing the null hypothesis that Endeavor is inferior to Taxus with respect to in-segment late loss was 0.0890 and the upper limit of the 95% Confidence Interval for the difference was 0.22. Therefore, the non-inferiority hypothesis could not be rejected, and the secondary endpoint was not met. The conclusion one might draw from this analysis is that the Endeavor stent is less effective in inhibiting neointimal proliferation compared to the Taxus stent. A similar conclusion might be reached from the angiographic outcome (primary endpoint) of the ENDEAVOR III study (Endeavor vs. Cypher stents).

Although in-segment late loss was chosen as the secondary endpoint for the angiographic studies in ENDEAVOR III and IV, other angiographic measures such as in-stent late loss and follow-up percent diameter stenosis have also been proposed as acceptable surrogates of coronary stent effectiveness. All of the surrogate measures of DES effectiveness (in-stent or segment late loss and percent diameter stenosis) favored the control stents (Cypher in ENDEAVOR III and Taxus in ENDEAVOR IV) compared to the Endeavor stent. The in-stent late lumen loss and percent diameter stenosis data (plus binary restenosis results) from the ENDEAVOR IV angiographic substudy are shown in Table 69.

| Table 69: ENDEAVOR IV Angiographic Substudy | | | |
|--|--------------------------------------|-----------------------------------|--|
| Effectiveness Measure | Endeavor (N=164 Patients) | Taxus (N=164 Patients) | Difference [Two-sided 95% CI] |
| 8-Month Follow-up Late Loss In-Stent (mm) Mean±SD (n) | 0.67±0.49 (142) | 0.42±0.50 (135) | 0.25 [0.13, 0.37] |
| 8-Month Follow-up In-Stent Percent Diameter Stenosis (%) Mean±SD (n) | 26.41±19.74 (143) | 16.09±17.99 (136) | 10.32 [5.85, 14.79] |
| 8-Month Follow-up In-Segment Percent Diameter Stenosis (%) Mean±SD (n) | 32.28±17.02(144) | 26.61±15.52 (135) | 5.68 [1.83, 9.52] |
| 8-Month In-Stent Binary Restenosis | 13.3% (19/143) | 6.7% (9/135) | 6.6% [-0.4%, 13.6%] |
| 8-Month In-Segment Binary Restenosis | 15.3% (22/144) | 10.4% (14/135) | 4.9% [-2.9%, 12.7%] |

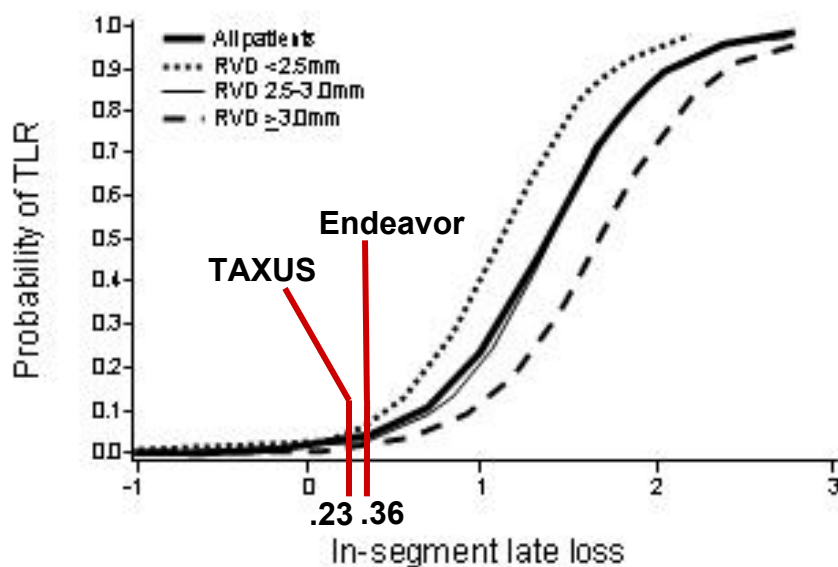
Given our understanding of the usefulness of late loss to predict effectiveness, outcomes of previous pivotal DES (vs. bare metal stent) trials being driven by differences in repeat revascularization rates, and the failure of the Endeavor to demonstrate statistical non-inferiority to the Taxus stent in the ENDEAVOR IV angiographic substudy, it might be reasonable to ask why the Endeavor stent met its primary TVF endpoint while failing to meet its angiographic effectiveness endpoint. Several factors are worth considering:

1. TVR vs. TLR. The TVF primary endpoint includes TVR and not only TLR. Although TLR and TVR usually track together, TLR and TVR assess different parameters. TLR is a measure of the ability of the stent to prevent neointimal growth within the stent at the stent margins (in-stent and in-segment). TVR assesses the treatment strategy on the level of the entire vessel, which includes lesions that may be present or develop during follow-up proximal or distal to the stented segment and the impact of any procedural factors (such as vascular trauma) that might lead coronary luminal compromise. Therefore, TVR is less of a metric of the effectiveness of implantation of a particular stent than TLR. The rates of TLR in ENDEAVOR IV through 9-months are shown in Table 70 and demonstrate a greater difference in outcome (albeit non-significantly) between Endeavor vs. Taxus (and are consistent with the late loss difference between stents) compared to the TVR results (5.5% vs. 5.0%, respectively).

| Table 70: TLR rates in ENDEAVOR IV | | | |
|---|--------------------------------------|-----------------------------------|--|
| | Endeavor (N=773 Patients) | Taxus (N=775 Patients) | Difference [Two-sided 95% CI] |
| Target Lesion Revascularization | 4.2% (31/740) | 2.7% (20/734) | 1.5% [-0.4%, 3.3%] |

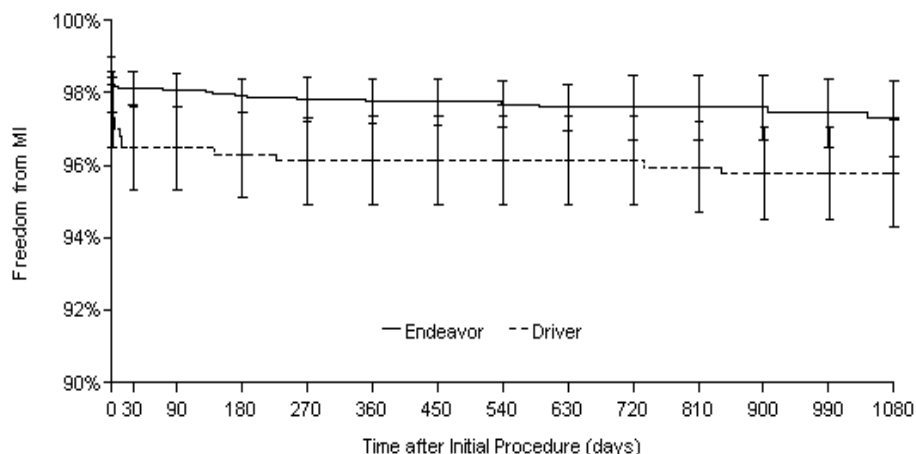
Although TLR may be a superior clinical measure of stent effectiveness compared with TVR, given the overall low rates of revascularization and the numerous factors that may affect whether a repeat revascularization to the target lesion or vessel is performed (e.g., symptom status, stress testing, coronary anatomy, propensity toward performing invasive studies), it is difficult to ascribe clinical relevance to these small differences between TLR or TVR.

2. The late lumen loss/TLR curve. Although there appear to be differences in late lumen loss and percent diameter stenosis among DES, these differences are of substantially less magnitude than those seen in DES vs. bare metal stent studies. More importantly, and notably for the ENDEAVOR IV angiographic substudy, the observed late loss values are located in the flat portion of the late loss/TLR curve. In the in-segment late loss vs. probability of TLR curve shown below, generated from an analysis of 11 randomized DES and bare metal stent trials (reproduced with permission Pocock S, et al., European Society of Cardiology Congress, Vienna, September 2007), the late loss measurements observed in the ENDEAVOR IV angiographic substudy are superimposed on the graph.



Thus, based on the curvilinear shape of the late loss/TLR curve, a statistically significant difference in late loss between stents (or failure to achieve statistical non-inferiority) may not translate into important difference in a clinical endpoint such as TLR.

3. TVF composite and MI. As noted above, TVF is a composite of cardiac death, MI, and TVR. With low revascularization rates in DES vs. DES studies, the other components of the TVF composite may assume relatively greater numerical importance in contrast to DES vs. BMS studies. In Endeavor IV, cardiac deaths were similar between Endeavor and TAXUS groups through 9 months (0.4% and 0.3% respectively), and as noted above, TVR Rates were also similarly low between Endeavor and Taxus (5.5% vs. 5.0%, respectively). For MI, the overall rate was low with slightly more events observed in Taxus (2.5%, 18/734) compared with Endeavor (1.5%, 11/740). The timing of MI post-stent implantation was different between treatment groups. Of the 18 Taxus MIs, 16 occurred in-hospital and 2 occurred between hospital discharge and 30 days. Of the 11 Endeavor MIs, 6 occurred in-hospital, 4 occurred between 30 and 180 days, and 1 occurred between 180 and 270 days. However, from the Kaplan-Meier plots of the Endeavor DES program, a late MI safety signal is not apparent:



4. Angiographic assessment at 8 months: Restenosis prevention vs. restenosis delay.

Based on their mechanism of action, DES delay neointimal healing, and there have been concerns that, over the long-term, DES restenosis might ultimately occur after complete elution of the antiproliferative drug. Long-term follow-up of the approved DES, however, has demonstrated that the reduction in rates of repeat revascularization associated with DES compared with bare metal stents are sustained through 3 to 4 years. In a pivotal DES vs. DES trial such as ENDEAVOR IV, it is uncertain whether the less effective angiographic results of the Endeavor stent will be associated with a significantly greater frequency of TLR/TVR compared to the Taxus stent. Long-term follow-up of ENDEAVOR IV patients will provide important information on this issue. From a review of the Endeavor program, cases of TLR/TVR continue to accrue over time in all treatment groups (Endeavor, Driver, and Cypher) without a trend toward reduced clinical effectiveness of the Endeavor stent. It should be noted that any loss of effectiveness over time must be balanced against an assessment of long-term safety (death, MI, and stent thrombosis).

Safety

The Endeavor DES program has compiled safety data from the following studies:

- ENDEAVOR I 4-Year Data
- ENDEAVOR II 3-Year Data
- ENDEAVOR II Continued Access 2-Year Data
- ENDEAVOR III 2-Year Data
- ENDEAVOR IV 9-Month Data
- ENDEAVOR PK 9 – Month Data

These 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), an increased rate of death, MI, death or MI, noncardiac death, or stent thrombosis for the Endeavor stent vs. the control stents has not been observed to date. Safety outcomes from the pooled Endeavor studies are discussed above in Section 7h and 7i.

8. POST-APPROVAL STUDY

The FDA review team, which includes an epidemiologist, recommends that if the Endeavor Zotarolimus-Eluting Coronary Stent System is approved, a post-approval study should be conducted as a condition of approval. It should be noted that the presence or content of a post-approval study cannot substitute for the requirement of a demonstration of a reasonable assurance of safety and effectiveness prior to approval for marketing.

FDA will provide a supplement to the panel package with additional information regarding the post-approval study.

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