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4.0 Sponsor Executive Summary

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4.0 Executive Summary

4.1 Background

Bare metal stents (BMS) became the preferred choice of treatment for percutaneous coronary interventions (PCI) after clinical trials indicated that stenting decreased reintervention rates compared with balloon angioplasty.[1,2,3] While BMS virtually eliminated many of the complications of abrupt artery closure and late vessel recoil associated with angioplasty, restenosis persisted, with rates as high as 20% to 40% in high-risk subgroups, necessitating a repeat procedure.[4,5,6] The principal cause of in-stent restenosis is neointimal hyperplasia resulting from migration and proliferation of smooth muscle cells and extracellular matrix production.[7]

Stents coated with anti-proliferative agents have been successful in addressing the problem of exuberant neointimal hyperplasia. Sometimes referred to as a "coated" or "medicated" stent, a drug-eluting stent (DES) is coated with a pharmacologic agent (drug) that is known to interfere with the process of restenosis (reducing neointimal growth). In multiple clinical trials, drug-eluting stents have been unequivocally shown to reduce reinterventions (angiographic restenosis) compared with bare metal stents (BMS), thereby reducing recurrent ischemia resulting in the need for repeat hospitalization and revascularization procedures.[8,9] Because of this, drug-eluting stents have become routine therapy in clinical practice, and a comparative standard for evaluation of novel anti-proliferative therapies and stent technologies.

The ideal drug eluting stent should provide for superior clinical efficacy compared to bare metal stents with equivalent safety as measured by cardiac death, myocardial infarction (MI) and stent thrombosis. Stent thrombosis associated with DES was the topic of the FDA Circulatory System Devices Panel meeting on December 7-8, 2006. FDA's purpose for this panel meeting was to provide a forum for the presentation of clinical data relevant to the issue of DES thrombosis and to address the appropriate duration of

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[1] Al Suwaidi J, Berger PB, Holmes DR Jr. Coronary artery stents. JAMA. 2000;284:1828 –1836.
[2] Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents: a hierarchical Bayesian meta-analysis. Ann Intern Med. 2003;138:777–786.
[3] Nordmann AJ, Hengstler P, Leimenstoll BM, et al. Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease: a meta-analysis of randomized controlled trials. Eur Heart J. 2004;25:69–80.
[4] Scheen AJ, Warzee F, Legrand VM. Drug-eluting stents: meta-analysis in diabetic patients. Eur Heart J. 2004;25:2167–2168.
[5] Nikol S, Huehns TY, Hofling B. Molecular biology and post-angioplasty restenosis. Atherosclerosis. 1996;123:17–31.
[6] Elezi S, Kastrati A, Neumann FJ, et al. Vessel size and long-term outcome after coronary stent placement. Circulation. 1998;98:1875–1880.
[7] Mercado N, Boersma E, Wijns W,et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. J Am Coll Cardiol. 2001;38:645–652.
[8] Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
[9] Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.

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antiplatelet therapy in DES patients.[10] Among the conclusions of this meeting, the panel found that the concerns about thrombosis do not outweigh the benefits of DES compared to bare metal stents when DES are implanted within the limits of their approved indications for use. In addition, the panel found that larger and longer premarket clinical trials and longer follow-up for post-approval studies are needed.

The phenomenon of stent thrombosis is not new to percutaneous coronary intervention (PCI). Early stent thrombosis of freshly deployed stents has been a concern since their introduction to human coronary circulation in 1986.[11] The unacceptably high rates (up to 24%) of thrombotic events seen in early clinical experience were dramatically reduced through a combined anticoagulation and antiplatelet therapy after "optimal" stent expansion with routine high pressure post-dilatation. This appreciation for the multifactorial nature of stent thrombosis continued to reduce the incidence of stent thrombosis through attention to the procedure and patient education regarding appropriate use of dual anti platelet therapy. Despite dramatic reductions in stent thrombosis, it has not been eliminated; in this modern stent era, the incidence is reported to be roughly 1%.[11]

Although the majority of stent thrombosis events occur early (within the first 30 days post procedure), late stent thrombosis (> 30 days post-implant) out to one year is not an uncommon finding with BMS.[12,13,14,15] More recently, there has been a heightened awareness surrounding the incidence of stent thrombosis beyond one year (very late). Compared to BMS, the increased rate of very late stent thrombosis (> 12 months) with DES compared to BMS highlights a risk that may be unique to DES.[16,17,18,19] This observation indicating the potential association of the product (DES) with stent thrombosis is in addition to the previously identified risk factors – such as inadequate stent expansion and poor patient drug compliance. It is important that the development program for any new drug eluting stent fully characterize the product's safety profile in

[10] Food and Drug Administration. Update to FDA Statement on Coronary Drug-Eluting Stents. January 4, 2007. http://www.fda.gov/cdrh/news/010407.html.
[11] Honda Y and Fitzgerald P. Stent thrombosis: An issue revisited in a changing world. Circulation 2003;108;2-5.
[12] Wenaweser P, Rey C, et al. Stent thrombosis following bare-metal stent implantation: success of emergency percutaneous coronary intervention and predictors of adverse outcome. Europena Heart Journal Journal 2005; 26: 1180-1187.
[13] Ramos AR, Morice M and Lefevre T. Late or very late stent thrombosis can also occur with bare metal stents. Catheterization and Cardiovascular Interventions 2007; 70: 229-232.
[14] BENESTENT: Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med. 1994;331: 489-495.
[15] STRESS: Fischman DL, Leon M, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med. 1994;331: 496-501.
[16] Jensen LO, Maeng M, et al. Stent Thrombosis, Myocardial Infarction, and Death After Drug-Eluting and Bare-Metal Stent Coronary Interventions. JACC 2007; 50: 463-470.
[17] Kaul S, Shah P and Diamond GA. Current status and future directions in the controversy over stenting. JACC 2007; 50: 128-137.
[18] Jaffe R, and Strauss BH. Late and very late thrombosis of drug-eluting stents. JACC 2007; 50: 119-127.
[19] Mauri L, Hsieh W, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007; 356: 1020-1029.

addition to demonstrating its efficacy. In the following sections, the Endeavor Zotarolimus-Eluting CSS is described, followed by summaries of the drug development and relevant non-clinical and clinical testing programs for both the zotoralimus drug substance and the Endeavor product. The drug studies were performed according to standard ICH pharmacology guidelines and with consultation with FDA's Center for Drug Evaluation and Research. The Endeavor drug/stent/polymer combination product studies are described separately and were developed in consultation with the FDA's Center for Devices and Radiological Health, which is the designated lead center responsible for the review and approval of drug-eluting stent pre-market approval applications.

4.2 Product Description

The Endeavor Zotarolimus-Eluting Coronary Stent System is a device / drug combination product comprised of device components (the Driver™ Coronary Stent and the Micro-Driver™ Coronary Stents and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus and Phosphorylcholine polymer coating).

The Endeavor product has four main components:

- Stent - the Endeavor stent component (bare metal substrate) is identical to the Driver and the Micro-Driver Coronary Stents
- Delivery Systems – the Endeavor OTW, RX and MX^2 delivery systems.
- Polymer - the Phosphorylcholine (PC) polymer is identical to that utilized in the Bio*divYsio*™ PC coated stent (P000011, approved September 29, 2000)
- Drug - the drug substance zotarolimus[20] (ABT-578), a member of the limus family of drugs commonly used for the indication.

The stent component of the Endeavor Zotarolimus-Eluting CSS is manufactured from a cobalt based alloy (MP35N) that has been successfully used in other implantable medical devices since 1985, including septal occluders, hip prostheses, aneurysm clips, pacing leads, vena cava filters, and bare metal coronary stents. The Endeavor stent is identical to the approved Driver (P030009, approved October 1, 2003) and the approved Micro-Driver (P030009/S002, approved April 21, 2006) coronary stents.

The Endeavor stent is mounted on one of three delivery systems. The three delivery systems offered with the Endeavor stent are the Over-The-Wire (OTW), Rapid Exchange (RX) and Multi Exchange II (MX^2) Delivery Systems. The delivery systems utilized for the Endeavor product are similar in materials, design and construction to the approved Driver OTW (P030009, approved October 1, 2003; Driver MX^2 P030009/S001, approved on August 4, 2004; Driver RX, P030009/S003, approved on December 22, 2005) and the approved Micro-Driver OTW and MX^2 (P030009/S002, approved on April 21, 2006) delivery systems.

The polymer coating on the Endeavor stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for the drug zotarolimus. PC polymer was originally developed by Biocompatibles UK, Ltd. to increase the biocompatibility and hemocompatibility of

[20] The drug substance previously referred to as ABT-578 has been assigned the name Zotarolimus (Reference USAN [QQ-84] at www.ama-assn.org)

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materials through biomembrane mimicry, as PC is the major lipid headgroup component found in the outer surface of biologic cell membranes. Reference Figure 4-1.

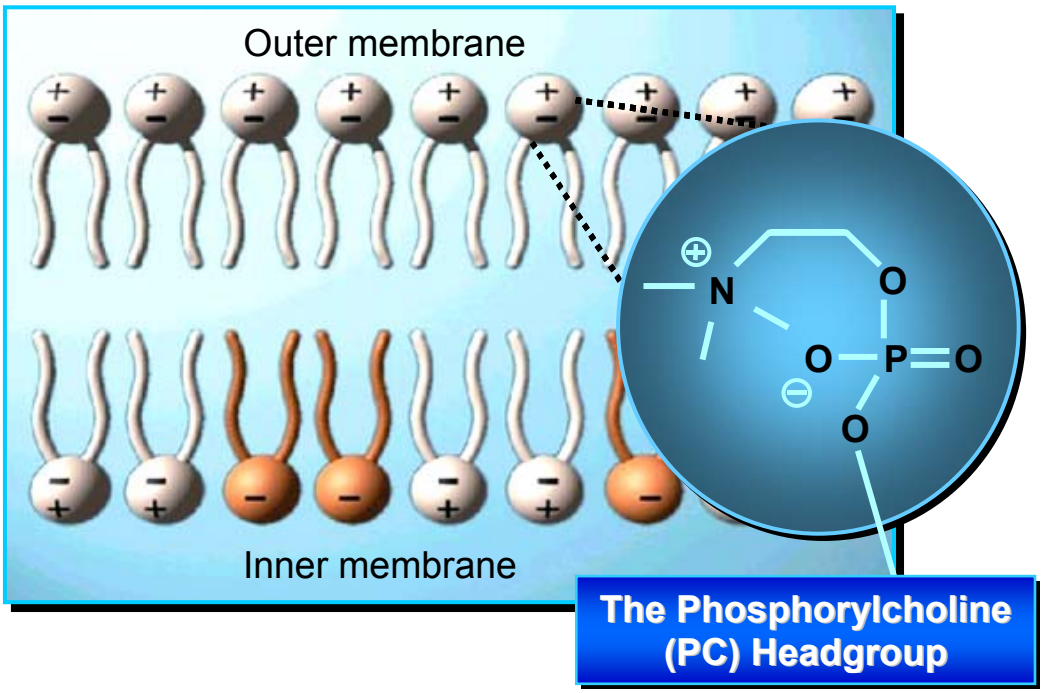

Figure 4-1: Graphical Depiction of Cell Membrane

PC polymer has been in use in Europe on coronary stents since 1997. The BiodivYsio PC coated stent was CE mark approved (Approval number: CE 02073) on September 4, 1998. PC-coated stents have also been in use since 2000 in the United States, marketed as the BiodivYsio™ as PC-Coated Stent and Delivery System (P000011, approved September 29, 2000). The BiodivYsio™ PC-coated stent has been successfully implanted worldwide in over 100,000 patients to date.[21,22,23,24,25,26,27] It has also been used in other medical implants where it has been shown to decrease thrombin formation on devices used for cardiac surgery [28] and to decrease platelet deposition when coated on

[21] Cumberland DC, et al. Biomimicry 1:PC. Seminars in Interventional Cardiology 1998 Sep-Dec; 3(3-4): 149-50.
[22] Kuiper KK, Robinson KA, Chronos NAF, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated metallic stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J 1998; 32(5): 261-268.
[23] Zheng H, Barragan P, Corcos T, Simeoni JB, Favereau X, Roquebert PO, et al. Clinical experience with a new biocompatible phosphorylcholine-coated coronary stent. J Invasive Cardiol; 1999 Oct; 11(10): 608-614.
[24] Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart 2000 Mar; 83(3): 338-345.
[25] Boland JL, Corbeij HAM, van der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, et al. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. Int J Cardiovasc Intervent 2000 Dec; 3(4): 215-225.
[26] Atalar E, Haznedaroglu I, Aytemir K, Aksoyek S, Ovonc K, Oto A, et al. Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation. Clin Cardiol 2001 Feb; 24(2): 159-164.
[27] Malik N, Gunn J, Shepherd L, Crossman D, Cumberland DC, Holt CM. Phosphorylcholine-coated stents in porcine coronary arteries: In-vivo assessment of biocompatibility. J Invasive Cardiol 2001 Mar; 13(3): 193-201.
[28] F. Pappalardo, P. D. Valle, G. Crescenzi, C. Corno, A. Franco, L. Torracca, O. Alfieri, L. Galli, A. Zangrillo, and A. D'Angelo Phosphorylcholine Coating May Limit Thrombin Formation During High-Risk Cardiac Surgery: A Randomized Controlled Trial Ann. Thorac. Surg., March 1, 2006; 81(3): 886 - 891.

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arteriovenous (AV) grafts.[29] Clinical investigations and *in-vivo* animal studies have shown that the polymer reduces thrombus formation and does not elicit inflammatory effect.[30,31,32,33,34,35,36] Animal data have also demonstrated that the Endeavor Zotarolimus-Eluting CSS with PC polymer has a low inflammation score of 0.1 and 0.6 similar to that of the BMS at 28 and 90 days post implant.[37] In concert, the above referenced clinical and *in-vitro* information available on the PC polymer, combined with the studies performed on the Endeavor Zotarolimus-Eluting CSS demonstrate that the polymer is biocompatible.

The Endeavor drug component, zotarolimus, is a tetrazole–containing macrocyclic immunosuppressant. The coating present on the Endeavor Zotarolimus-Eluting CSS is comprised of a base coating layer consisting of 100% PC polymer, followed by a zotarolimus and PC polymer matrix layer. A 100% PC polymer overspray is applied once the stent is mounted on the balloon. Coating layer thickness is greater on the abluminal side of the stent. A representative schematic is shown in Figure 4-3 (not to scale).

[29] Chen C, Ofenloch JC, Yianni YP, Hanson SR, Lumsden AB. Phosphorylcholine coating of ePTFE reduces platelet deposition and neointimal hyperplasia in arteriovenous grafts. J Surg Res 1998; 77: 119–125.
[30] Cumberland DC, et al. Biomimicry 1:PC. Seminars in Interventional Cardiology 1998 Sep-Dec; 3(3-4): 149-50.
[31] Kuiper KK, Robinson KA, Chronos NAF, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated metallic stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J 1998; 32(5): 261-268.
[32] Zheng H, Barragan P, Corcos T, Simeoni JB, Favereau X, Roquebert PO, et al. Clinical experience with a new biocompatible phosphorylcholine-coated coronary stent. J Invasive Cardiol; 1999 Oct; 11(10): 608-614.
[33] Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart 2000 Mar; 83(3): 338-345.
[34] Boland JL, Corbeij HAM, van der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, et al. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. Int J Cardiovasc Intervent 2000 Dec; 3(4): 215-225.
[35] Atalar E, Haznedaroglu I, Aytemir K, Aksoyek S, Ovonc K, Oto A, et al. Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation. Clin Cardiol 2001 Feb; 24(2): 159-164.
[36] Malik N, Gunn J, Shepherd L, Crossman D, Cumberland DC, Holt CM. Phosphorylcholine-coated stents in porcine coronary arteries: In-vivo assessment of biocompatibility. J Invasive Cardiol 2001 Mar; 13(3): 193-201.
[37] Virmani, R. "Past Predictions, Current Perspectives, Future Forecasts of Drug-Eluting Stents: View of the Pathologist." Presented at the: *EuroPCR Conference*; official annual meeting of the European Association of Percutaneous Cardiovascular Interventions (2006)

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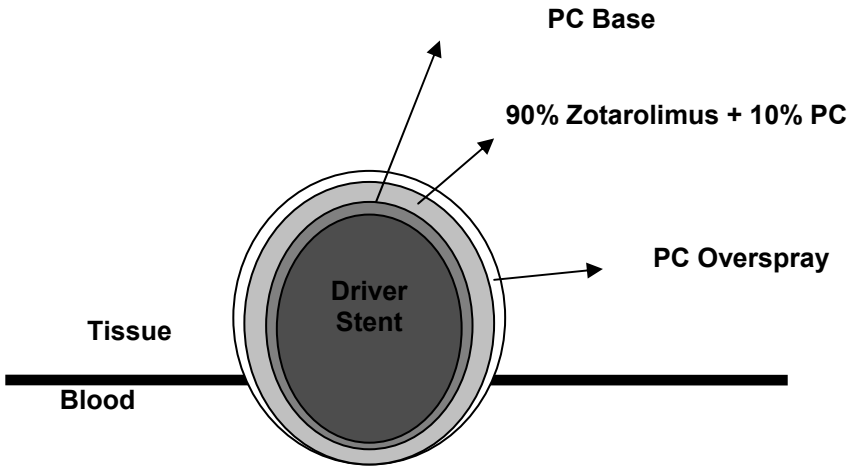

Figure 4-2: Cross Section of an Endeavor Stent Strut – a schematic (not to scale)

The relative thickness is such that the PC overspray is not a distinguishable layer. A scaled schematic of the various coating layers is provided in Figure 4-3.

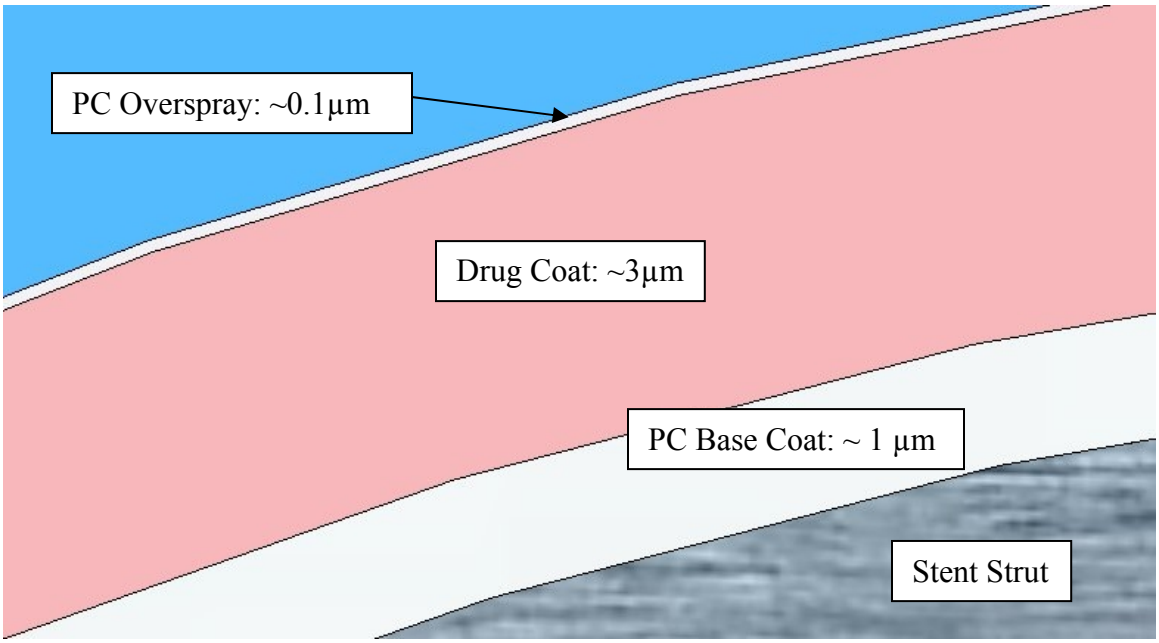

Figure 4-3: Schematic of Endeavor coatings, drawn to relative scale

The product matrix associated with this PMA application for the Endeavor Zotarolimus-Eluting OTW, RX and MX2 products is provided in Table 4-1, below:

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Table 4-1: The Endeavor Product Size Matrix

Diameter (mm)	Stent Length (mm)							
	8	9	12	14	15	18	24	30
2.5	✓	N/A	✓	✓	N/A	✓	✓	✓
3.0	N/A	✓	✓	N/A	✓	✓	✓	✓
3.5	N/A	✓	✓	N/A	✓	✓	✓	✓

4.3 Drug Substance (Zotarolimus)

The drug substance, zotarolimus, is utilized on the Endeavor Zotarolimus-Eluting Coronary Stent System (CSS) at a dose of 10µg/mm of stent length. Zotarolimus (also referred to as ABT-578) is supplied to Medtronic Vascular through a licensing agreement with Abbott Laboratories and is manufactured by

Zotarolimus, which was originally developed in 1997 as an immunosuppressant to treat rheumatoid arthritis, is a semi-synthetic tetrazole-containing molecule of the limus family. In 1998, zotarolimus had been identified as a potent smooth muscle cell inhibitor and recognized its potential for use as an active ingredient on a drug eluting stent. By 2001, animal studies had been performed that showed potential for the anti-proliferative mechanism of zotarolimus to be used in coronary stent applications. On the basis of review of these studies, Medtronic Vascular licensed the use of zotarolimus from Abbott Laboratories in 2002 for use in Endeavor Zotarolimus-Eluting CSS and other development projects. There are currently no oral or intravenous formulations of zotarolimus available.

A detailed description of the drug substance zotarolimus and its physicochemical characteristics is provided in Drug Master File (DMF) #16960 (submitted to FDA on Nov 14, 2003 by Abbott Laboratories). A summary of those physicochemical characteristics important to use of the drug substance in Endeavor Zotarolimus-Eluting CSS is provided in the following pages.

The mechanism of action of zotarolimus is to bind to the intracellular protein, FKBP12, leading to the formation of a trimeric complex with mTOR (mammalian target of rapamycin). The protein kinase activity of mTOR is thus inhibited which results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. The mechanism of action is graphically represented in Figure 4-4. *In vitro*, zotarolimus demonstrated binding affinity with FKBP-12 and potently inhibited growth factor-induced proliferation of human coronary artery smooth muscle cells.

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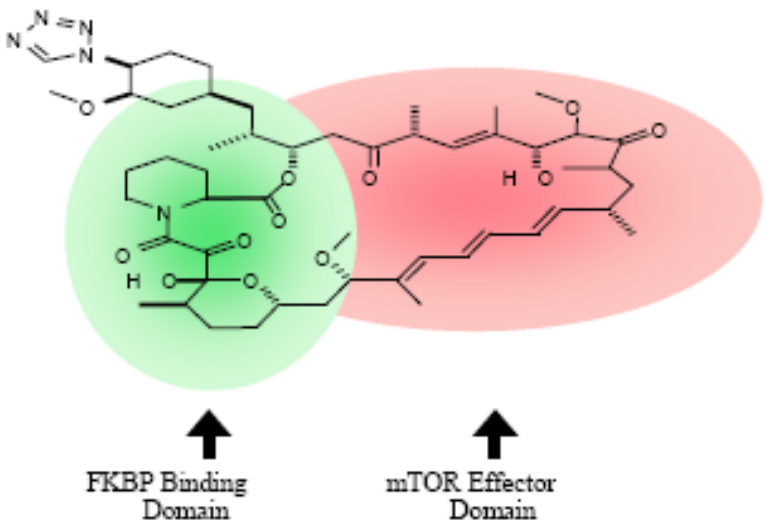

Figure 4-4: Suggested Mechanism of Action of Zotarolimus

Drugs of the limus family have been previously approved by FDA. For example, rapamycin (sirolimus) is the one limus drug approved for application on a drug eluting stent and is also approved as co-medication for renal transplant immunosuppression. Zotarolimus is a cytostatic cell cycle inhibitor that inhibits cells from entering the S phase of mitosis, as shown in Figure 4-5.

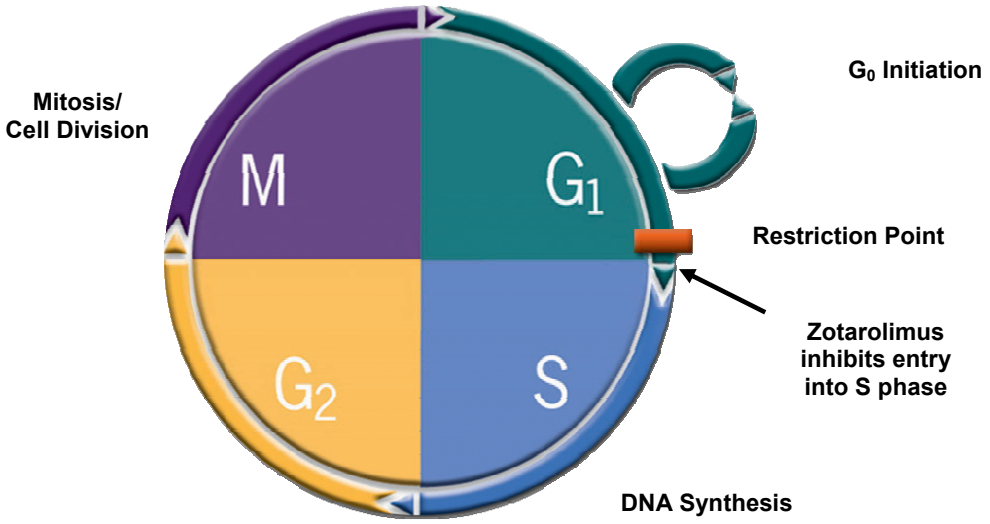

Figure 4-5: Cytostatic Cell Cycle Inhibition

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Table 4-2 below shows measures of lipophilicity and potency for the limus family of drugs involved in drug-eluting stent applications. The low nanomolar concentration in the tissue would indicate little anticipated difference in the tissue effect for the differences in IC50. Also of note, zotarolimus is highly protein bound in man, distributed to the whole blood with a red blood cell-to-plasma appropriation of 20:1. The drug is not available as an oral formulation and when administered via stent or IV formulation, is metabolized and excreted primarily by the liver. Radiolabel studies in several species including man confirm approximately 84% excretion through the liver and gut, with only approximately 6% by renal excretion.

Table 4-2: Lipophilicity and Potency of Limus Family Drugs

	Rapamycin	Zotarolimus
Lipophilicity	logD 3.6	logD >4.5
Potency	IC50 0.4nM	IC50 0.3nM

By replacing the hydrophilic hydroxyl group with a lipophilic tetrazole group, the drug substance zotarolimus becomes substantially more lipophilic than sirolimus, thereby increasing its tissue retention time. Although there has been a lot of focus on the elution curves associated with many drug eluting stents, the important measure is time in tissue discussed below.

Lipophilicity is demonstrated by very high octanol: water partition coefficient (>4.5 at pH 6.5 and pH 7.4), represented as follows:

$$\text{Log}_{10}D = \text{Log}_{10}P_{\text{octanol/pH 7.4 buffer}}$$
$$= > 4.5, \text{ indicative of high lipophilicity.}$$

The lipophilic properties of zotarolimus are thought to enhance absorption of the drug across the cellular membrane of target tissues. Limited water solubility (0.47 µg/ml at pH 6.5 and 0.53 µg/ml at pH7.4) is highly amenable to the design of a drug-coated stent, in that low water solubility may impede systemic distribution from the stent. In addition, the lipophilic character of zotarolimus may favor an ability to cross cell membranes to inhibit neointimal proliferation of target tissue and be retained in tissue longer than less lipophilic drugs. Consequently, despite the fact that zotarolimus elutes from the stent within 14 days, it remains in tissue at detectable levels up to 28 days. Reference Figure 4-6 and Figure 4-7 below for curves generated from studies of porcine drug elution kinetics and pharmacokinetics.

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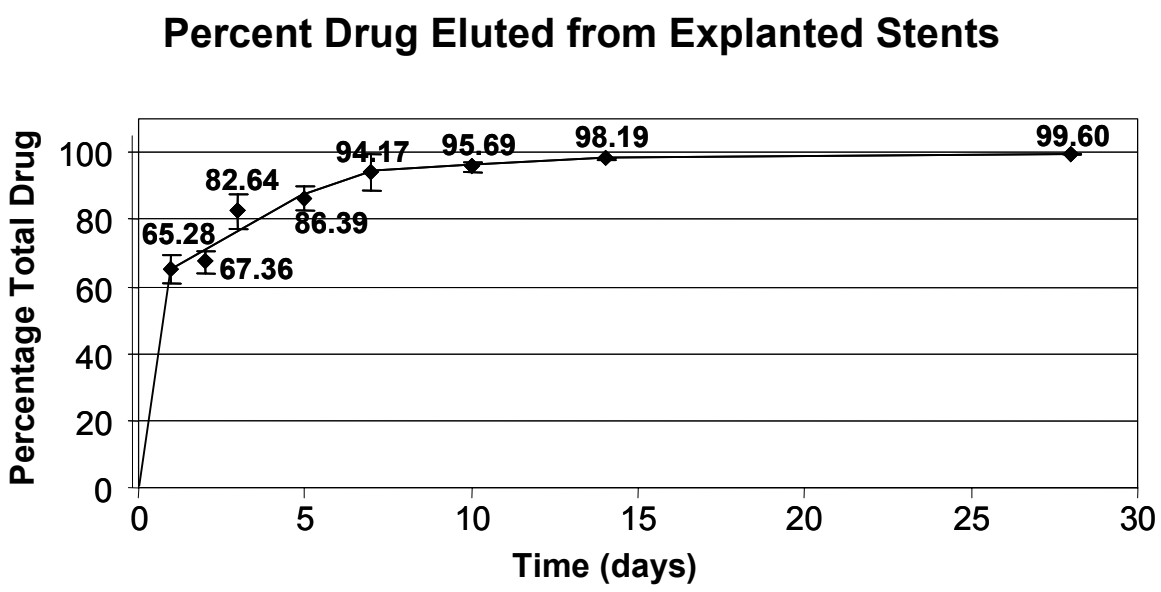

Figure 4-6: Percent Drug Eluted from Explanted Stents

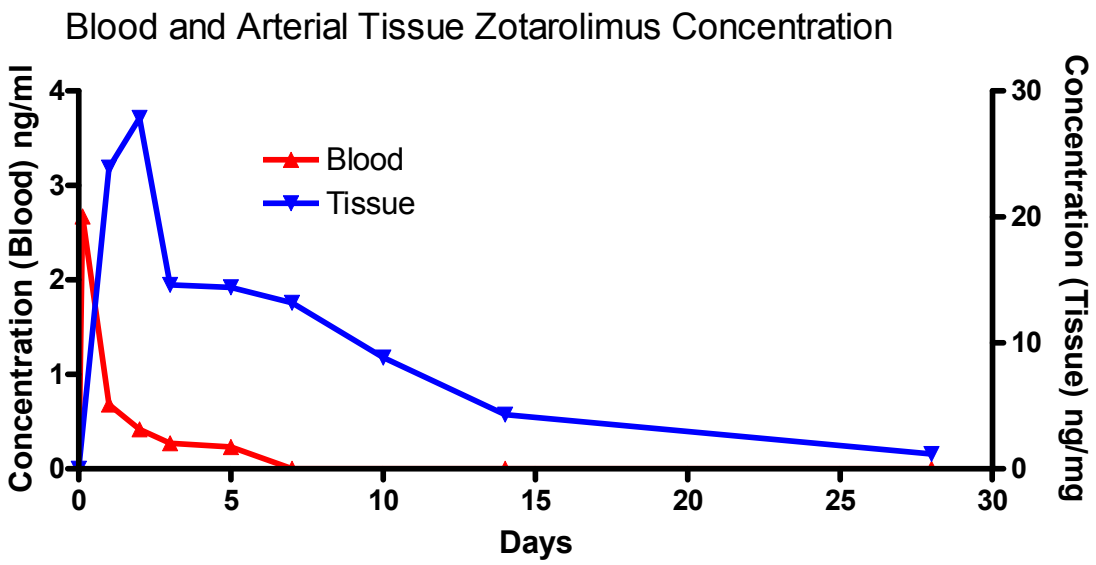

Figure 4-7 Blood and Arterial Tissue Zotarolimus Concentration

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4.3.1 Studies of the Drug Substance (Zotarolimus)

The standard ICH-required battery of tests for a new chemical entity were performed in the development of zotarolimus. Testing performed on the drug substance is appropriate to the duration and levels of exposure in the Endeavor product. The drug substance testing most relevant to the DES application includes: 1) toxicological studies across multiple species including primates to define the margins of safety to the drug substance; 2) definition of metabolic pathways (CYP3A4) with no evidence of the drug interfering with the CYP3A4 pathway and lack of amplification (less than 2x) with co-administered ketoconazole, hence low opportunity for drug to drug interactions; and 3) identification of the metabolites and routes of excretion using radiolabeled drug across species, including man. In addition, a study was conducted in which approximately 100-fold drug exposure above anticipated clinical levels demonstrated that there was no impact of zotarolimus on stimulated platelet aggregation. Hence, the potential for alteration of platelet adhesion and aggregation is low.

Table 4-3 provides a list of the *in vitro* and *in vivo* pharmacological studies conducted on zotarolimus to confirm mechanisms of action, potency, toxicological effects, and to characterize the drug substance.

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Table 4-3: Studies Supporting Zotarolimus Safety and Efficacy

Test	Test Strain	Administration
1. Mechanism and Interaction Studies		
FKBP-12 Affinity	PBMC, mice and rat-derived lymphocytes	in vitro
Concanavalin A-induced T-Cell Proliferation	PBMC, mice and rat-derived lymphocytes	in vitro
Mixed Lymphocyte Reaction	PBMC, mice and rat-derived lymphocytes	in vitro
Effect of PC-1036 on the Inhibition of IL-2 Secretion in Activated Human CD4+ T-Helper Cells	PBMC	in vitro
Effect on Human Platelet Function in Whole Blood	Human platelets	in vitro
Effect of BHT on Inhibition of Human Coronary Artery Smooth Muscle Cell Proliferation in Vitro	Human smooth muscle cells	in vitro
Comparative Potency in Inhibiting Human Coronary Artery Smooth Muscle Cell Proliferation	Human smooth muscle cells/endothelial cells	in vitro
Various Receptor Binding Assays	Radioligand binding method	in vitro
2. Pharmacological Safety Studies		
Effect on the Central Nervous System	SD rats	intravenous
Effect on the Central Nervous System	Wistar rats	oral
Effect on the Respiratory System	Wistar rats	intravenous
Cardiovascular functions/hematology tests (hematocrit)/body temperature	Wistar rats	intravenous
Cardiovascular functions/hematology tests/clinical chemistry tests	Wistar rats	intravenous
Cardiovascular functions (heart rate, blood pressure)	Wistar rats	intravenous
Effects on *HERG* Current	HEK293 cells	In vitro
Effects on Purkinje Fiber Repolarization	Beagles	In vitro

This standard battery of tests failed to demonstrate any concerns regarding cardiovascular, respiratory, or central nervous system effects.

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4.3.2 Toxicity Studies

Table 4-4 below list the toxicity and toxicokinetic evaluations conducted to support the safety of zotarolimus.

Table 4-4: Single and Repeat Dose Toxicity Assays, Reproductive Toxicity Assays, Genotoxicity and Other Assays

Test	Test Strain	Administration	Administration Period	Amount Administered (µg/kg)
Single Dose Administration Toxicity Assays	SD Rats	Intravenous	-	3, 8, 25, 75
	Cynomolgus Monkeys	Intravenous	-	8, 25, 75
Repeat Dose Administration Toxicity Assays	SD Rats	Intravenous	28 days	3, 8, 25
	SD Rats	Intravenous	28 days	10, 30, 100
	Cynomolgus Monkeys	Intravenous	28 days	3, 8, 25
	Cynomolgus Monkeys	Intravenous	28 days	10, 30, 100
Testicular Toxicity Assay	SD Rats	Intravenous	70 days	3, 10, 30, 100
Genotoxicity Assays	S.typhimurium/ E.coli	In Vitro	-	-S9: 33.3-5, 000µg/plate +S9: 33.3-5, 000µg/plate
			-	-S9: 50-5, 000µg/plate +S9: 50-5, 000µg/plate
	Human lymphocytes	In Vitro	-	-S9: 12.5-800µg/mL +S9: 12.5-800µg/mL
			-	-S9: 25-125µg/mL +S9: 25-125µg/mL
	CD-1 Mice	Intravenous	2 days	0.85, 1.7, 3.4
Reproductive Development Toxicity Assays	SD Rats	Intravenous	G6-17	10, 30, 100, 300
	NZW Rabbits	Intravenous	G7-19	10, 30, 100, 300
	SD Rats	Intravenous	28 days	30, 100, 300
	SD Rats	Intravenous	14 days	30, 100, 300
	SD Rats	Intravenous	G6-17	10, 25, 60
	NZW Rabbits	Intravenous	G7-19	10, 30, 100
Local Stimulus-induced Assays	Not conducted			
Other toxicity Assays Antigenicity Assays	Hartley Guinea Pigs	Subcutaneous	Weekly intervals, 4 times	15, 30
	CBA/J Mice	Applied	3 days	10, 25, 50%

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Based on the results of the studies listed above, zotarolimus was demonstrated to be safe for use as a coating on an implanted coronary stent.

4.3.3 ADME and Pharmacokinetic Testing

A number of studies were conducted to study the absorption, distribution, metabolism and excretion (ADME) of zotarolimus. Table 4-5 lists the ADME studies conducted, followed by a brief summary of some of the findings from these studies.

Table 4-5: ADME Studies Conducted on Zotarolimus

Test	Test Strain	Administration	Amount administered/ concentration of additive
1. Absorption			
1) Concentration in the blood for single dose administration	Mice/Rats	Intravenous/ oral	2.5mg/kg
	Rabbits	Intravenous	1mg/kg
	Pigs	Intravenous	1.0mg 1mg/kg
	Monkeys	Intravenous/ oral	2.5mg/kg • 1mg/kg
2. Distribution			
1) Histological Distribution	Rats	Intravenous	2.5mg/kg • 1mg/kg
	Rabbits	Intravenous	0.5mg/kg
2) Plasma Protein Binding	Rabbits/Dogs/Pigs/Humans	in vitro	300, 3, 000ng/mL
	Mice/Rats/ Dogs /Monkeys/ Humans	in vitro	10, 25, 50, 100, 500, 1, 000ng/mL*
	Humans/HSA binding/AAG binding	in vitro	10, 25, 50, 100, 500, 1, 000ng/mL
3) Transition to Blood Cells	Humans	in vitro	1, 5, 10, 50, 100, 1, 000ng/mL
3. Metabolism			
1) Metabolites in the blood and plasma	Rats	Intravenous	2.5mg/kg • 1mg/kg
	Rabbits		0.5mg/kg
	Pigs/Monkeys		1mg/kg
	Humans		0.8mg
2) Metabolites in the urine and feces	Rats/Pigs/Monkeys	Intravenous	1mg/kg
	Humans		0.8mg
3) Metabolism in Hepatocytes	Rats/Dogs/Monkeys/Humans	in vitro	5μM (4, 831ng/mL)
4) Metabolism in Liver Microsomes	Humans	in vitro	5μM • 10μmol/L
5) Cytochrome P450 Inhibition	Humans	in vitro	66-6, 645ng/mL• 50-5, 000ng/mL
6) Study of the Metabolic	Humans	in vitro	25μM

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Table 4-5: ADME Studies Conducted on Zotarolimus

Test	Test Strain	Administration	Amount administered/ concentration of additive
Pathway			
4. Excretion			
1) Excretion in the urine and feces	Rats	Intravenous	2.5mg/kg • 1mg/kg
	Rabbits		0.5mg/kg
	Monkeys		1mg/kg
2) Excretion in the bile	Rats	Intravenous	2.5mg/kg
5. Pharmacokinetic Drug-to-Drug Interactions			
Pharmacokinetics of combined used with Ketoconazole	Dogs	Intravenous Oral (Ketoconazole)	2.5mg/kg 35mg x 2 times/day drug combined with (Ketoconazole)
6.Other Assays			
Assay to Study 28-day Elution from Stents	Rabbit Illiac Arteries	in vivo	10μg/mm

The absorption following single dose intravenous administration of zotarolimus to mice, rats and monkeys was rapid and the maximum blood drug concentration was observed within one hour following administration.

The mean blood-to-plasma ratio of concentration following single dose intravenous administration of ^{3}H-labeled zotarolimus to monkeys and swine increased, indicating a substantial amount of radioactivity bonds with the blood cell component.

The assay to study the protein-binding of zotarolimus in the plasma of mice, rats, dogs and humans suggested that a clinical concentration (less than 25 ng/mL) of zotarolimus has a protein-binding affinity of 97% or more in human plasma. While zotarolimus exhibited a high binding affinity to HSA and AAG, it binds to a greater extent with blood cells (the *in vivo* blood-to-plasma ratio is 20:1). Therefore, the drug-protein interaction with HSA and AAG is not considered to have a significant effect on the systemic concentration of circulating zotarolimus from a clinical standpoint.

The mean zotarolimus blood concentration time profile following IV-bolus administration is at least biphasic, with the terminal phase becoming evident after the distribution phase at about 8 hours post-administration. Zotarolimus is distributed to a greater extent in the cellular fraction of the whole blood than in plasma and is extensively bound to plasma proteins in healthy subjects.

Metabolism is oxidative in the liver, and enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities; however, the IC50 values (3 μM and above) are many fold higher than the systemic concentrations following stent implantation, and the

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potential for interaction with co-administered drugs is low. Co-administration with ketaconazole demonstrates little amplification of the zotarolimus exposure as a result of ketakonazole inhibition of zotarolimus metabolism through the CYP3A4 pathway. In two different species, the increase in zotarolimus exposure is less than two fold (less than the five-fold or greater amplification usually associated with a significant effect).

Following IV infusion of [^{3}H] zotarolimus, the majority of the circulating activity was due to the parent drug as the profiling of the blood samples showed metabolites contributing no more than 0.2%. These results suggest that following an IV dose, zotarolimus is taken up and bound by the blood cells with little free drug available. This binding and the subsequent slow release of the zotarolimus into the plasma over time appear to prevent rapid metabolism.

Elimination of [^{3}H] zotarolimus through the urine was about 6% of the dose (Study M03-646) over 216 hours after IV administration and about 82% in the feces over 288 hours. Over the course of the study (288 hours), 88% of administered radioactivity was accounted for. Dose proportionality assessments were made for single and multiple IV doses of zotarolimus in these Phase 1 studies.

Overall, these studies indicate that the pharmacokinetics of zotarolimus are essentially dose proportional over the single dose range of 100 to 900 µg and 14-day QD multiple dose range of 200 to 800 µg. Additionally, zotarolimus pharmacokinetics are time linear over the studied 14-day QD multiple dose range of 200 to 800 µg. Clearance showed a difference between IV-bolus and IV-infusion administration and was partly due to zotarolimus adsorption (9-12%) to the infusion sets during IV infusion and could partly be due to the difference in the rate at which the drug is sequestered in blood cells following administration.

4.3.4 Clinical Studies of the Drug Substance

Single and repeat dose administration assays were conducted to evaluate the safety, tolerability and pharmacokinetics of intravenous administration of zotarolimus in healthy subjects. Administration doses were selected based on the anticipated stent dosage (10µg/mm) and the results of the animal safety testing. Dose escalation was performed with subject safety a priority. Dosing began at the lowest dosage, and dose administration followed only after safety was confirmed at the previous dose, consistent with most early pK studies in man. The drug is formulated with propylene glycol with World Health Organization (WHO) limits to the maximum amount to be administered daily. The single dose administration given was to the maximum allowable dose per day based on these WHO and ethics committee guidelines. The subsequent multiple dose study included a dose that was slightly under the maximum daily limits for the 14 days of multiple infusions.

The safety and pharmacokinetics of intravenous zotarolimus administration have been investigated in four Phase 1 studies.

Study M01-336 was a randomized, double-blind placebo controlled study, to evaluate the safety, tolerability and pharmacokinetics of IV bolus doses of zotarolimus from 100 to 900 µg administered to 40 of 60 healthy adult male subjects. The study concluded that there were no apparent differences among the doses with regard to safety and no serious

adverse events. The treatment emergent adverse events included mostly injection site complaints with the rapid bolus injection of a very high osmolality drug solution.

Because of the issues with the formulation of the drug and the injection site complaints, the multidose study below allowed for a push of the drug through a side branch arm to the IV given slowly, over an hour. This avoided many of the complaints associated with the rapid injection of the drug in the single dose rapid bolus administration. Because of the high lipophilicity, high osmolality, and formulation issues, the subsequent set of studies mandated careful planning for data collection and avoidance of IV formation-related issues.

Study M02-501 was a randomized, double-blind, placebo controlled study to evaluate the safety, tolerability, pharmacokinetics, potential immunosuppressive and QT effects of zotarolimus. Fourteen consecutive days of IV dosing with zotarolimus included doses of 200, 400 and 800 µg administered over by IV side branch injection over 1 hour in 48 of 72 healthy adult subjects. There were no deaths or other serious adverse events. Results of other safety analyses including individual values for vital signs, laboratory safety assessments and physical exams were unremarkable for each treatment group. Additionally, the proportion of subjects reporting treatment-emergent adverse events was similar among the zotarolimus and placebo groups with no statistically significant mean differences seen related to QT_c interval prolongation between the 800 µg dose group and placebo. Additionally, there were no significant trends found related to dose on either Study Day 1 or 14 and no positive correlation between changes from baseline QT_c interval with the individualized correction method and plasma concentration of zotarolimus. The study confirmed the pharmacokinetics of zotarolimus seen in the single dose study, providing predictable kinetics with linear and dose-proportional findings. The multiple dose also confirmed the steady state achievement at day 10 of daily dosing. In addition and in general, all evaluated immunological markers showed unremarkable differences in treatment groups as compared to placebo over time. The study report indicates the drug does not appear to affect the immunocompetency of the healthy subjects over the studied doses and over the study period (44 days), a conclusion supported by the absence of any clinical connection.

The two pharmacokinetic studies above provide the bulk of the human exposure of the drug substance not associated with the stent drug combination product known as Endeavor. This exposure provides the basis for the kinetics of the drug, also confirmed with drug/stent elution pharmacokinetics and gives the basis for the calculation of the systemic drug exposure margins of safety. The Cmax achieved with the single bolus dose provided the highest Cmax and is approximately 25-fold the exposure anticipated in patients with 48 mm of stent length. In addition, the prolonged daily exposure in the multiple dose study provides human AUC exposure margins of approximately 15-fold for 48 mm of stent length.

Study M03-646 was a single-dose, open-label study investigated the disposition of [^{3}H] zotarolimus in 5 healthy adult male subjects. One subject received a single 3-minute IV bolus of 800 µg (200 µg/mL) and four subjects received a single 60-minute infusion of 800 µg (200 µg/mL) of [^{3}H]- zotarolimus. The results demonstrated that the dosing regimen was generally well tolerated. Two subjects reported adverse events including one severe reaction that was vasovagal in origin and possibly related to study drug.

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Concentrations of total blood radioactivity measured in this study were similar to zotarolimus concentrations in previous Phase 1 studies. A comparison of the plasma and blood concentrations indicates an association of the radiolabel with red blood cells. Total radioactivity was quantitatively recovered and slowly eliminated in the urine and feces over the collection period, with the main route of excretion via the feces, with limited renal excretion (6%), and little drug not ultimately accounted for.

Study M03-653 was a sequential, single dose, open-label study conducted in 18 healthy adult subjects to evaluate the effect of the CYP3A inhibitor, ketoconazole on the pharmacokinetics of zotarolimus (which is metabolized by CYP3A4) and to assess the safety and tolerability of zotarolimus (400 µg via 60-minute infusion on Days 1 and 10) when co-administered with ketoconazole (200 mg orally BID on Study Days 6-14). The results indicated that zotarolimus alone and administered with ketoconazole were generally well tolerated. No deaths or other serious adverse events were reported. Seven of 18 subjects (39%) reported at least one treatment-emergent event, the most common (reported in two or more subjects) were headache and sore throat. The zotarolimus exposure when co-administered with ketoconazole was amplified less than two-fold and did not reflect a significant drug-to-drug interaction.

In summary, among all subjects who participated in the four Phase 1 studies using zotarolimus, no clinical or biochemical evidence of immunosuppression or clinically significant electrocardiographic findings were found. Additionally, the most commonly experienced treatment-emergent adverse events among zotarolimus treated subjects were injection site reaction, pain and headache. The percentages of subjects reporting adverse events were similar between those receiving zotarolimus and those receiving placebo. The majority of the adverse events in the four clinical pharmacology studies were mild to moderate in severity. The studies characterized the drug's linear and dose proportional kinetics, provided margins of safety for a 48 mm stent, and confirmed the lack of significant drug exposure amplification with co-administered drugs metabolized through the CYP3A4 path. Many cardiovascular drugs are metabolized through the same pathway and the data indicate the minimal potential for interaction toxicity.

The combination of *in vitro*, *in vivo* animal and human studies confirm the drug ADME, toxicology and kinetics and characterize the molecule, zotarolimus.

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4.4 Endeavor Non-Clinical Studies

A series of non-clinical laboratory studies were performed, pertaining to the stent and the stent delivery system (i.e. the stent mounted on either the Endeavor OTW, RX and MX^2 stent delivery system), the polymer substance [i.e., Phosphorylcholine (PC)], the drug substance (i.e., zotarolimus), and the finished combination product (i.e., Endeavor Zotarolimus-Eluting CSS). Following is a listing of the non-clinical design verification testing performed.

Table 4-6: Overview of Non-Clinical Testing

	Test	Description
Functional Design Verification and Shelf Life Testing	Material Characterization	Material characterization of the Endeavor bare metal stent and delivery system components per FDA January 13, 2005 Guidance (Part A)
	Stent Dimensional and Functional Attributes	Evaluation of Endeavor stent dimensional and functional attributes per FDA January 13, 2005 Guidance (Part B)
	Delivery System Dimensional and Functional Attributes	Evaluation of Endeavor delivery system dimensional and functional attributes per FDA January 13, 2005 Guidance (Part C)
	Functional and Dimensional Shelf life Testing	Evaluation of the Endeavor stent and delivery system Functional and Dimensional attributes post aging
Analytical/ Coating Integrity and Stability Testing	Drug Coating Integrity and Analytical Testing	Evaluation of the analytical and coating integrity attributes of the Endeavor stent per FDA January 13, 2005 Guidance
	Stability Testing	Evaluation of the analytical and coating integrity attributes of the Endeavor stent and integrity of the primary packaging per ICH Q1A
Elution	Elution Method Development	Elution Assay was developed to measure the *in vitro* release kinetics of zotarolimus from the Endeavor stent system
Packaging Integrity	Packaging Integrity Testing	Evaluation of packaging integrity per ISO 11607

The following standards and guidance documents were considered in the development of test plans used in non-clinical testing of the Endeavor Zotarolimus-Eluting CSS. Appropriate rationales are provided to justify any deviations from testing standards or guidance listed.

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Table 4-7: Guidance Documents Considered

Guidance for Industry and FDA staff:	Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, January 2005
Guidance for Industry:	SUPAC-MR: Modified Release Solid Oral Dosage Forms. Scale-UP and Postapproval Changes: Chemistry. Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997
ICH Q1A (R2)	Stability testing of new drug substances and product, ICH August 2001
ICH Q1B	Photostability Testing of New Drug Substances and Products, November 1996
ICH Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, January 2003
ICH Q1E	Evaluation of Stability Data, June 2004
ICH Q2A	Text on Validation of Analytical Procedures, March 1995
ICH Q2B	Validation of Analytical Procedures: Methodology, May 1997
ICH Q3B(R)	Impurities in New Drug Products (Revision 2), August 2006
ICH Q3C	Impurities: Residual Solvents, December 1997
ICH Q6A	International Conference on Harmonization; Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, December 2000
FDA CDER Guidance for Industry	Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997
FDA CDER Guidance for Industry	Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations, September 1997
FDA CDER Guidance for Industry	Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, March 2003
Guidance for Industry:	Statistical Approaches to Establish Bioequivalence, January 2001
21 CFR §58	FDA Good Laboratory Practices (GLP) regulations
Guideline	FDA Guideline on Validation of the Limulus Amebocyte Lysate test as an end –product Endotoxin test for human and animal parenteral drugs, biological products and medical devices, December 1987

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Table 4-8: Product Standards

ASTM E8	Standard Test Methods for Tension Testing of Metallic Materials, April 2004
ASTM E112	Standard Test Methods for Determining Average Grain Size, November 2004
ASTM E384	Microindentation Hardness of Materials, August 2005
ASTM F562	Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy (UNS R30035), April 2002
ASTM F688	Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy Plate, Sheet, and Foil for Surgical Implants (UNS R30035), August 2005
ASTM E45	Inclusion content in steel, November 2005
ASTM F2052	Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment, March 2006
ASTM F2119	Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants, June 2001
ASTM F2182	Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging, November 2002
ASTM F2213	Standard Test Method for Measurement of Magnetically Induced Torque on Passive Implants in the Magnetic Resonance Environment, May 2006
ASTM F2129	Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices, May 2006
ASTM F746	Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials, October 2004
ASTM G71	Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes, October 2003
ASTM F2079	Standard Test Method for Measuring Intrinsic Elastic Recoil of Balloon-Expandable Stents, January 2001
ASTM F2081	Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents, September 2006
EN 14299	Non Active Surgical Implants-Particular Requirements for Cardiac and Vascular Implants-Specific Requirements for Arterial Stents, August 2004
ISO 10555-1	Sterile, Single – Use Intravascular Catheters, General Requirements, July 2005

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Table 4-9: Packaging Standards

EN 868	Packaging Materials and Systems for Medical Devices which are to be sterilised, August 1999
ANSI/AAMI/ISO 11607	Packaging for Terminally Sterilized Medical Devices, July 2004
ASTM D3985	Oxygen Gas Transmission Rate Through Plastic Film and Sheeting using a Coulometric Sensor, June 2005
ASTM D4169	Practice for Performance Testing of Shipping Containers and Systems, October 2005
ASTM D6653	Test Method for Determining Effects of High Altitude on Packaging Systems by Vacuum Method, April 2001
ASTM F88	Test Method for Seal Strength of Flexible Barrier Materials, April 2006
ASTM F1249	Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor, June 2006
ASTM F1980	Standard Guide for Accelerated Aging of Sterile Medical Device Packages, January 2002
ASTM F2096	Test method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test), April 2004
ASTM D4332	Practice for Conditioning Containers, Packages, or Packaging Components for Testing, April 2001
ASTM D999	Standard Test Method for Vibration Testing of Shipping Containers, April 2001
ASTM F1929	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration, November 1998
ASTM D5276	Test Method for Drop Test of Loaded Containers by Free Fall, April 1998
ASTM D642	Test Method for Determining Compression Resistance of Shipping Containers, Components, and Unit Loads, June 1994
ASTM D4728	Test Method for Random Vibration Testing of Shipping Containers, April 2001

Table 4-10: Labelling Standards

EN980	Graphical Symbols for Use in the Labeling of Medical Devices, September 2006
EN 1041	Terminology, Symbols and Information provided with Medical Devices – Information supplied by the Manufacturer with Medical Devices, April 1998
ISO15223	Medical Devices – Symbols to be used with Labels, Labelling and Information to be Supplied, April 2000
ASTM F2503	Standard Practice for Marketing Medical Devices and Other Items for Safety in the Magnetic Resonance Environment, August 2005

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Table 4-11: Biocompatibility Standards

ISO10993-01	Biological Evaluation of Medical Devices, October 1997
ISO10993-01	Biological Evaluation of Medical Devices, August 2003
Blue Book Memorandum G95-1	Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices, May 1995

Table 4-12: Sterilization Standards

EN550	Sterilization of medical devices- validation and routine control of ethylene oxide sterilization of health care products – Requirements for validation and routine control – EtO sterilization, November 1994
EN556-1 2002 + A1 2002	Sterilization of Medical devices-Requirements for Medical Devices to be designated “Sterile” – Part 1: Requirements for terminally sterilized medical devices, 2002
ISO 11138-1	Sterilization of Health care products – Biological Indicators – Part 1: General, October 1994
ISO 11138-2	Sterilization of Health care products – Biological Indicators – Part 2: Biological Indicators for Ethylene Oxide Sterilization, October 1994
ISO 11135	Medical Devices – validation and routine control of ethylene oxide sterilization, February 1994
ISO 11737-1	Sterilization of health care products – Microbiological methods – Part 1: Estimation of population of micro-organisms on products, August 2006
ISO 11737-2	Sterilization of health care products – Microbiological methods – Part 2: Tests of sterility performed in the validation of a sterilization process, July 1998
ISO10993-7	Biological evaluation of medical devices- Ethylene oxide sterilization residuals, October 1995
USP 29	United States Pharmacopoeia 29 – National Formulary 24, 2006
EP 2005	European Pharmacopoeia 5th edition, January 2005
AAMI/ST72	Bacterial Endotoxins – Test methodologies, routine monitoring and alternatives to batch testing, September 2002
AAMI TIR19	Guidance for ANSI/AAMI/ISO 10993-7 1995. Biological Evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals, 1998/ A1:1998
ANSI/AAMI TIR No. 15	Ethylene oxide sterilization equipment, process considerations, and pertinent calculations, 1997
AAMI TIR14	Contract Sterilisation for Ethylene Oxide, 1997/ A1:2004
AAMI TIR16: 2000	Process Development and Performance Qualification for Ethylene Oxide sterilisation – Microbiological aspects, March 2000

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Table 4-12: Sterilization Standards

EN886-1	Biological Systems for testing sterilizers and sterilization processes- Part 1 – General requirements, November 1997
ISO10993-7	Biological evaluation of medical devices- Ethylene oxide sterilization residuals, October 1995

4.4.1 Biocompatibility Studies

A series of GLP biocompatibility tests and USP Physicochemical tests were conducted to demonstrate that the components of the Endeavor Zotarolimus-Eluting Coronary Stent System (OTW, RX and MX^2) are non-toxic. Tests were conducted on ethylene oxide-sterilized Endeavor coated stents, stent delivery systems (finished product) and polymer-only coated stainless steel (SS) coupons. These test articles were processed in the same manner as the finished Endeavor product. The polymer only coated coupons did not include drug substance but were manufactured to simulate the processing of Endeavor stents with equivalent surface treatment, cross-linking and sterilization processes utilized. In all of these test systems, the materials were non-reactive and met all acceptance criteria. The results of the biocompatibility studies indicated that the Endeavor Zotarolimus-Eluting CSS was biologically safe and acceptable for clinical use.

Table 4-13: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Cytotoxicity	ISO 10993-5: *In Vitro* Cytotoxicity (L929 MEM Elution)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-cytotoxic)
Pyrogenicity	ISO-10993-11: Systemic Toxicity (Material Mediated Rabbit, Injection)	• Endeavor stent and delivery systems	Pass (non-pyrogenic)
Sensitization	ISO-10993-10: Sensitization (Guinea pig Maximization)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-sensitizing)
Acute Intracutaneous Reactivity	ISO-10993-10: Irritation (Injection)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non- irritant)
Acute Systemic Toxicity	ISO-10993-11: Systemic Toxicity (Acute)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-toxic)
Hemocompatability	ISO-10993-4: *In Vivo* Thromboresistance	• Endeavor stent and delivery systems	Pass (non-thrombogenic)
	ISO-10993-4: C3a Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)

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Table 4-13: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Hemocompatability	ISO-10993-4: SC5b9 Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)
	ISO-10993-4: Plasma Recalcification	• Endeavor stent and delivery systems	Pass (no significant change in coagulation time)
	ISO-10993-4: *In Vitro* Hemolysis Study	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-hemolytic)
	ISO-10993-4: White Blood Cell Morphology	• Endeavor stent and delivery systems	Pass (no change in WBC morphologically)
Genotoxicity	ISO-10993-3: Bacterial Reverse Mutation (AMES)	• Endeavor stent	Pass (non-mutagenic)
	ISO-10993-3: *In Vitro* Chromosomal Aberration in Mammalian Cells	• Endeavor stent	Pass (non-clastogenic)
	ISO-10993-3: *In Vivo* Mouse Bone Marrow Micronucleus Test	• Endeavor stent	Pass (non-mutagenic)
Material Characterization (USP Physicochemical Testing)	USP Physicochemical Extracts <661> (Aqueous)	• Balloon Material • Polyethylene Sheath • PC Polymer-only Coated Coupons	Pass

4.4.2 Pre-clinical Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials; therefore, a series of animal studies were conducted to evaluate safety, proof of concept and overall product performance.

Medtronic Vascular conducted a series of animal studies evaluating a variety of Zotarolimus-Eluting stent formulations (e.g., various drug dosages), polymer-coated control stents and/or bare metal control stents. These studies were conducted in coronary arteries of pigs, or iliac arteries of rabbits. Data from these studies served as the basis for the dose selection for the Endeavor Zotarolimus-Eluting CSS used in the Endeavor clinical studies.

The intravascular safety and biocompatibility of zotarolimus-eluting stents were evaluated in a series of animal studies in a porcine model of stent mediated vascular injury. Time points evaluated include 7, 28, 90, and 180 days. In addition, drug content was evaluated at 1, 2, 3, 5, 7, 10, 14 and 28 days. All study phases (feasibility, safety,

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pharmacokinetic and acute) are represented by studies that were conducted in accordance with § 21CFR 58 (Good Laboratory Practices), except where noted and the methods described by the Schwartz et al article entitled "*Drug-Eluting Stents in Preclinical Studies – Recommended Evaluation from a Consensus Group*."[38] The results of these studies support the safety and biocompatibility of the Endeavor Zotarolimus-Eluting CSS. Summaries of the major animal studies performed to support product safety are included in Table 4-14 below.

[38] Schwartz RS, Edelman ER, Carter A, Chronos N, Rogers C, Robinson KA, Waksman R, Weinberger J, Wilensky RL, Jensen DN, Zuckerman BD, Virmani R; Consensus Committee. Drug-eluting stents in preclinical studies: recommended evaluation from a consensus group. Circulation. 2002 Oct 1;106:1867-1873.

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS102	Test Article: Zotarolimus-eluting Endeavor stent, 5 and 10 µg/mm doses Control: BMS* GLP: Yes	Diameter: 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control: 15 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control	Test: 32 Control: 20	7 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Cell proliferation Acute delivery
FS135	Test Article: Zotarolimus-eluting Endeavor stent, 10 and 30 µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.25, 2.5mm Lengths: 8 mm	Juvenile Yorkshire Swine Test and Control: 21 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 24 Control: 20 Control (Polymer Coated Stents): 12	28 days	Angiographic patency Histologic and histomorphometric evaluation Acute Delivery Chronic vascular response at 28 days
FS99	Test Article: Zotarolimus-eluting Endeavor stent, 1, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control : 51 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 99 Control: 64 Control (Polymer Coated Stents): 13	28 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 28 days

* BMS = bare metal stent – Driver for these studies.

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS100	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 31 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 58 Control: 43 Control (Polymer Coated Stents): 9	90 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 90 days
FS101	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 30 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 55 Control: 40 Control (Polymer Coated Stents): 11	180 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 180 days
FS114	Test Article: Zotarolimus-eluting Endeavor stent 10µg/mm dose GLP: Yes	Diameter: 3.0mm Lengths: 12mm	Domestic Swine (LAD, LCX, RCA) One stent per vessel.	48	1, 2, 3, 5, 7, 10, 14 and 28 days	Evaluation of drug release rate, arterial drug levels & systemic drug levels over time.
FS102	Test Article: Zotarolimus-eluting Endeavor stent 5 and 10 µg/mm doses Control: BMS* GLP: Yes	Diameter: 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control: 15 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control	Test: 32 Control: 20	7 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Cell proliferation Acute delivery

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS135	Test Article: Zotarolimus-eluting Endeavor stent, 10 and 30 µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.25, 2.5mm Lengths: 8 mm	Juvenile Yorkshire Swine Test and Control: 21 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 24 Control: 20 Control (Polymer Coated Stents): 12	28 days	Angiographic patency Histologic and histomorphometric evaluation Acute Delivery Chronic vascular response at 28 days
FS99	Test Article: Zotarolimus-eluting Endeavor stent, 1, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12, 18 mm	Domestic Swine Test and Control : 51 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 99 Control: 64 Control (Polymer Coated Stents): 13	28 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 28 days
FS100	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents GLP: Yes	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 31 (LAD, LCX, RCA) Single and overlapping stents Animals received both test and control.	Test: 58 Control: 43 Control (Polymer Coated Stents): 9	90 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 90 days
FS101	Test Article: Zotarolimus-eluting Endeavor stent, 5, 10 and 30µg/mm doses Control: BMS* and Polymer only coated stents	Diameter: 2.5, 3.0, 3.5, 4.0 mm Lengths: 12mm	Yucatan Miniswine Test & Control: 30 (LAD, LCX, RCA) Single and overlapping stents	Test: 55 Control: 40 Control (Polymer Coated Stents): 11	180 days	Angiographic patency Histologic and histomorphometric evaluation of single and overlapping stents Acute Delivery Chronic vascular response at 180

Table 4-14: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
	GLP: Yes		Animals received both test and control.			days
FS114	Test Article: Zotarolimus-eluting Endeavor stent 10µg/mm dose GLP: Yes	Diameter: 3.0mm Lengths: 12mm	Domestic Swine (LAD, LCX, RCA) One stent per vessel.	48	1, 2, 3, 5, 7, 10, 14 and 28 days	Evaluation of drug release rate, arterial drug levels & systemic drug levels over time.

*BMS = bare metal stent – Driver for these studies.

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Toxicity

The systemic toxicity of the intact Endeavor Zotarolimus-Eluting Coronary Stent System has been investigated in a number of studies that were intended principally to define the local tolerance and healing response to the implanted Endeavor Zotarolimus-Eluting Coronary Stent System (Studies FS97, FS99, FS100, FS101, FS102, FS110, FS124 and FS135). In these studies, animal survival, body weights, body temperature, total blood counts, liver function tests, serum creatinine, cholesterol, and triglycerides were evaluated before and at varying times (7, 28, 90, and 180 days) after implantation of stents. Also, animals were subject to complete necropsies at 7, 28, 90, and 180 days after stent implantation and in Studies FS99, FS100, FS101, FS107, FS124 and FS135, sections of spleen, liver, kidneys, and/or lungs were examined histopathologically.

All of the rabbits (n=45) and 206 out of 209 of the swine that were implanted with stents survived for the duration of the studies (Studies FS97, FS99, FS100, FS101, FS102, FS107, FS110, FS114, FS124 and FS135). A total of three deaths occurred in these studies. Two swine that died 24 hours after implantation were from the polymer group in FS100 and in the Endeavor 30ug/mm dose group from FS124. In addition, one pig in FS124 was euthanized at day 20 from the polymer group due to a respiratory infection. Necropsy and careful examination of the organs, including the heart from the spontaneous deaths revealed no obvious cause for these events. The stents in these animals had deployed successfully and the hearts showed no abnormalities. Consequently, these deaths are believed to be due to non-stent-related issues.

Body weight data, clinical laboratory measurements, necropsies, and histopathological examination of selected tissues from the animals implanted with stents demonstrated only infrequent adverse systemic effects and no effects that could be attributed to stent implantation. Furthermore, since animals were each implanted with both control bare Driver stents and one or more Endeavor Zotarolimus-Eluting Coronary Stent Systems, it was not possible to distinguish effects due to the product that is the subject of this submission (the Endeavor Zotarolimus-Eluting Coronary Stent System) or its comparator (the Driver stent). Overall, however, implantation of single or overlapped Driver and Endeavor Zotarolimus-Eluting Coronary Stent Systems (with zotarolimus coating doses as high as 30 µg/mm) yielded no significant adverse systemic effects.

Pharmacodynamics

Multiple considerations were applied during the finalization of the optimal dose. Medtronic's selection of dose was based upon measurement of drug concentration in tissue, pharmacological activity of zotarolimus on smooth muscle cells level *in vitro* and *in vivo*, and a documented inhibition of porcine neointimal responses.

In vivo drug concentration and in vitro SMC studies
Medtronic has determined *in vivo* that the average arterial concentration of zotarolimus at 28 days post-stenting with a dose of 10 µg/mm is 1.18 ng/mg tissue (1180 ng/ml assuming 1 g/ml; FS114). Based upon the *in vitro* determination of SMC inhibition in vitro (EC_{50}= 2.9 nanomolar or 2.8 ng/ml), a sufficient concentration of drug is present for at least 28 days, to provide inhibition of neointimal proliferation with approximately a two hundred-fold margin (Comparison of Activity with Zotarolimus and other Drugs in Inhibiting Human Coronary Artery Smooth Muscle and Endothelial Cell Proliferation:

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Abbott Study 51R-002-AP-03-R0). This study, when combined with the findings of arterial drug concentration, confirmed that a sufficient amount of drug was present to mediate a local therapeutic response at the targeted dose.

Smooth muscle cell proliferation

The efficacy of the zotarolimus incorporated into the coating of the Endeavor Zotarolimus-Eluting Coronary Stent System in inhibiting smooth muscle proliferation at the site of implantation has been examined in studies FS102 and FS107. In Study FS102, 7 days after implanting the Endeavor Zotarolimus-Eluting CSS into the coronary arteries of farm swine, animals were administered bromodeoxyuridine to identify proliferating cells and sacrificed 55-100 minutes later. There were significantly fewer proliferating cells found in sections of stented tissue when zotarolimus was incorporated into the stent coating than when bare Driver stents were implanted.

Table 4-15: Bromodeoxyuridine Results (Study FS102)

	Bromodeoxyuridine-positive cells/mm^2	Percent Bromodeoxyuridine-positive cells
Bare Driver stent (n=40 areas)	237.09 ± 224.21*	6.50 ± 6.40*
Endeavor 5 µg/mm (n=24 areas)	131.96 ± 125.46*	3.21 ± 2.81*
Endeavor 10 µg/mm (n=28 areas)	110.63 ± 134.86	2.77 ± 3.81

* $p<0.05$ versus bare control stents

These findings were confirmed in a rabbit iliac model of stent implantation (FS107). At 7 days after implantation, there were significantly fewer proliferating cells found in sections of stented tissue when zotarolimus was incorporated into the stent coating than when bare Driver stents were implanted. These findings of *in situ* inhibition of SMC proliferation are consistent with the anticipated response to drug in tissue.

Neointimal Response

A multi-dose study of neointimal response to zotarolimus on the Endeavor stent in porcine coronary arteries (FS99) showed a trend for increased neointimal suppression when compared to the PC polymer control (0µg/mm zotarolimus dose) with increasing drug up to 10 µg/mm, supporting this target dose for clinical use (see below) and suggesting a potential for clinical utility.

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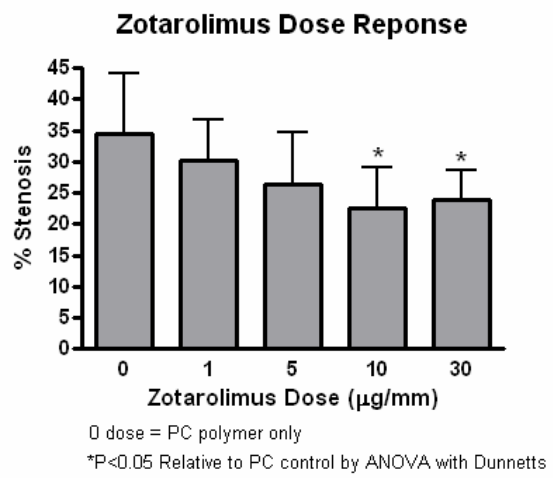
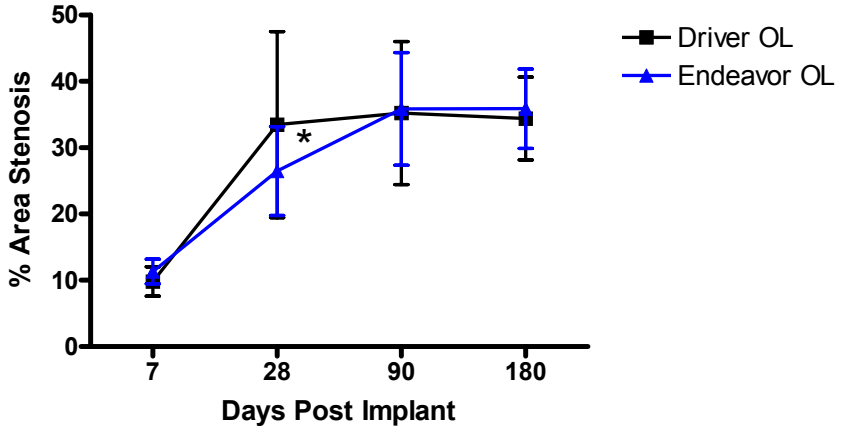


Examination of neointimal suppression relative to bare metal stents can best be observed over multiple time periods (below). While not the objective of these studies, significant inhibition of restenosis can be observed, resulting in blunting of the neointimal response at the 28 day (overlapped stents) and 90 day (single stents) time points.

Overlapped Stents



* P<0.05

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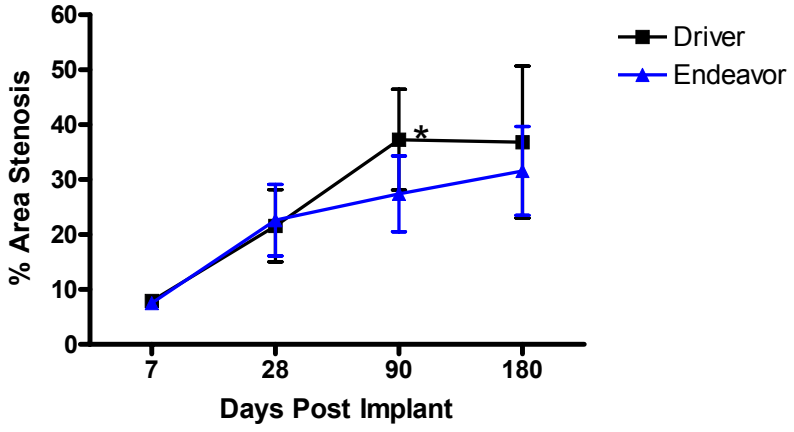
Single Stents



* P<0.05

Due to the thin strut width and other design features, the bare Driver control stent used in these studies often does not provoke a pronounced neointimal proliferative response. Consequently 90 days of neointimal growth was required to permit statistical differentiation of the single Driver and Endeavor responses. In contrast, the additional mechanical burden of overlapped stents amplified the early neointimal response, facilitating separation of the Driver and Endeavor responses at 28 days. In both cases, the inhibitory effect of zotarolimus is lost at later time points due to the robust nature of smooth muscle cell proliferation in the porcine arteries. However, the less intense proliferation of human neointima is anticipated to allow for durable responses.

Pharmacokinetics

The rate of elution of zotarolimus from the implanted Endeavor Zotarolimus-Eluting Coronary Stent System and the distribution of zotarolimus from the stent to surrounding arterial tissues, plasma, and distant organs has been measured using the rabbit iliac artery model (FS97) and the swine coronary artery model (FS114).

Implantation of 12 mm Endeavor Zotarolimus-Eluting Coronary Stent Systems containing 10µg/mm of zotarolimus in either the rabbit iliac artery or the swine coronary artery released over 50% of the drug coating within the first 24 hours after implantation. Stents removed from rabbit iliac arteries at 24 hours after implantation retained on average 43.8% of the initial drug load. Stents removed from swine coronary arteries 24 hours after initial implantation retained on average 34.7% of the initial drug load. By 7 days after implantation, only approximately 2.8% and 5.8% of the initial drug load was retained on stents implanted in rabbit and swine arteries, respectively (Table 4-16).

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Table 4-16: Drug Remaining on Explanted Stents (µg/stent; % remaining in parentheses; Studies FS97 and FS114)

	24 hours	2 days	3 days	5 days	7 days	10 days	14 days	28 days
Rabbit (n=6) Study FS97	49.20 ± 6.31 (43.8)	29.25 ± 4.55 (25.6)	18.02 ± 2.83 (16.0)	9.27 ± 3.54 (8.2)	3.32 ± 0.83 (2.9)	--	ND	ND
Swine (n=6) Study FS114	41.67 ± 5.05 (34.7)	39.17 ± 3.76 (32.6)	20.83 ± 6.18 (17.4)	16.33 ± 4.13 (13.6)	7.00 ± 6.42 (5.8)	5.17 ± 1.83 (4.3)	2.17 ± 0.41 (1.8)	0.48 ± 0.26 (0.4)

--, not done; ND, none detected

Blood levels resulting from implantation of the drug-coated stents were generally low and rapidly decreased to levels below the limit of detection. In the rabbit study, blood levels of zotarolimus exhibited a sharp peak at the earliest time point evaluated (0.25 hours) and declined rapidly (Table 4-17). In the swine, much lower peak blood levels were obtained and were observed at a later time after implantation (3 hours). Despite the higher peak blood levels seen in the rabbit, by 7 days after implantation, blood levels were not detectable in either the rabbit or swine.

Table 4-17: Blood Levels of Zotarolimus (ng/mL)

	15 min	1 hr	3 hr	6 hr	24 hr	2 day	3 day	5 day	7 day	10 day	14 day	28 day
Rabbit (n=3-5) Study FS97	177.68 ± 167.07	6.48 ± 1.58	5.26 ± 1.06	3.42 ± 0.77	1.88 ± 0.31	0.99 ± 0.12	0.74 ± 0.11	0.35 ± 0.31	ND	--	ND	ND
Swine (n=3) Study FS114	1.39 ± 0.25	2.36 ± 0.43	2.67 ± 0.67	1.57 ± 0.33	0.68 ± 0.11	0.42 ± 0.05	0.27 ± 0.03	<0.23[1]	ND	ND	ND	ND

[1] Actual value from one swine = 0.23 ng/mL; values from other 2 swine were <0.2 ng/mL; ND, not detected; --, not done

The vessel wall surrounding the stent exhibited much higher drug concentrations than the blood and exhibited sustained levels for longer than drug could be detected in blood. The highest concentration of zotarolimus was observed in the vessel wall surrounding the stent two days after implantation in both the rabbit and swine. This level declined over time, but trace amounts were still detectable 28 days after implantation (Table 4-18). Thus, despite the rapid elution of zotarolimus from the Endeavor stent, the drug was retained within the vessel wall providing for long-lasting pharmacological effects at the intended site of action.

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Table 4-18: Drug Present in the Vascular Wall Surrounding the Stent (ng/mg)

	1 day	2 days	3 days	5 days	7 days	10 days	14 days	28 days
Rabbit Study FS97	53.29 ± 36.73 (n=10)	69.07 ± 30.68 (n=6)	36.16 ± 35.22 (n=6)	25.94 ± 33.82 (n=6)	3.92 ± 0.93 (n=6)	--	0.85 ± 0.93 (n=6)	1.38 ± 0.60 (n=6)
Swine Study FS114	23.92 ± 16.95 (n=6)	27.85 ± 9.59 (n=6)	14.61 ± 8.61 (n=6)	14.41 ± 6.97 (n=6)	13.19 ± 7.87 (n=5)	8.85 ± 1.46 (n=6)	4.31 ± 2.82 (n=6)	1.18 ±0.64 (n=5)

Vessel segments distal and proximal to the stent exhibited 2% or less of that found in tissue immediately in contact with the stent.

In the swine, the drug levels in myocardium immediately beneath the stents were also measured. Detectable levels were present for 14 days following implantation, but the levels were somewhat lower than those measured in stented vessels either immediately surrounding the stent or proximal or distal to the stent itself (Table 4-18 and Table 4-19).

Table 4-19: Drug Present in Tissues Near the Stent (ng/mg; Study FS114)

	1 day	2 days	3 days	5 days	7 days	10 days	14 days	28 days
Myocardium	0.34 ± 0.20 (n=6)	0.23 ± 0.08 (n=5)	0.10 ± 0.06 (n=6)	0.06 ± 0.04 (n=4)	0.04 ± 0.02 (n=6)	0.02 ± 0.01 (n=6)	0.01 ± 0.003 (n=4)	ND (n=6)
Proximal vessel	0.42 ± 0.10 (n=6)	0.56 ± 0.29 (n=6)	0.19 ± 0.09 (n=4)	0.30 ± 0.22 (n=4)	0.14 ± 0.11 (n=6)	0.09 ± 0.06 (n=6)	0.06 ± 0.05 (n=6)	0.03 ± 0.02 (n=6)
Distal vessel	0.46 ± 0.23 (n=6)	0.51 ± 0.24 (n=6)	0.27 ± 0.10 (n=6)	0.22 ± 0.09 (n=6)	0.17 ± 0.09 (n=6)	0.39 ± 0.16 (n=6)	0.03 ± 0.02 (n=4)	0.03 ± 0.02 (n=6)

ND, not detected

Distant tissues (lungs, liver, spleen, kidneys, lymph, myocardium, and carotid artery) in the rabbit had levels ≤ 0.05 ng/mg from 24 hours after dosing until measurement was discontinued at 28 days after implantation (Study FS97). Kidney tissue taken from swine had detectable levels of zotarolimus only at 24 hours after dosing, and liver and lung tissue had no detectable zotarolimus present at any time point from 24 hours to 28 days after implantation (Study FS114). Thus, the tissue surrounding the stent received the greatest exposure to the zotarolimus and this exposure persisted long after drug had completely eluted from the stent. Exposure of the rest of the body to zotarolimus from the stent was short lived and very limited in magnitude.

Local Tolerance

The local tolerance and healing of coronary vessels after implantation of the Endeavor stent have been evaluated at various times (i.e., 7, 28, 90, and 180 days) after stent implantation into swine coronary arteries (Studies FS99, FS100, FS101, FS102, FS135) and rabbit iliac arteries (Study FS107). Local tolerance was evaluated by assessing the inflammatory response of the surrounding blood vessel to the stent placement, the degree of medial necrosis or thinning and the amount of vessel injury, and effects on the

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myocardium. The healing of coronary vessels was inferred from the degree of endothelialization and the fibrin score.

4.4.2.1 Inflammatory Response

Semi-quantitative histological grading of inflammation yielded scores that were highest at the earliest time point irrespective of treatment group and that decreased to very low levels over time. In the rabbit study (Study FS107), the inflammation scores for both the bare and drug-coated stents decreased substantially between Days 7 and 28. The decrease for the drug-coated stents in the rabbit was slightly less at Day 28 than for the bare stents resulting in a slightly higher inflammation score. In the swine studies (Studies FS99, FS100, FS101, FS102, FS135), both the polymer-coated and drug-coated stents had slightly higher inflammation scores than the bare control stents at multiple time points evaluated after implantation (i.e., 7, 28, 90, and 180 days). Although inflammation scores were statistically significantly higher for coated than the bare stents at up to 90 days after implantation, the inflammation scores for all stents were generally less than 1 after Day 7, indicating a very low level inflammatory response (i.e., involvement of 3 or fewer struts and 10 or fewer inflammatory cells surrounding each strut). By 6 months after implantation, no significant differences were seen between the bare stents and Endeavor stents. Thus, in general, the slightly greater inflammatory response initially seen with the Endeavor stent resolved over time.

As shown in Figure 4-8 below, porcine inflammation scores demonstrated mild response at all chronic time points up to 180 days with single and overlapped stents.

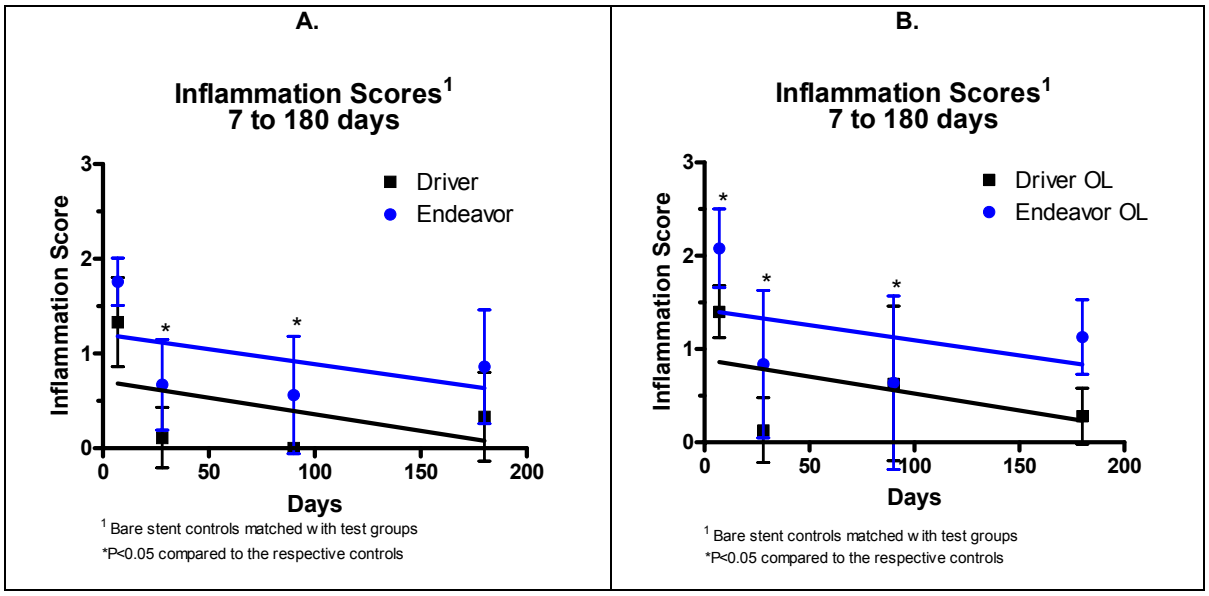

Figure 4-8: Inflammation scores in response to single Endeavor or Driver stents at multiple timepoints up to 180 days (A) indicate Endeavor mean scores of less than one from 28 to 180 days. Inflammation scores in response to overlapped Endeavor and Driver stents (B), show a similar profile to single stents but with slightly higher scores in response to the greater stent burden in the overlapped segment. Lines indicate the trend in inflammation response with time.

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Furthermore, as shown in Figure 4-9 below, porcine inflammation scores demonstrated mild response to a 3X or 6X drug over dose at all chronic time points up to 180 days with single and overlapped stents.

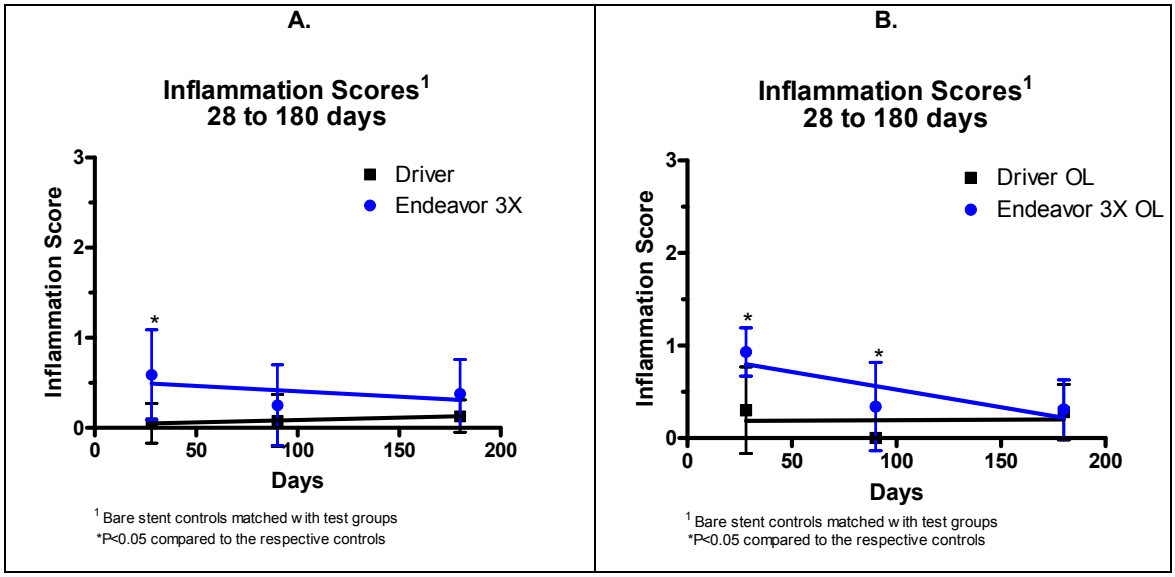

Figure 4-9: Inflammation scores in response to single Endeavor (3x drug load) or Driver stents at multiple timepoints up to 180 days (A) indicate Endeavor (3X drug load) mean scores of less than one from 28 to 180 days which are similar to scores seen with the 1X drug load. Inflammation scores in response to overlapped Endeavor (3X drug load, i.e. 6X drug load in overlap segment) and Driver stents (B), also show a closely similar profile to single stents but without increased scores in response to the greater drug load in the overlapped segment. Lines indicate the trend in inflammation response with time.

In addition, as shown in Figure 4-10 below, porcine inflammation scores demonstrated mild response to PC Polymer at all chronic time points up to 180 days with single stents.

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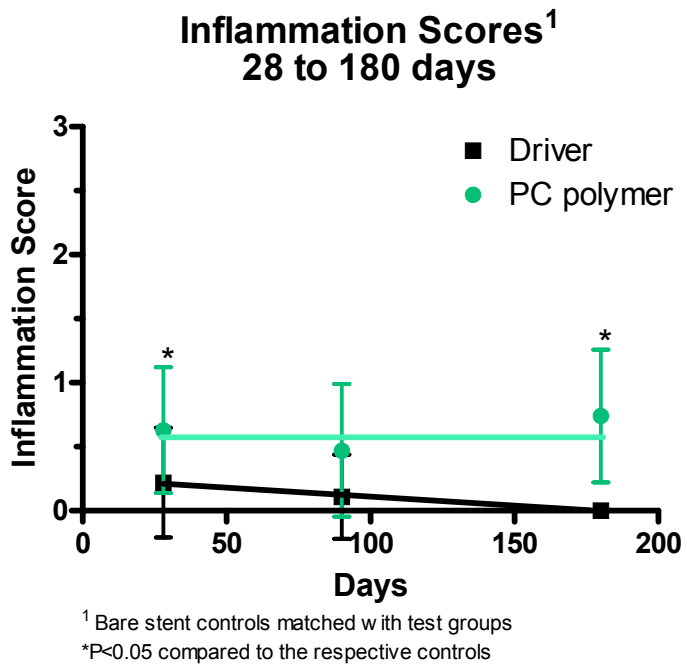

Figure 4-10: Inflammation scores for PC polymer were consistently lower than 1 for time points ranging from 28 to 180 days without a trend in increasing sensitivity to polymer with time. Inflammatory response to polymer alone is no greater than that observed with the PC polymer-drug combination, indicating that drug was not masking the host response to polymer. Lines indicate the trend in inflammation response with time.

Light microscopy revealed that the inflammatory response consisted mainly of mononuclear macrophages and giant cells around stent struts. Lymphocytes were rarely seen and eosinophils were not observed near the stent struts. The presence of eosinophils in these responses was highly exceptional and could only be observed as a minimal cellular component not associated with the stent or PC polymer in three sections covering up to 180 days of exposure. At 40x magnification, giant cells were seen in some cases around the struts at sites where deposits of basophilic material were observed. Further description of the material is provided in the following section, *Interaction of the Stent with the Adjacent Vessel Wall*.

A summary of the inflammatory response in swine is provided in Table 4-20 followed by a summary of the inflammatory response in rabbits in Table 4-21.

Table 4-20: Swine Inflammatory Response (Score)[1] at the Site of Stent Implantation (Studies FS99, FS100, FS101, FS102 and FS135)

	Single Stents										Overlapped Stents			
	Bare	1ug	Bare	5ug	Bare	10ug	Bare	30ug	Bare	Polymer	Bare	10ug	Bare	30ug
Day 7 Study FS102	--	--	1.17 ± 0.43	1.91 ± 0.16*	1.33 ± 0.47	1.76 ± 0.25	--	--	--	--	1.40 ± 0.28	2.08 ± 0.42*	--	--
	--	--	n=4	n=7	n=4	n=7	--	--	--	--	n=5	n=5	--	--
Day 28 Study FS99	0.22 ± 0.43	0.53 ± 0.57*	0.17 ± 0.38	0.85 ± 0.72*	0.11 ± 0.32	0.67 ± 0.48*	0.05 ± 0.22	0.59 ± 0.50*	0.22 ± 0.43	0.63 ± 0.49*	0.13 ± 0.35	0.84 ± 0.79*	0.30 ± 0.47	0.93 ± 0.26*
	n=6	n=10	n=6	n=9	n=6	n=9	n=7	n=9	n=6	n=10	n=6	n=10	n=6	n=9
Day 90 Study FS100	--	--	0.00 ± 0.00	0.50 ± 0.52*	0.00 ± 0.00	0.56 ± 0.62*	0.08 ± 0.29	0.25 ± 0.45	0.11 ± 0.33	0.47 ± 0.52	0.63 ± 0.83	0.64 ± 0.93	0.00 ± 0.00	0.34 ± 0.48*
	--	--	n=5	n=4	n=4	n=6	n=4	n=4	n=3	n=5	n=4	n=7	n=4	n=7
Day 180 Study FS101	--	--	0.00 ± 0.00	0.58 ± 0.71	0.33 ± 0.47	0.86 ± 0.60	0.13 ± 0.18	0.38 ± 0.38	0.00 ± 0.00	0.74 ± 0.52*	0.28 ± 0.30	1.13 ± 0.40*	0.28 ± 0.30	0.31 ± 0.32
	--	--	n=5	n=8	n=5	n=7	n=5	n=8	n=5	n=9	n=5	n=9	n=5	n=7
Day 28 Study FS135					n=5	n=10	n=6	n=10	n=6	n=10				
	NA	NA	NA	NA	0.02 ± 0.08[2]	1.73 ± 0.56	0.02 ± 0.08	1.23 ± 0.98	0.02 ± 0.08	0.10 ± 0.32	NA	NA	NA	NA

[1] Inflammation score
[2]Grouped control for 5 to 30 μg/mm doses
*p≤0.05 compared to the respective controls; -- not done

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Table 4-21: Rabbit Inflammatory Response (Score)[1] at the Site of Stent Implantation (Study FS107)

	Bare	10 µg/mm
Day 7	2.14 ± 0.38 (n = 7)	2.29 ± 0.76 (n = 7)
Day 28	0.00 ± 0.00 (n = 9)	1.03 ± 0.43* (n = 9)

[1] Inflammation score as described by Schwartz et al. (1992); *p<0.0001 compared to the respective controls

Porcine inflammation scores show mild response at all chronic time points up to 180 days with single and overlapped stents

Interaction of the Stent with the Adjacent Vessel Wall

No medial necrosis or thinning was observed in the swine studies for any of the single stents evaluated at Days 7, 28, 90, or 180 or for any of the overlapped stents evaluated at Days 7, 28, or 90. At 180 days the overlapped stents coated with 10 µg/mm of zotarolimus exhibited significantly greater medial thinning than the control overlapped stents (Study FS101). This was attributed to differential expansion of the stents at the time of placement rather than the drug coating since similar effects were not seen with overlapped stents coated with a higher concentration of zotarolimus (30µg/mm). Medial fractures or laceration by the stents were infrequently observed (i.e., semi-quantitative histology injury scores using the method of Schwartz et al.[39] were much less than 1), but were statistically higher for the Endeavor stent than the bare controls in some studies.

In addition, a study was conducted to specifically address the thrombogenic safety of the Endeavor Drug Eluting Stent System on various delivery system platforms (FS161) through evaluation of QCA and histomorphometry as compared to a bare metal Driver control group. All devices in this study were successfully delivered to the target site with no major device related complications and angiographic examination 11 days after implantation confirmed that all the stents had widely patent lumens without edge effect, aneurysm formation, filling defects or late thrombosis. All stented vessels had TIMI-3 flow. Morphometric evaluation showed that the Endeavor arms (RX, OTW and MX2) were statistically similar to the bare Driver control for intimal area, percent stenosis and intimal thickness. Histological evaluation showed that the Endeavor arms (RX, OTW and MX2) were statistically similar to bare Driver control in strut malapposition, percent struts with RBCs, percent endothelialization, inflammation score and percent granulomas. The bare metal Driver control showed statistically lower percent of struts with residual fibrin when compared to the three Endeavor arms as a consequence of drug action. No incidents of thrombosis or abnormal red blood cell extravasion were noted for any of the arms and the Endeavor stent was determined to be non-thrombogenic.

PC Polymer

The polymer portion of the drug-polymer layer of Endeavor may be left behind following drug elution. This is supported by the histopathological analysis of explanted porcine

[39] Schwartz, R.S., Huber, K.C., Murphy, J.G., Edwards, W.D., Camrud, A.R., Vlietstra, R.E., and Holmes, D.R. 1992. Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. J. Am. Coll. Cardiol. 19:267-274.

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vessels from the Endeavor pre-clinical safety studies. This analysis found incidences of PC polymer, detectable as a basophilic deposit, adjacent to the stent struts that had been encapsulated in the neointima which is indicative of residual PC trapped between the stent and the vessel wall or on the abluminal surface of the strut. This material was seen as early as 7 days after implantation and was surrounded initially by giant cells and within 28 days by neointimal cells and matrix. This material was not seen protruding into the vessel lumens. There was minimal to no inflammatory response associated with these deposits. Further, no thrombotic events and >98% survival of the animals were seen in these studies. Thus, the residual PC polymer does not appear to adversely affect the safety of the stents.

Fibrin Deposition

Semi-quantitative histology scores for fibrin exhibited a decrease over time from average values of between 1.00 and 1.50 at Day 7 to average values of 0.00 by Day 90 (Table 4-22). Although no difference in fibrin scores was observed at 7 days after implantation (a time when fibrin scores were highest), by 28 days after implantation, the Endeavor stent had more residual fibrin than the bare control stents. The greater residual fibrin deposition observed with the zotarolimus-coated stents is similar to that seen with sirolimus-coated stents with the swine model (Suzuki et al. 2001). It is unknown whether the greater residual fibrin reflects a delay in arterial repair or impaired fibrin degradation secondary to the local effects of the drug. However, by 90 days after implantation, fibrin was no longer observed around either the control or drug-treated stents. Thus, no long-term effects on fibrin removal occurred with the Endeavor stent.

Table 4-22: Fibrin Score[1] at the Site of Stent Implantation (Swine studies)

	Single Stents										Overlapped Stents			
	Bare	1 ug	Bare	5 ug	Bare	10 ug	Bare	30 ug	Bare	Polymer	Bare	10 ug	Bare	30 ug
Day 7 FS102	--	--	1.00 ± 0.00	1.29 ± 0.49	1.25 ± 0.50	1.43 ± 0.54	--	--	--	--	1.80 ± 0.43	1.96 ± 0.36	--	--
	--	--	n=4	n=7	n=4	n=7	--	--	--	--	n=5	n=5	--	--
Day 28 FS99	0.72 ± 0.46	1.00 ± 0.53	0.56 ± 1.42	1.22 ± 0.42*	0.33 ± 0.49	1.15 ± 0.46*	0.48 ± 0.51	0.96 ± 0.34*	0.28 ± 0.46	0.27 ± 0.45	0.67 ± 0.48	1.46 ± 0.65*	0.30 ± 0.47	1.00 ± 0.44
	n=6	n=10	n=6	n=9	n=6	n=9	n=7	n=9	n=6	n=10	n=6	n=10	n=6	n=9
Day 90 FS100	--	--	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.17 ± 0.38	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.18 ± 0.39*	0.00 ± 0.00	0.00 ± 0.00
	--	--	n=5	n=4	n=4	n=6	n=4	n=4	n=3	n=5	n=4	n=7	n=4	n=7
Day 180 FS101	--	--	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.04 ± 0.12	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.06 ± 0.00
	--	--	n=5	n=8	n=5	n=7	n=5	n=8	n=5	n=9	n=5	n=9	n=5	n=7
Day 28 FS135 (SVS)					n=10	n=10	n=10	n=10	n=10	n=10				
	NA	NA	NA	NA	0.02 ± 0.08[2]	1.00 ± 1.25	0.02 ± 0.08[2]	0.73 ± 1.21	0.02 ± 0.08[2]	0.07 ± 0.21	NA	NA	NA	NA

[1] Fibrin score
[2] Grouped control for 5 to 30 μg/mm doses
*p<0.05 compared to the respective bare controls; -- not done

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Taken together the studies evaluating local tolerance and healing demonstrate that initially the stent produced a slightly greater level of inflammation surrounding stents than the bare control Driver stents. This effect was observed early after implantation but did not persist. Also, a slight delay in endothelialization and fibrin removal between overlapped bare and overlapped drug-coated stents was observed. However, no differences in long-term healing attributable to the presence of the drug coating on the stents was observed. Importantly, the slightly greater inflammation observed with the Endeavor stent did not result in greater levels of restentosis (see Pharmacodynamics, above).

Endothelialization

The effect of the stents on vascular endothelialization after stent placement was also evaluated by SEM in both swine and rabbits. At 7 days after implantation, vessels implanted with overlapping stents coated with 10 µg/mm of zotarolimus exhibited a lower degree of endothelialization (69% vs. 95% in the swine; 1.43% vs. 48.9% in the rabbit) than the bare Driver controls. However, single stents did not show a similar difference and at subsequent times after implantation (28, 90, and 180 days) in either swine or rabbits, all of the stents exhibited complete endothelialization at both the 90 and 180 day timepoints. Thus, the endothelium did not demonstrate any persistent inhibition of healing after implantation of the Endeavor stent.

As shown in Figure 4-11 below, porcine histology data shows rapid endothelial replacement with both single and overlapped stents.

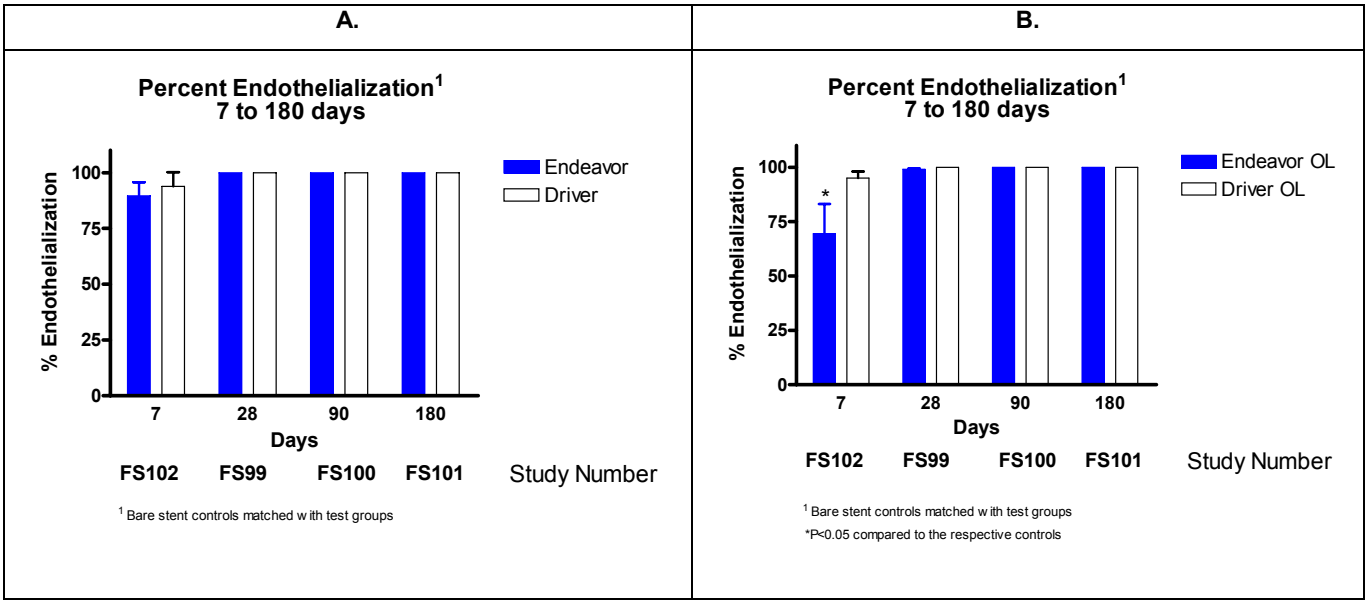

Figure 4-11: Rapid endothelialization was observed following single stent implantation in the porcine model (A), with extensive coverage of the Endeavor stent observed within one week (not significantly different from Driver) and complete coverage at 28 days. Endothelialization of overlapped stents was delayed relative to Driver at 7 days (B) but complete at 28 days.

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Furthermore, as shown in Figure 4-12 below, porcine histology data shows rapid endothelial replacement with Endeavor 3X and 6X drug overdose using both single and overlapped stents.

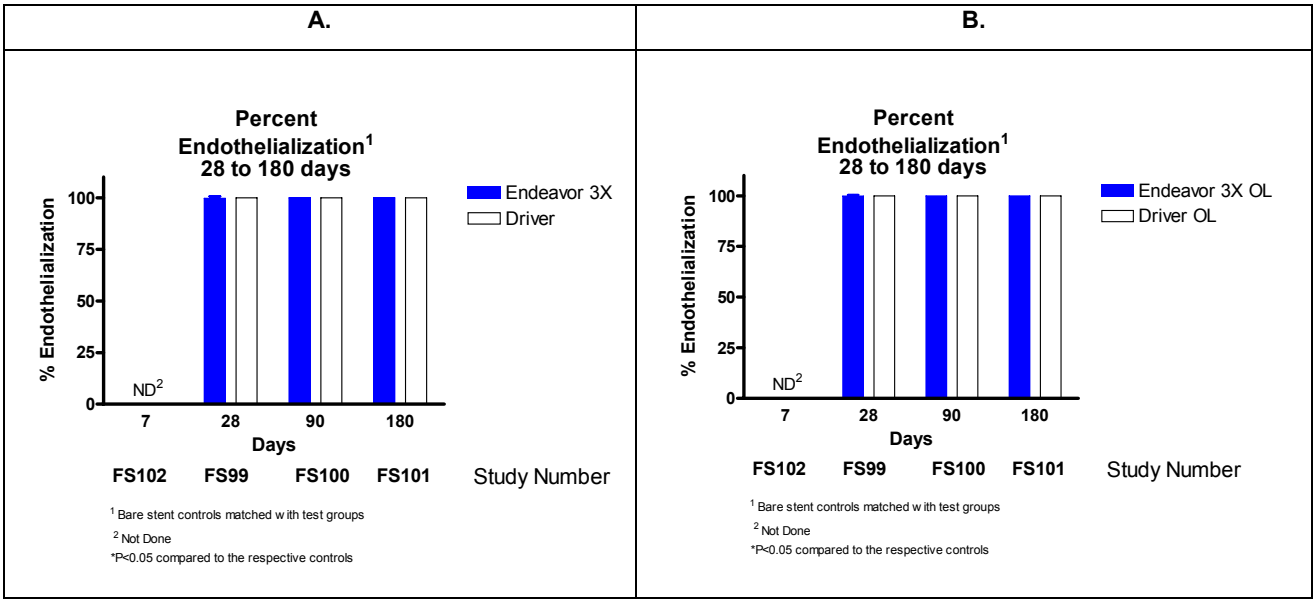

Figure 4-12: Increased Endeavor drug load (3X) did not impact the degree of endothelialization observed with the Endeavor stent at 28 days or later time points relative to bare Driver stents in single stent implants (A), or with overlapped stents (B); 6X drug load within overlapped segments.

The Endeavor Zotarolimus-Eluting CSS did not show a difference in rates of endothelialization when compared to BMS at 28, 90, and 180 days after implantation in either swine or rabbits, and exhibited complete endothelialization at both the 90 and 180 day time points.

Endothelial Nitric Oxide Synthase

Endothelial Nitric Oxide Synthase (eNOS) and the role of vessel function is one area of research Medtronic is conducting to better understand the safety profile of drug-eluting stents. Endothelial Nitric Oxide Synthase (eNOS) produces Nitric Oxide (NO), an important mediator for proper arterial vasodilation and an indicator of normal arterial function.

Medtronic Vascular has conducted research studies looking at eNOS levels after implantation with various drug-eluting stents including Endeavor. This research was presented at Transcatheter Cardiovascular Therapeutics (TCT) 2006. Cypher, Taxus, Endeavor and Driver stents were implanted in porcine coronary arteries. An acetylcholine challenge was conducted just prior to euthanasia and evaluated by QCA for diameter changes. Vessels were harvested at 28 and 90 days after stenting for the purpose of looking for the presence of eNOS in the stented vessels by immunohistochemistry and PCR probes. As a precursor to NO, the presence of high levels of eNOS was noted as indicating healthy xarterial function.

At 28 days in regions proximal to stent implantation as well as the in-stent segments of arteries, eNOS mRNA expression was greater for Endeavor than for Cypher and Taxus

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(P<0.05) and similar to Driver. At 28 days, eNOS protein expression was strongly recognized in proximal regions of Endeavor- and Driver-implanted arteries but not in Cypher- and Taxus-implanted arteries. In the presence of an acetylcholine at 28 days, 6 of 7 Endeavor- and 13 of 15 Driver-implanted arteries showed vasodilation (normalization of endothelial function), whereas 7 of 9 Cypher - and 5 of 9 Taxus -implanted arteries showed vasoconstriction. These findings indicate rapid healing and normalization of endothelial function with the use on the Endeavor stent, potentially providing decreased risk of inflammation and thrombosis. At 90 days, however, all the stent-implanted arteries demonstrated vasodilation in the presence of an acetylcholine challenge, suggesting a similar level of healing was reached by this time point. At 90 days, in the region of the arteries proximal to the stents, eNOS mRNA expression was significantly greater for Endeavor than for Cypher ($P<0.05$) although the relative level of eNOS mRNA expression within the in-stent regions were greater for Cypher than for Endeavor and Taxus ($P<0.05$).

These findings suggest that rapid healing and normalization of endothelial function can be observed with the Endeavor stent at the 28 day time point in this model, potentially providing a mechanism for decreased risk of inflammation and thrombosis through NO production.

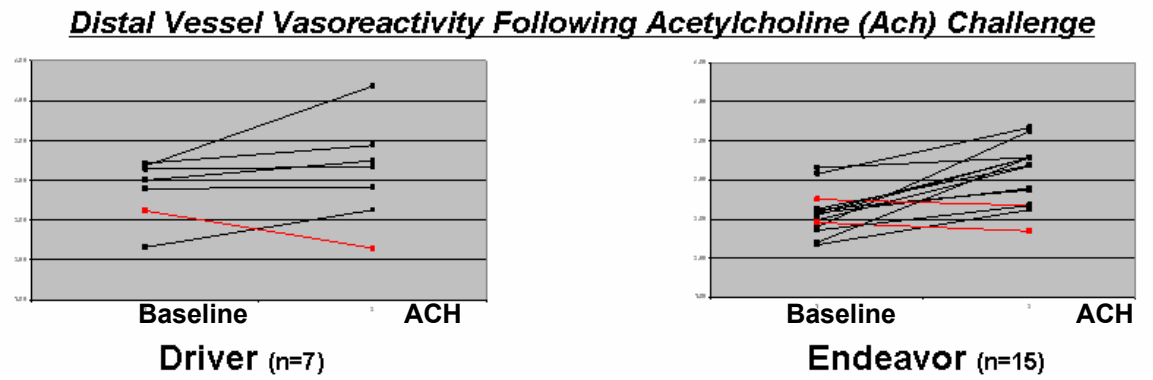

Figure 4-13: Endeavor and Driver-implanted arteries showed vasodilation (normalization of endothelial function) following exposure to acetylcholine. These findings indicate rapid healing and restoration of endothelial function with the use on the Endeavor stent, potentially decreasing the risk of inflammation and thrombosis.

Myocardial Pathology

In addition to assessment of inflammation and injury to the vessel in which the stents had been placed, the myocardium of the swine was assessed for evidence of pathologic changes. Anterior, lateral, posterior, and septal sections were taken from both the apex and mid sections, and the sections were obtained from the area beneath the epicardial arteries. Few microscopic lesions related to presence of stents and no significant inflammatory changes were detected at 28, 90, or 180 days after implantation. Each of studies FS99, FS100, FS101, FS102, and FS110 included between 3% and 13% of animals with small myocardial vessels containing amorphous basophilic material with or without perivascular inflammatory cells. This material could also be seen as early as 11

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days post-implant (FS161). In approximately half of the instances where the microemboli were observed, very small scars were observed in the myocardium adjacent to the vessels containing the material. Although, these findings were more numerous in the myocardium in the distribution of arteries implanted with Endeavor stents compared to control stents, additional studies suggest that these foreign body microemboli may be particles of the hydrophilic coating used on guidewires. The size of the amorphous basophilic fragments were quite small, and the clinical significance of the microemboli was thought to be minimal since none of the hearts examined exhibited gross lesions, and animal survival was >98%.

Pre-clinical Conclusions

In summary, the available data from studies submitted in the Endeavor Zotarolimus-Eluting CSS PMA has demonstrated:

- Drug safety and pharmacology
- Rapid, complete and functional endothelialization
- Low levels of drug/polymer induced inflammation and fibrin deposition
- No medial necrosis
- Low risk of thrombosis
- Broad margin of safety at 3x and 6x dose

Studies evaluating the elution of the drug, zotarolimus, from the Endeavor Zotarolimus-Eluting CSS after implantation demonstrate that the drug rapidly elutes from the stent, with less than 50% of the drug remaining on the stent at 24 hours after implantation and less than 6% remaining at 7 days. Blood levels rapidly decline to undetectable levels by 7 days after implantation and peripheral tissues have highly limited exposures. Thus, while systemic exposure is limited, drug remains at the implantation site for at least 28 days.

Overall it can be concluded that the stents performed as expected in the animal models, without evidence of increased toxicity due to the presence of the drug coating.

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4.5 The Endeavor Clinical Program

The Endeavor Zotarolimus-Eluting Coronary Stent System clinical development program includes clinical safety and efficacy data from six multi-center trials conducted in the United States and abroad in support of PMA approval. Three of the six trials were randomized controlled studies and three were open-label trials. The randomized studies compared the safety and efficacy of the Endeavor stent to each of three marketed coronary stents: the uncoated bare metal Driver™ stent, the Cypher Sirolimus-Eluting Stent™, and the Taxus Paclitaxel-Eluting Coronary Stent System™. An additional registry was conducted in Japan to support regulatory approval in that country.

These studies provide extensive clinical safety and efficacy data for the Endeavor Zotarolimus-Eluting CSS. Among the PMA trials, 2,133 patients were assigned to receive the Endeavor stent and substantial follow up data is now available; 2,088 patients to 9 months, 1,301 patients to 12 months, 1,287 patients to 24 months, 675 patients to 36 months, and 97 patients to 48 months. Through randomized, controlled trials, the Endeavor stent was shown to be superior to a bare metal stent and non-inferior to a drug-eluting stent based on the composite endpoint of Target Vessel Failure (TVF). In addition, with substantial follow-up data available, there is no trend towards increased rates of cardiac death, MI, or stent thrombosis compared to the bare metal stent when assessed within the first year or in the critical post-one year time frame.

Table 4-23 below illustrates the key objective of each of the ENDEAVOR clinical trials. The subsequent section of this panel package provides additional details regarding each of these trials.

Table 4-23: ENDEAVOR Trial Objectives

Trial	Trial Objective
ENDEAVOR I	First in-man / proof of concept
ENDEAVOR II	Double blind randomized controlled trial intended to prove superior clinical efficacy vs. BMS control and including a pharmacokinetic subset
ENDEAVOR II - CA	Open-label continued access registry until CE mark approval was granted, utilizing the same protocol as Endeavor II and allowing for direct stenting
ENDEAVOR III	Single-blind randomized controlled trial intended to confirm the results from the OUS ENDEAVOR II trial in a US population
ENDEAVOR IV	Single-blind randomized controlled trial intended to show non-inferiority to market leading US DES product
ENDEAVOR PK	Registry intended to evaluate pharmacokinetic properties in a US population
ENDEAVOR Japan	Registry intended to meet requirements for Japanese regulatory approval

The strongest evidence for the safety and effectiveness is available from the three randomized controlled trials: ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV.

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ENDEAVOR II was a double-blind randomized comparison to the currently marketed Driver bare metal stent. This OUS study was performed to determine if Endeavor produced significant reductions in re-intervention when compared to a BMS, as had been observed in previous DES vs. BMS trials. In this trial, Endeavor demonstrated superiority on the primary endpoint of Target Vessel Failure (TVF), a composite of cardiac death, Myocardial Infarction (MI), and Target Vessel Revascularization (TVR). In addition to demonstrating a significant reduction in TVF, statistically significant reductions in the secondary angiographic endpoints were also observed at 8 months. With three year follow-up now available, the reductions in clinical events seen at 9 months are preserved, and there is no increase in the critical events of stent thrombosis, cardiac death, or MI compared to the control. There has been no increase in revascularization compared to the bare metal stent from year one to year three. A more detailed discussion on the data supporting the safety and effectiveness of Endeavor is provided in Section 4.5.1 below.

ENDEAVOR III was a single-blind randomized comparison to the Cypher drug-eluting stent. The purpose of this trial was to confirm the results from the OUS ENDEAVOR II trial in a US population. An angiographic surrogate endpoint of in-segment late lumen loss was chosen as the primary endpoint, as it was believed to be correlated with clinical events. While the 8-month primary non-inferiority late lumen loss endpoint was not met, the TVF rate at 9 months was 11.8% for Endeavor vs. 11.5% for Cypher. Endeavor demonstrated a very low peri-procedural myocardial infarction rate. Although this trial was not powered to detect differences in clinical events, the only differences that have been demonstrated in follow-up out to two years have favored the Endeavor stent, driven by lower peri-procedural events.

ENDEAVOR IV was a single-blind randomized comparison to the Taxus drug-eluting stent. The purpose of the trial was to demonstrate non-inferiority to a marketed DES using an established clinical endpoint. The selected primary endpoint was the composite endpoint of TVF at 9 months, the same endpoint used in the ENDEAVOR II Trial. Clinical event rates were similar between Endeavor and Taxus based on non-inferiority being demonstrated for the primary clinical endpoint. While clinical rates were similar, it is interesting to note that differences were observed in terms of angiographic profiles between Endeavor and Taxus. The non-inferiority, powered secondary endpoint of in-segment late loss at 8 months was not demonstrated. Similar to ENDEAVOR III, the Endeavor stent also showed lower peri-procedural events compared to the Taxus stent.

These three trials provide a reasonable assurance of safety and effectiveness of the Endeavor system. No evidence of systemic toxicity was apparent in patients treated with the Endeavor Zotarolimus-Eluting CSS in clinical studies to date. In addition, there is no information indicating that the addition of zotarolimus leads to an increase in adverse events when compared to a placebo, a sirolimus-coated stent, or a paclitaxel-coated stent.

A summary of the major study characteristics of ENDEAVOR trials are provided in Table 4-24 below, followed by a summary of the key findings from this program. In addition, detailed summaries of each of the studies are provided in Section 6, and each of the final reports from the most recent follow-up are provided in the Appendices for reference.

Table 4-24: Major Study Characteristics of ENDEAVOR Trials

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR II-CA	ENDEAVOR III	ENDEAVOR IV	ENDEAVOR PK REGISTRY	ENDEAVOR JAPAN
Study Description	Multi-Center (8 OUS sites), Non-Randomized	Multi-Center (72 OUS sites), Prospective, Double-Blind, Randomized, Controlled	Multi-Center (15 OUS sites), Prospective, Open-Label Non-Randomized, Single Arm Continued Access Sub-Study	Multi-Center (29 US sites), Prospective, Single-Blind, Parallel, Two-Arm, Randomized, Controlled	Multi-Center (80 US sites), Prospective, Single-Blind, Randomized, Two-Arm	Multi-Center (6 US sites), Prospective, Open-Label, Single Arm	Multi-center (11 Japan sites, Prospective, Open-Label, Single Arm
Status	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Follow-up Complete	48 months	36 months	24 Months	24 Months	9 Months	9 Months	9 Months
Number of Patients	100 enrolled	1197 enrolled	296 enrolled	436 enrolled	1,548 enrolled	43 enrolled	99 enrolled
	100 total patients with Endeavor Zotarolimus-Eluting CSS	1:1 randomization to Endeavor Zotarolimus-Eluting CSS or Driver™ stents	296 patients with Endeavor Zotarolimus-Eluting CSS	3:1 randomization to Endeavor Zotarolimus-Eluting CSS or Cypher Sirolimus-Eluting Coronary Stent	1:1 randomization to Endeavor Zotarolimus-Eluting CSS or Taxus Paclitaxel-Eluting Coronary Stent; patients stratified by diabetic status	43 patients with Endeavor Zotarolimus-Eluting CSS	99 patients with Endeavor Zotarolimus-Eluting CSS
Lesion Criteria	*De novo* lesion in native coronary artery, 3.0 to 3.5 mm in diameter, lesion coverable by one 18 mm stent	*De novo* lesion in native coronary artery >2.25 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and ≤27 mm	*De novo* lesion in native coronary artery >2.25 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and ≤27 mm	*De novo* lesion in native coronary artery >2.5 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and ≤27 mm	*De novo* lesion in native coronary artery >2.5 to <3.5 mm in diameter, and lesion lengths of ≤27 mm	*De novo* lesions in native coronary artery >2.5 to <3.5 mm in diameter, and lesion lengths of ≤27 mm	*De novo* lesions in native coronary artery ≥2.5 to <3.5 mm in diameter, and lesion lengths of ≥14 mm and≤ 27 mm

Table 4-24: Major Study Characteristics of ENDEAVOR Trials

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR II-CA	ENDEAVOR III	ENDEAVOR IV	ENDEAVOR PK REGISTRY	ENDEAVOR JAPAN
Device Products Used	Endeavor Zotarolimus-Eluting CSS, 3.0-3.5mm diameter, 18 mm length	Endeavor Zotarolimus-Eluting CSS, 2.25-3.5mm diameter and 8-30 mm in length or Driver Coronary Stent System	Endeavor Zotarolimus-Eluting CSS, 2.25-3.5mm diameter and 8-30 mm in length	Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length or Cypher Sirolimus-Eluting Coronary Stent System	Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length or Taxus Paclitaxel-Eluting Coronary Stent System	Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length	Endeavor Zotarolimus-Eluting CSS, 2.5-3.5mm diameter and 8-30 mm in length
Anti-platelet Therapy	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 6 months	Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 12 weeks	Aspirin indefinitely, and Ticlopidine for a minimum of 12 weeks
Endpoints	1º: 30 day MACE and angiographic late lumen loss at 4 months	1º: Target vessel failure (TVF) rate at 9 months	1º: 30 day MACE	1º: In-segment late lumen loss at 8 months	1º: Target vessel failure (TVF) rate at 9 months	1º: Pharmacokinetic parameters at 30 days.	1º: Target vessel failure (TVF) rate at 9 months
	2º: 1) Target vessel failure (TVF); 2) Clinically-driven Target lesion revascularization (TLR) rate at 9 months; 3) Late lumen loss at 12 months as measured by angiography; 4) Neointimal hyperplastic volume at	2º: Lesion success, procedure success, device success, late lumen loss at 8 months, MACE at 30 days, 6, 9 and 12 months, TLR and Target vessel revascularization (TVR) at 9 months, angiographic in-stent and in-lumen diameter at 8 months, neointimal hyperplastic	2º: Device success, lesion success, procedure success, late lumen loss at 8 months, MACE at 30 days, 6, 9 and 12 months, in-stent and in-lesions binary restenosis rate at 8 months, angiographic in-stent and in-lumen diameter at 8 months, neointimal hyperplastic volume	2º: Device success, lesion success, procedure success, in-stent late lumen loss, target site revascularization (TSR) at 9 months, TVR and TVF at 9 months, angiographic binary restenosis (ABR) at 8 months, in-stent and in-segment minimum lumen diameter at 8	2º: Device success, lesion success, procedure success, angiographic in-stent and in-segment percent diameter stenosis (%DS), late lumen loss, late loss index, angiographic binary restenosis rate, minimum luminal diameter at 8 months, neointimal hyperplastic volume and percent volume	2º: Device success, lesion success, procedure success for all patients MACE at 30 days, 6, 9 and 12 months. For patients receiving overlapping stents: in-stent and in-segment percent diameter stenosis	2º: Device Success, Lesion Success, Procedure Success, Major adverse cardiac events (MACE) – 30 days, 6 and 9 months post-procedure Clinically-driven target lesion revascularization (TLR) – 9 months post-procedure, Clinically-driven target

Table 4-24: Major Study Characteristics of ENDEAVOR Trials

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR II-CA	ENDEAVOR III	ENDEAVOR IV	ENDEAVOR PK REGISTRY	ENDEAVOR JAPAN
	baseline, 4, and 12 months by IVUS.	volume at 8 months by IVUS, TLR at 8 months, PK analyses	at 8 months by IVUS, TVR and TVF at 9 months.	months, neointimal hyperplastic volume at 8 months by IVUS	obstruction (%VO) at 8 months by IVUS, target site revascularization (TSR) rate and TVR at 9 months	(%DS), late lumen loss, late loss index, angiographic binary restenosis (ABR) rate, minimum luminal diameter, neointimal hyperplastic volume and percent volume obstruction (%VO) at 8 months by IVUS, target site revascularization (TSR), TVF and TVR at 9 months	vessel revascularization (TVR) – 9 months post-procedure, In stent and in segment late loss – 8 months post-procedure (measured by Quantitative Coronary Angiography [QCA]), In stent and in segment binary angiographic restenosis (50% diameter or more stenosis) – 8 months post-procedure (measured by QCA), In stent and in segment minimal lumen diameter (MLD) – 8 months post-procedure (measured by QCA)

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The ENDEAVOR clinical program was established to demonstrate the safety and effectiveness of this new DES system in patients with progressively greater levels of clinical complexity. The initial feasibility study (ENDEAVOR I) conducted in Australia and New Zealand was limited to a group of patients in whom the treated arteries were relatively low-risk (e.g., 3.0-3.5 mm in diameter, discrete or tubular (<15 mm), coverable by a single 18 mm length stent). In the ENDEAVOR I study, history of hypertension and/or diabetes were modest, 53% and 16%, respectively. Based on excellent results in ENDEAVOR I, the subsequent trials were designed to include patients with smaller vessel diameters and greater lesion lengths. The double-blind, randomized controlled trial against the Driver stent (ENDEAVOR II) included a more complicated group of patients, including subjects with smaller native arteries (the 2.25 mm diameter stent was included), longer stented lesions (up to 27 mm per protocol), greater frequency of ≥20 mm lesions (15%), more complex B2 (53%) and C (26%) class lesions, and a slightly larger subset of patients with hypertension (66%) or diabetes (20%). The subsequent single-blind, randomized controlled US trials against Cypher (ENDEAVOR III) and Taxus (ENDEAVOR IV) stents retained or exceeded the level of complexity of the subjects seen in ENDEAVOR II, while the open-label continued access trial ENDEAVOR II-CA was even more challenging, including a majority of patients with history of hypertension (82%), a large subset with diabetes (26%), and the most complex lesions (27% ≥20 mm and 44% class C lesions). In addition, this continued access study also allowed for direct stenting of lesions < 20 mm in length at physicians' discretion. The ENDEAVOR Japan study was a 99-patient registry conducted to meet requirements for Japanese regulatory approval.

The clinical utility of the Endeavor Zotarolimus-Eluting CSS was established in each of the studies with remarkably consistent results across studies. All quantitative results (e.g., angiographic and intravascular ultrasound data) from the ENDEAVOR I, II, IICA, III, IV, and PK studies were evaluated in the same highly-experienced core laboratories in the US (Brigham and Women's Angiographic Core Laboratory and Stanford University Cardiovascular Intravascular Ultrasound Core Laboratory, respectively), ensuring a high level of consistency for these critical analyses. This consistency in data analysis across the entire dataset of patients receiving the Endeavor Zotarolimus-Eluting CSS is an important feature in interpreting the entire body of clinical data, and especially in supporting the utility of data from experience outside of the US. With only minor exceptions, the clinical studies also consistently incorporated a standard patient assessment schedule for the key core evaluations, thus ensuring reproducible evaluations of: 1) acute success parameters; 2) standard nine-month outcomes related to extent of restenosis; and 3) long-term clinical safety and efficacy related to freedom from stent failure.

The acute success parameters relate to stent deliverability. Overall, lesion and device success rates were excellent across the studies of the Endeavor Zotarolimus-Eluting CSS, in the range of 97-100% for over 2,100 recipients. Procedure success rates were similarly high for all studies, with only a slightly lower procedure success in the ENDEAVOR II-CA study (94.9%) which is expected due to a greater number of complex lesions and higher risk patients than other Endeavor trials. Delivery of the Endeavor Zotarolimus-Eluting CSS was compelling in comparison to patients receiving either the Cypher stent

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in ENDEAVOR III or the Taxus stent in ENDEAVOR IV. Procedure success rates were higher with the Endeavor stent compared to the Cypher stent (99.4% vs 95.6%) or the Taxus stent (98.7% vs 96.8%). The Endeavor Zotarolimus-Eluting CSS was associated with a lower incidence of peri-procedural non-Q wave myocardial infarctions in both ENDEAVOR III (0.6% vs 3.5%) and ENDEAVOR IV (0.5% vs 2.2%). This significant difference in non-Q wave myocardial infarctions drove the difference in procedure success in both trials.

Randomized clinical comparison of the efficacy of the Endeavor Zotarolimus-Eluting CSS to marketed drug-eluting stents provided the first head-to-head evaluation of the DES and their clinical performance in the United States. The large multi-center randomized comparisons of the Endeavor Zotarolimus-Eluting CSS and the Cypher Sirolimus-Eluting Stent (ENDEAVOR III) or Taxus Paclitaxel-Eluting Stent (ENDEAVOR IV) enrolled nearly 2,000 patients with coronary artery lesions to include lesions between 2.5 mm and 3.5 mm in diameter and up to 27 mm in length. ENDEAVOR III and IV present a unique opportunity to evaluate safety results that are directly comparable due to randomization. In addition, ENDEAVOR III and ENDEAVOR IV represent a new era in drug-eluting stent trials (a shift towards non-inferiority comparisons) which help to elucidate the relationship between angiographic parameters and clinical outcomes.

Comparison of the Endeavor Zotarolimus-Eluting CSS to the Cypher stent in ENDEAVOR III provided Endeavor clinical data in a US population. Acute success (discussed above) and 30-day MACE rates favored the Endeavor Zotarolimus-Eluting CSS over the Cypher stent, with an in-hospital MACE rate of 0.6% in the Endeavor arm vs. 3.5% in the Cypher arm.. At later time points, the two groups demonstrated generally similar efficacy based on rates of MACE, target lesion or vessel revascularization, or target vessel failure during nine-month, 12 month or 24 month follow-up evaluations, recognizing that the study was underpowered for these endpoints. The designated primary endpoint of in-segment late lumen loss at eight months was significantly higher among patients treated with Endeavor Zotarolimus-Eluting CSS versus the Cypher stent (0.36±0.46 mm vs. 0.13±0.33mm, $p<0.001$), corresponding to a higher frequency of in-segment binary restenosis (12.3% vs. 4.3%). It is noteworthy that the in-segment late loss value of the Cypher stent was lower than the observed values in other recent Cypher stent clinical trials.[40,41,42]

A significant objective in designing the ENDEAVOR III clinical trial was to determine if the angiographic and clinical results seen with the Endeavor Zotarolimus-Eluting CSS in this US clinical trial were harmonious with those from previous international clinical trials assessing Endeavor Zotarolimus-Eluting CSS. Angiographic outcomes for the

[40] Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
[41] Morice, M-C., Serruys, P.W., Sousa, J.E., Fajadet, J., Hayashi, E.B., Perin, M., Colombo, A., *et al.* "A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization." *New England Journal of Medicine* 346(23):1773-1781 (2002).
[42] Morice, M-C., Colombo, A., Meier, B., Serruys, P., Tamburino, C., Guagliumi, G., Sousa, E., Stoll, H-P. "Sirolimus – vs Paclitaxel-Eluting Stents in De Novo Coronary Artery Lesions." *Journal of the American Medical Association* 295(8):895-904 (2006).

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Endeavor Zotarolimus-Eluting CSS in the ENDEAVOR III trial were virtually identical to those observed in the ENDEAVOR II, indicating that the performance of the Endeavor Zotarolimus-Eluting CSS was consistent in randomized trials conducted abroad (ENDEAVOR II) and in the US (ENDEAVOR III). The subsequent ENDEAVOR IV trial further confirmed the consistency of these outcomes. Reference Table 4-25 below for the angiographic outcomes across trials.

Table 4-25: Consistency Across Randomized Trials

	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Follow up	8 months	8 months	8 months
In-segment late loss (n)	0.36±0.46 (246)	0.36 mm ±0.46 (277)	0.36 mm ±0.47 (143)
% diameter stenosis (n)	32.67±16.27 (264)	30.42±15.57 (277)	32.28±17.02 (144)
Binary in-segment restenosis	13.3% (35/264)	12.3% (34/277)	15.3% (22/144)

These angiographic parameters were lower than the BMS in ENDEAVOR II and higher than Cypher in ENDEAVOR III and Taxus in ENDEAVOR IV. Specifically, the in-segment late loss values for the Driver, Cypher and Taxus arms were 0.72 mm, 0.13 mm, and 0.23 mm, respectively. While Endeavor's angiographic profile is different from those of the other DES products, Endeavor has sufficiently controlled neointimal proliferation to sustain good clinical outcomes as evidenced by superior clinical outcomes compared to Driver and non-inferior clinical outcomes compared to Taxus.

4.5.1 Safety and Effectiveness

The ideal drug eluting stent should provide for superior clinical efficacy compared to bare metal stents with equivalent safety as measured by cardiac death, myocardial infarction (MI) and stent thrombosis.

In a PMA clinical program comprised of six multi-center trials, 2,133 patients assigned to receive the Endeavor stent, and 675 patients followed to three years, it has been shown that the Endeavor DES is both safe and effective and provides a net patient benefit. Endeavor significantly reduces the need for repeat revascularization vs. the Driver bare metal stent (BMS) and exhibits a long-term clinical efficacy rate that is similar to the currently available DES.

In addition, Endeavor exhibits a safety profile that may be unique among other drug eluting stents:

- Lower rates of cardiac death and MI vs. BMS based on FDA-requested post hoc, pooled analysis
- An overall rate of stent thrombosis no different than the BMS
- Numerically lower rates of periprocedural MI vs. two DES controls

The collective evidence provides assurance that Endeavor is both safe and effective.

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Effectiveness

The efficacy profile of Endeavor can be characterized as follows:

- Endeavor shows statistically superior clinical efficacy vs. the BMS control in ENDEAVOR II; this treatment effect is sustained out to three years of follow-up.
- Endeavor shows statistically non-inferior efficacy vs. the Taxus control stent at 9 months in ENDEAVOR IV. At 24 months, the TVF rate was 14.4% for Endeavor and 13.4% for Cypher in ENDEAVOR III.

Statistical improvement in clinical efficacy vs. the BMS control.

In the ENDEAVOR II trial, as shown in Table 4-26, Endeavor demonstrated clear superiority against the Driver BMS for the composite primary endpoint of Target Vessel Failure (TVF).

Table 4-26: ENDEAVOR II Primary Endpoint

	Endeavor	Driver Control	Difference [95% CI]	P value
Target Vessel Failure to 270 days	7.9% (47/592)	15.1% (89/591)	-7.1% [-10.7%,-3.5%]	<0.001

The dramatic reduction in TVF was largely driven by the reduced need for revascularization as measured by Target Lesion Revascularization (TLR). As shown in Table 4-27 below, the significant reduction in TLR vs. the BMS control has been shown to be sustained over time.

Table 4-27: ENDEAVOR II TLR Over Time

	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]*
Target Lesion Revascularization to 270 days	4.6% (27/592)	11.8% (70/591)	-7.3% [-10.4%,-4.2%]
Target Lesion Revascularization to 360 days	5.9% (35/590)	13.1% (77/589)	-7.1% [-10.5%,-3.8%]
Target Lesion Revascularization to 720 days	6.5% (38/587)	14.2% (83/586)	-7.7% [-11.1%,-4.2%]
Target Lesion Revascularization to 1080 days	7.3% (42/577)	14.7% (85/579)	-7.4% [-11.0%,-3.8%]

* Unadjusted for multiple comparisons

Endeavor exhibits a long-term clinical efficacy rate that is similar to the currently available products.

The ENDEAVOR IV trial was the first head-to-head randomized controlled trial comparing two DES using a clinical primary endpoint, Target Vessel Failure (TVF). In

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the ENDEAVOR IV trial, as shown in Table 4-28, Endeavor demonstrated clear non-inferiority to the market-leading Taxus Paclitaxel-Eluting Coronary Stent System.

Table 4-28: ENDEAVOR IV Primary Endpoint

	Endeavor	TAXUS Control	Difference [One-sided 95% CI]	P value*
Target Vessel Failure to 270 days	6.8% (50/740)	7.4% (54/734)	-0.6% [-100%, 1.6%]	0.0005

*P-value is for the test of Non-Inferiority.

In addition to the primary endpoint, as shown in Table 4-29, the rates for other major clinical endpoints in ENDEAVOR IV were also similar for Taxus and Endeavor groups.

Table 4-29: 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)	***
ARC definite + probable**	0.9% (7/740)	0.1% (1/734)	***

* Unadjusted for multiple comparisons

** Reported ARC rates are uncensored and include events that occured both before and after TLR events

*** Confidence intervals are only provided for components of the primary endpoint.

ENDEAVOR III provided for an angiographic comparison to the other marketed DES, the Cypher Sirolimus-Eluting Coronary Stent System. ENDEAVOR III was not powered to evaluate clinical endpoints. TVF results are shown in Table 4-30 for reference.

Table 4-30: ENDEAVOR III TVF

	Endeavor	CYPHER Control
Target Vessel Failure to 270 days	11.8% (38/321)	11.5% (13/113)
Target Vessel Failure to 360 days	12.8% (41/320)	11.6% (13/112)
Target Vessel Failure to 720 days	14.4% (45/313)	13.4% (15/112)

Protocol-mandated angiographic follow-up led to a slight increase in TLR as reported at 9 months. This was consistently demonstrated across each of the randomized trials. As shown in Table 4-31 through Table 4-33 below, for patients in ENDEAVOR II and ENDEAVOR IV with angiographic follow-up, the 270 day TLR rate ranged from 5.7% to 6.9% compared to patients with clinical follow-up who had TLR rates ranging from 3.5% to 3.7%.

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Table 4-31: Angiographic vs. Clinical Follow-up TLR (ENDEAVOR II)

	Angiographic Follow-up		Clinical only Follow-up	
	Endeavor N=264	Driver N=265	Endeavor N=334	Driver N=334
TLR at 270 days	5.7% (15/264)	16.2% (43/265)	3.7% (12/328)	8.3% (27/326)

Table 4-32: Angiographic vs. Clinical Follow-up TLR (ENDEAVOR III*)

	Angiographic Follow-up		Clinical only Follow-up	
	Endeavor N=277	Cypher N=94	Endeavor N=46	Cypher N=19
TLR at 270 days	6.7% (19/277)	4.3% (4/94)	2.3% (2/44)	0.0% (0/19)

* All patients were scheduled to receive angiographic follow-up in ENDEAVOR III

Table 4-33: Angiographic vs. Clinical Follow-up TLR (ENDEAVOR IV)

	Angiographic Follow-up		Clinical only Follow-up	
	Endeavor N=144	Taxus N=135	Endeavor N=629	Taxus N=640
TLR at 270 days	6.9% (10/144)	3.0% (4/133)	3.5% (21/596)	2.7% (16/601)

Safety

As mentioned in the opening comments in this section, the ideal drug eluting stent should not only exhibit superior efficacy as compared to a BMS, but it should also exhibit equivalent safety as measured by stent thrombosis, cardiac death, and MI. In both head-to-head comparisons of Endeavor vs. Driver in ENDEAVOR II and in the post-hoc pooled analysis requested by FDA (ENDEAVOR I, II, IICA, III, IV and PK vs. Driver), Endeavor exhibits an equivalent or better safety profile than the bare metal control. As demonstrated in Table 4-34, in Endeavor II, at both the 9 month timepoint and the 36 month timepoint, Endeavor shows rates of death, MI, and stent thrombosis that are not statistically different from the Driver BMS control.

Table 4-34: ENDEAVOR II Clinical Measures at 270 and 1080 Days

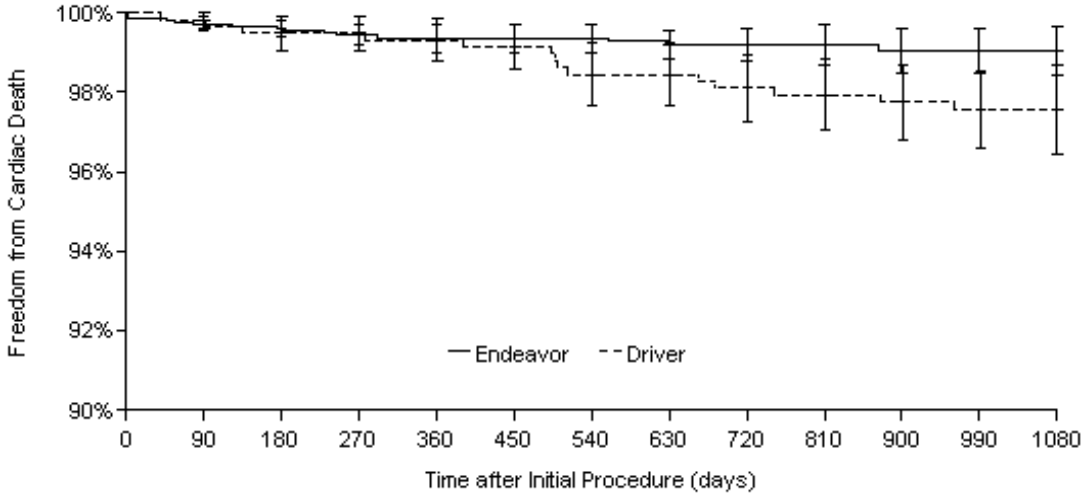
	270 days			1080 days		
	Endeavor	**Driver Control**	**Difference [95% CI]***	**Endeavor**	**Driver Control**	**Difference [95% CI]***
TVF Rate	7.9% (47/592)	15.1% (89/591)	-7.1% [-10.7%,-3.5%]	12.8% (74/577)	21.4%(124/579)	-8.6% [-12.9%,-4.3%]
Death	1.2%(7/592)	0.5%(3/591)	0.7% [-0.4%,1.7%]	3.3% (19/577)	4.5% (26/579)	-1.2% [-3.4%,1.0%]
Cardiac Death	0.8%(5/592)	0.5%(3/591)	0.3% [-0.6%,1.3%]	1.6% (9/577)	2.4% (14/579)	-0.9%[-2.5%,0.8%]
MI	2.7%(16/592)	3.9%(23/591)	-1.2% [-3.2%,0.8%]	3.3% (19/577)	4.3%(25/579)	-1.0% [-3.2%,1.2%]
Q-wave MI	0.3%(2/592)	0.8%(5/591)	-0.5% [-1.4%,0.4%]	0.3% (2/577)	1.0%(6/579)	-0.7% [-1.6%,0.3%]
Non Q-wave MI	2.4%(14/592)	3.0%(18/591)	-0.7% [-2.5%,1.2%]	2.9% (17/577)	3.3% (19/579)	-0.3% [-2.3%,1.7%]
TLR	4.6%(27/592)	11.8%(70/591)	-7.3% [-10.4%,-4.2%]	7.3% (42/577)	14.7%(85/579)	-7.4% [-11.0%,-3.8%]
TVR	5.6%(33/592)	12.5%(74/591)	-6.9% [-10.2%,-3.7%]	9.5% (55/577)	17.6%(102/579)	-8.1% [-12.0%,-4.2%]
Stent thrombosis						
Protocol	0.5%(3/592)	1.2%(7/591)	***	0.5% (3/577)	1.2% (7/579)	***
ARC definite + probable **	0.5%(3/592)	1.4%(8/591)	***	0.9% (5/577)	1.6% (9/579)	***

* Unadjusted for multiple comparisons

** Reported ARC rates are uncensored and include events that occured both before and after TLR events

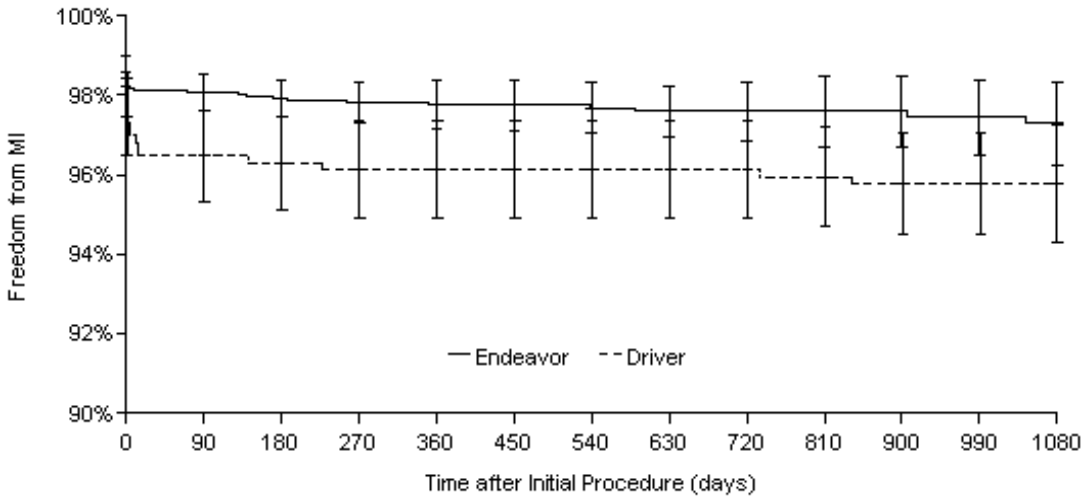
*** Confidence intervals are only provided for components of the primary endpoint.

Moreover, when examining the FDA-requested pooled Endeavor data set vs. the BMS control, the safety trends shown in the ENDEAVOR II trial are further demonstrated. As shown in this post hoc analysis provided in Figure 4-14 through Figure 4-16below, at three years, Endeavor shows lower critical event rates of cardiac death, MI, and combined cardiac death and MI compared to Driver.



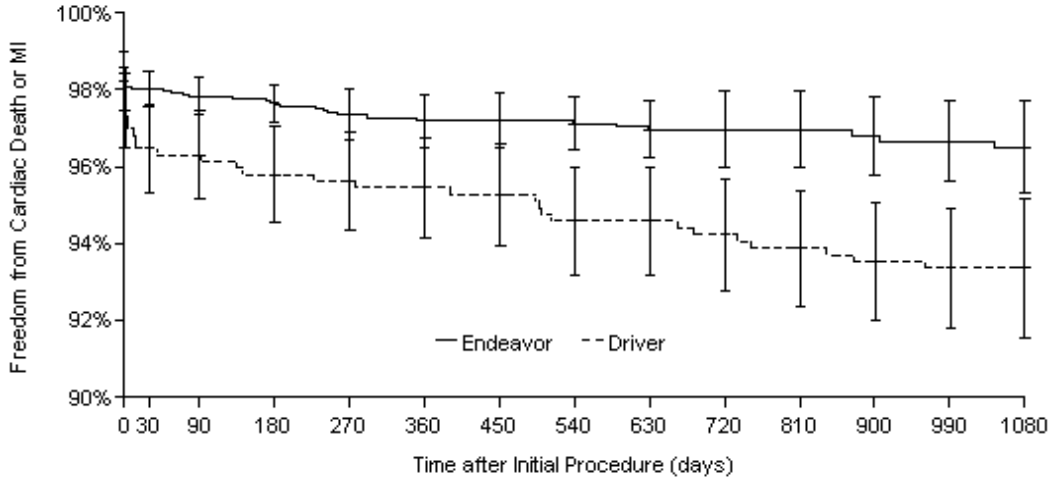
Cardiac Death	0	30	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor														
# Entered	2132	2132	2116	2103	2090	1291	1278	1261	1256	1251	665	655	653	651
# Censored	0	13	10	11	795	12	17	5	3	586	10	1	2	121
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	0	3	3	2	4	1	0	0	2	0	0	1	0	0
% Survived	100.0%	99.9%	99.7%	99.6%	99.4%	99.4%	99.4%	99.4%	99.2%	99.2%	99.2%	99.0%	99.0%	99.0%
SE	0.0%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.2%	0.3%	0.3%	0.3%	0.4%	0.4%	0.4%
Driver														
# Entered	596	596	594	592	588	583	576	572	568	568	562	557	555	551
# Censored	0	2	1	2	5	6	3	0	0	4	4	1	3	134
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	0	0	1	2	0	1	1	4	0	2	1	1	1	0
% Survived	100.0%	100.0%	99.8%	99.5%	99.5%	99.3%	99.1%	98.5%	98.5%	98.1%	97.9%	97.8%	97.6%	97.6%
SE	0.0%	0.0%	0.2%	0.3%	0.3%	0.3%	0.4%	0.5%	0.5%	0.6%	0.6%	0.6%	0.6%	0.7%
Tests Between Groups														
	Test	Chi-Square	Deg Frdm	P Value										
	Log-Rank	5.00	1	0.025										
	Wilcoxon	2.89	1	0.089										

Figure 4-14: Survival Free from Cardiac Death to 1080 Days



MI	0	30	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor														
# Entered	2132	2102	2077	2063	2048	1259	1246	1230	1224	1219	649	639	637	634
# Censored	0	12	9	10	780	11	15	1	1	570	7	0	0	113
# Incomplete	0	3	4	2	7	1	1	4	3	0	3	2	2	2
# Events	30	10	1	3	2	1	0	1	1	0	0	0	1	1
% Survived	98.6%	98.1%	98.1%	97.9%	97.8%	97.8%	97.8%	97.7%	97.6%	97.6%	97.6%	97.6%	97.4%	97.3%
SE	0.3%	0.3%	0.3%	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.6%	0.6%	0.6%	0.6%	0.7%
Driver														
# Entered	596	581	573	571	566	560	553	549	545	545	539	534	532	528
# Censored	0	2	1	2	5	6	2	0	0	3	2	0	1	123
# Incomplete	0	0	1	2	0	1	2	4	0	3	2	1	3	5
# Events	15	6	0	1	1	0	0	0	0	0	1	1	0	0
% Survived	97.5%	96.5%	96.5%	96.3%	96.1%	96.1%	96.1%	96.1%	96.1%	96.1%	96.0%	95.8%	95.8%	95.8%
SE	0.6%	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%	0.9%	0.9%	1.0%
Tests Between Groups														
	Test	Chi-Square	Deg Frdm	P Value										
	Log-Rank	3.93	1	0.047										
	Wilcoxon	4.57	1	0.033										

Figure 4-15: Survival Free from MI to 1080 Days



Cardiac Death or MI	0	30	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor														
# Entered	2132	2102	2077	2063	2048	1259	1246	1230	1224	1219	649	639	637	634
# Censored	0	12	9	10	780	11	15	1	1	570	7	0	0	113
# Incomplete	0	1	1	1	3	0	1	4	2	0	3	1	2	2
# Events	30	12	4	4	6	2	0	1	2	0	0	1	1	1
% Survived	98.6%	98.0%	97.8%	97.6%	97.4%	97.2%	97.2%	97.1%	97.0%	97.0%	97.0%	96.8%	96.7%	96.5%
SE	0.3%	0.3%	0.3%	0.3%	0.4%	0.5%	0.5%	0.5%	0.5%	0.7%	0.7%	0.7%	0.7%	0.8%
Driver														
# Entered	596	581	573	571	566	560	553	549	545	545	539	534	532	528
# Censored	0	2	1	2	5	6	2	0	0	3	2	0	1	123
# Incomplete	0	0	0	0	0	0	1	0	0	1	1	0	2	5
# Events	15	6	1	3	1	1	1	4	0	2	2	2	1	0
% Survived	97.5%	96.5%	96.3%	95.8%	95.6%	95.5%	95.3%	94.6%	94.6%	94.2%	93.9%	93.5%	93.4%	93.4%
SE	0.6%	0.8%	0.8%	0.8%	0.8%	0.9%	0.9%	0.9%	0.9%	1.0%	1.0%	1.0%	1.0%	1.2%
Tests Between Groups														
	Test	Chi-Square	Deg Frdm	P Value										
	Log-Rank	9.80	1	0.002										
	Wilcoxon	8.44	1	0.004										

Figure 4-16: Survival Free from Cardiac Death or MI at 1080 Days

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For the critical safety endpoint of stent thrombosis, Endeavor rates have been reported using two different reporting mechanisms: the pre-specified protocol definition and the retrospective Academic Research Consortium (ARC) event rates. Regardless of the method for reporting, both the randomized ENDEAVOR II comparison and the FDA-requested pooled analysis have shown Endeavor to have low event rates that are similar to or lower than the Driver BMS. The ENDEAVOR II stent thrombosis rates at 270 days and 1080 days are provided in Table 4-35 below.

Table 4-35: ENDEAVOR II Stent Thrombosis Rates*

	270 days		1080 days	
	Endeavor	**Driver Control**	**Endeavor**	**Driver Control**
Protocol	0.5%(3/592)	1.2%(7/591)	0.5% (3/577)	1.2% (7/579)
ARC definite + probable	0.5%(3/592)	1.4%(8/591)	0.9% (5/577)	1.6% (9/579)

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

Similarly, upon examination of the pre-specified protocol definition and the more conservative uncensored ARC definitions, the pooled comparison provided in Table 4-36 continues to show no increase in stent thrombosis events for the Endeavor stent compared to the Driver stent.

Table 4-36: Pooled Stent Thrombosis*

	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 Plus Probable	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 Plus Probable	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 Plus Probable	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 Plus Probable	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 Plus Probable	0.9% (6/675)	[0.3%,1.9%]	1.6% (9/579)	[0.7%,2.9%]

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

When comparing the rates of stent thrombosis, it is important to analyze the timing of stent thrombosis events. It has been reported that the timing of stent thrombosis events with currently available drug-eluting stents appears to be different from that of bare metal stents, with a numerical increase in the frequency of very late stent thrombosis.[43]

[43] Laskey WK, Yancy CW, Maisel WH, Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. Circulation. 2007 May 1;115(17):2352-7.

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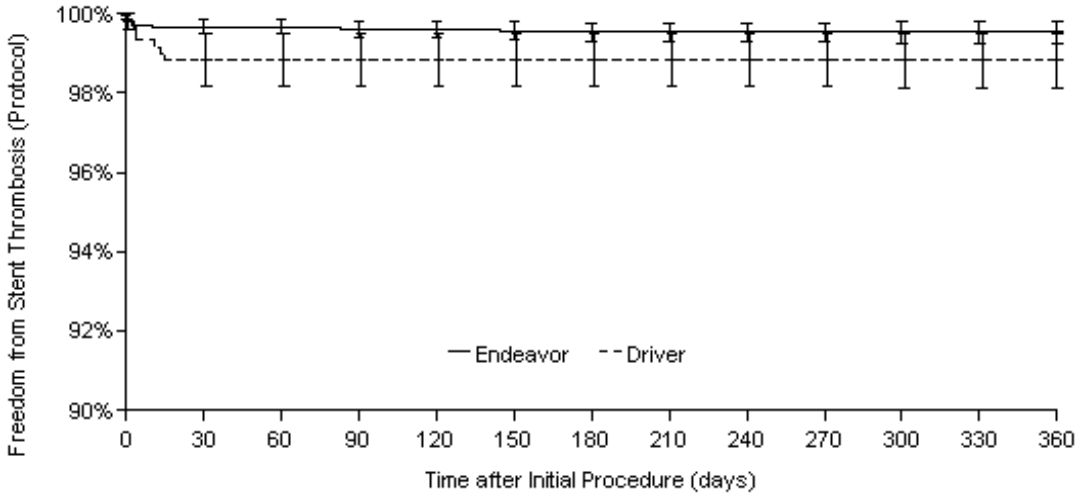
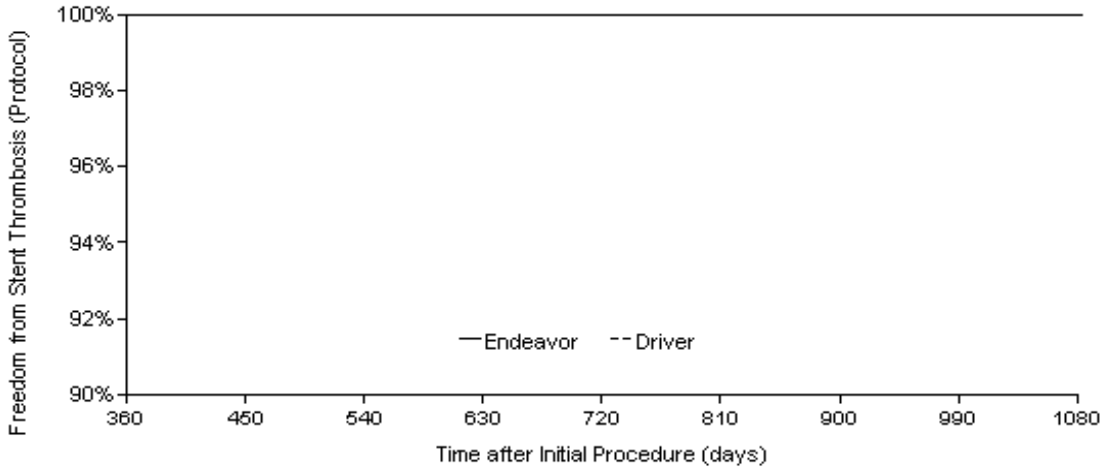
The rates of stent thrombosis in the Endeavor program were analyzed prior to six months and after six months, as well as prior to one year and after one year in order to determine if there was an increase in late events. When examining stent thrombosis, at each interval analyzed, Endeavor exhibits a rate of stent thrombosis that is no different from that of the Driver bare metal stent. Beyond one year, the Endeavor stent showed zero stent thrombosis by the pre-specified protocol definition, and there was one event in both Endeavor and Driver arms of the ENDEAVOR II clinical trial by the *post hoc* ARC definition (definite plus probable). The pre- and post-one-year stent thrombosis rates are provided in Figure 4-17 through Figure 4-20 below.



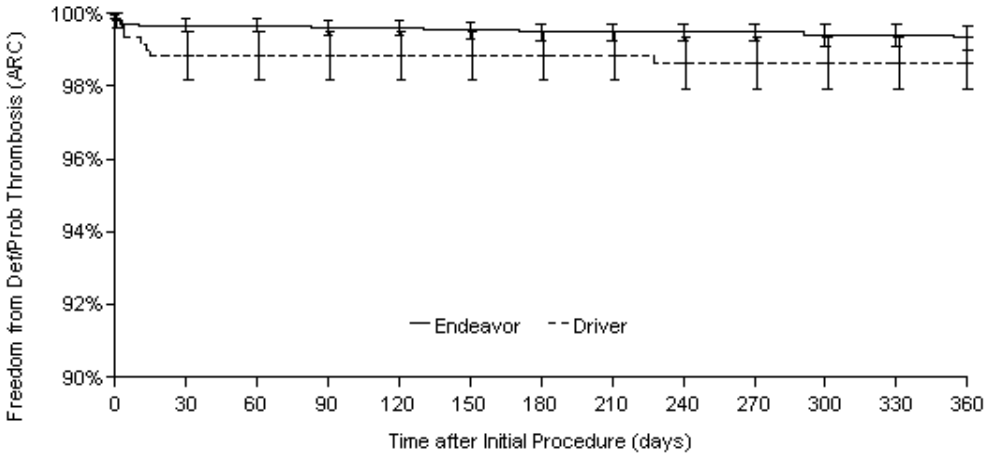
Stent Thrombosis (Protocol)	0	30	60	90	120	150	180	210	240	270	300	330	360
Endeavor													
# Entered	2132	2131	2111	2100	2097	2097	2094	2082	2074	2065	1918	1283	1278
# Censored	0	12	8	1	0	0	10	7	7	143	634	5	3
# Incomplete	0	2	3	1	0	2	1	1	2	4	1	0	0
# Events	1	6	0	1	0	1	1	0	0	0	0	0	0
% Survived	100.0%	99.7%	99.7%	99.6%	99.6%	99.6%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%
SE	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Driver													
# Entered	596	595	587	586	585	584	582	581	580	580	576	570	570
# Censored	0	2	0	1	0	1	1	1	0	4	5	0	1
# Incomplete	0	0	1	0	1	1	0	0	0	0	1	0	0
# Events	1	6	0	0	0	0	0	0	0	0	0	0	0
% Survived	99.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%
SE	0.2%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Log-Rank	3.73	1	0.053									
	Wilcoxon	3.75	1	0.053									

Figure 4-17: Survival Free from Stent Thrombosis (Protocol) Prior to 360 Days



Stent Thrombosis (Protocol)	360	450	540	630	720	810	900	990	1080
Endeavor									
# Entered	1278	1278	1261	1256	1251	1008	655	653	651
# Censored	0	16	1	1	242	350	0	0	119
# Incomplete	0	1	4	4	1	3	2	2	2
# Events	0	0	0	0	0	0	0	0	0
% Survived	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
SE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Driver									
# Entered	576	576	572	568	568	562	557	555	551
# Censored	0	2	0	0	3	2	0	1	129
# Incomplete	0	2	4	0	3	3	2	3	5
# Events	0	0	0	0	0	0	0	0	0
% Survived	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
SE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Tests Between Groups									
	Test	Chi-Square	Deg Frdm	P-value					
	Log-Rank	0.00	0	--					
	Wilcoxon	0.00	0	--					

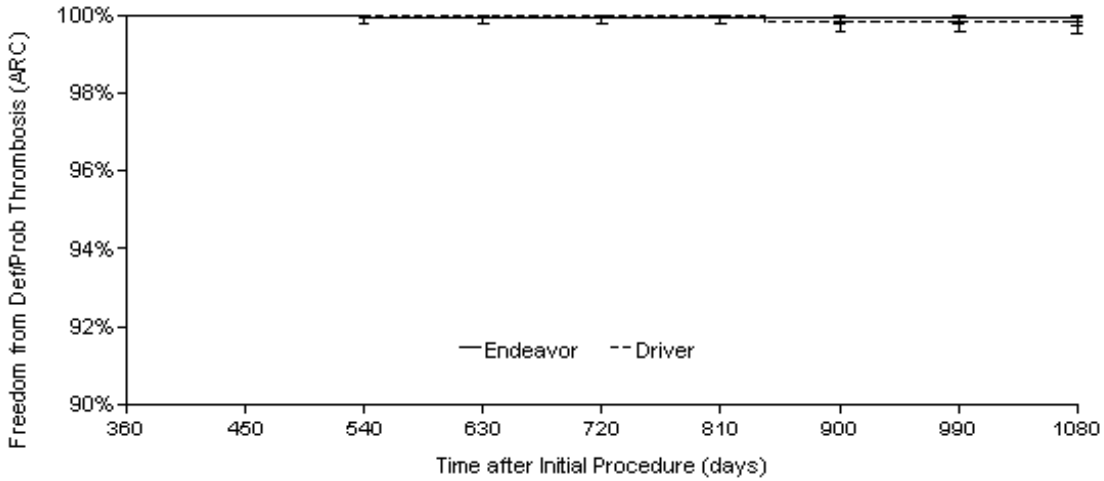
Figure 4-18: Survival Free from Stent Thrombosis (Protocol) between 361 and 1080 Days



Def/Prob Thrombosis (ARC)	0	30	60	90	120	150	180	210	240	270	300	330	360
Endeavor													
# Entered	2132	2131	2111	2100	2097	2097	2093	2081	2073	2064	1917	1283	1278
# Censored	0	12	8	1	0	0	10	7	7	143	633	5	3
# Incomplete	0	2	3	1	0	2	1	1	2	4	0	0	0
# Events	1	6	0	1	0	2	1	0	0	0	1	0	1
% Survived	100.0%	99.7%	99.7%	99.6%	99.6%	99.5%	99.5%	99.5%	99.5%	99.5%	99.4%	99.4%	99.3%
SE	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Driver													
# Entered	596	595	587	586	585	584	582	581	580	579	575	569	569
# Censored	0	2	0	1	0	1	1	1	0	4	5	0	1
# Incomplete	0	0	1	0	1	1	0	0	0	0	1	0	0
# Events	1	6	0	0	0	0	0	0	1	0	0	0	0
% Survived	99.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.8%	98.7%	98.7%	98.7%	98.7%	98.7%
SE	0.2%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.5%	0.5%	0.5%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Log-Rank	2.86	1	0.091									
	Wilcoxon	3.42	1	0.064									

Figure 4-19: Survival Free from Def/Prob Thrombosis (ARC) Prior to 360 Days*

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events



Def/Prob Thrombosis (ARC)	360	450	540	630	720	810	900	990	1080
Endeavor									
# Entered	1278	1278	1261	1255	1251	1008	655	653	651
# Censored	0	16	1	1	242	350	0	0	119
# Incomplete	0	1	4	3	1	3	2	2	2
# Events	0	0	1	0	0	0	0	0	0
% Survived	100.0%	100.0%	99.9%	99.9%	99.9%	99.9%	99.9%	99.9%	99.9%
SE	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Driver									
# Entered	576	576	572	568	568	562	557	554	550
# Censored	0	2	0	0	3	2	0	1	129
# Incomplete	0	2	4	0	3	3	2	3	5
# Events	0	0	0	0	0	0	1	0	0
% Survived	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.8%	99.8%	99.8%
SE	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.2%	0.2%
Tests Between Groups									
	Test	Chi-Square	Deg Frdm	P-value					
	Log-Rank	0.11	1	0.737					
	Wilcoxon	0.01	1	0.934					

Figure 4-20: Survival Free from Definite/Probable Thrombosis (ARC) between 361 and 1080 Days*

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

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Diabetes has been a patient population of interest with drug-eluting stents.[44] Post-hoc subset analyses have been performed at the FDA's request to assess the outcomes of patients with diabetes. As shown in Table 4-37, for the pooled Endeavor patients, there were no increases in the rates of death, cardiac death, MI, or stent thrombosis among all diabetics or insulin or non-insulin dependent diabetics. There was an expected increase in the rates of TLR and TVR among diabetics.

Table 4-37: Diabetes - Pooled Endeavor Clinical Events at 270 Days

	Non-Diabetics N=1549	All Diabetics N=537
Death	0.8% (12/1522)	0.8% (4/521)
Cardiac Death	0.5% (7/1522)	0.6% (3/521)
MI	2.4% (37/1522)	1.5% (8/521)
Cardiac Death or MI	2.8% (43/1522)	1.9% (10/521)
Protocol ST	0.5% (7/1522)	0.6% (3/521)
Definite and Probable ST (ARC)*	0.5% (7/1522)	0.8% (4/521)
TLR	4.1% (62/1522)	6.3% (33/521)
TVR	5.8% (89/1522)	9.4% (49/521)
	Non-Diabetics N=1549	**Insulin-Dependent N=154**
Death	0.8% (12/1522)	0.7% (1/150)
Cardiac Death	0.5% (7/1522)	0% (0/150)
MI	2.4% (37/1522)	2% (3/150)
Cardiac Death or MI	2.8% (43/1522)	2% (3/150)
Protocol ST	0.5% (7/1522)	0.7% (1/150)
Definite and Probable ST (ARC)*	0.5% (7/1522)	1.3% (2/150)
TLR	4.1% (62/1522)	6% (9/150)
TVR	5.8% (89/1522)	8% (12/150)
	Non-Diabetics N=1549	**Non-Insulin-Dependent N=381**
Death	0.8% (12/1522)	0.8% (3/369)
Cardiac Death	0.5% (7/1522)	0.8% (3/369)
MI	2.4% (37/1522)	1.4% (5/369)
Cardiac Death or MI	2.8% (43/1522)	1.9% (7/369)
Protocol ST	0.5% (7/1522)	0.5% (2/369)
Definite and Probable ST (ARC)*	0.5% (7/1522)	0.5% (2/369)
TLR	4.1% (62/1522)	6.5% (24/369)
TVR	5.8% (89/1522)	9.8% (36/369)

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

[44] Pinto Slottow TL, Waksman R, Overview of the 2006 Food and Drug Administration Circulatory System Devices Panel meeting on drug-eluting stent thrombosis. Catheter Cardiovasc Interv. 2007 Jun 1;69(7):1064-74.

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In addition, the clinical event rates for diabetic patients from the pooled Endeavor studies and the diabetic Driver patients from ENDEAVOR II are also provided. These data show no increase in the rates of death, cardiac death, MI, or stent thrombosis with Endeavor compared to Driver.

Table 4-38: Diabetes – Pooled Endeavor Clinical Events and Driver at 270 Days

	Endeavor N=537	Driver N=132
Death	0.8% (4/521)	1.5% (2/132)
Cardiac Death	0.6% (3/521)	1.5% (2/132)
MI	1.5% (8/521)	3.8% (5/132)
Cardiac Death or MI	1.9% (10/521)	5.3% (7/132)
Protocol ST	0.6% (3/521)	2.3% (3/132)
Definite and Probable ST (ARC)*	0.8% (4/521)	2.3% (3/132)
TLR	6.3% (33/521)	15.2% (20/132)
TVR	9.4% (49/521)	15.9% (21/132)

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

The clinical event rates for Endeavor and Taxus patients in the randomized ENDEAVOR IV study are also provided which show no demonstrated increase in the rates of death, cardiac death, MI, or stent thrombosis with Endeavor compared to Taxus.

Table 4-39: Diabetes – ENDEAVOR IV Clinical Events at 270 Days

	Endeavor N=241	Taxus N=236
Death	0% (0/227)	0.4% (1/223)
Cardiac Death	0% (0/227)	0.4% (1/223)
MI	0.9% (2/227)	0.9% (2/223)
Cardiac Death or MI	0.9% (2/227)	1.3% (3/223)
Protocol ST	0.9% (2/227)	0.4% (1/223)
Definite and Probable ST (ARC)*	1.3% (3/227)	0.4% (1/223)
TLR	6.2% (14/227)	5.8% (13/223)
TVR	7.9% (18/227)	7.6% (17/223)

* Reported ARC rates are uncensored and include events that occurred both before and after TLR events

Interim data is also available from an Endeavor OUS postmarket registry. After commercialization of the Endeavor Zotarolimus-Eluting Coronary Stent System (CSS) outside the United States (US), Medtronic initiated the Endeavor-FIVE (E-FIVE) post approval study to continue to monitor safety and performance in the commercial market place. Approximately 200 centers located in Europe, Asia, Australia, New Zealand and South America enrolled over 8000 patients into this registry. Patient enrollment started in September 2005 and is currently ongoing. There were 2015 patients enrolled through March 16, 2006 at 73 centers. Per FDA's request, an interim report was compiled with 30-day data on the first 2000 patients enrolled into the study and submitted in the original PMA for Endeavor. In addition, one year data is now available from the first approximately 1000 patients enrolled in the study. The interim E-FIVE data presented below in Table 4-40 at one year demonstrates low rates of critical events in the

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postmarket setting. The pooled Endeavor rates from the analysis described above are also provided for reference.

Table 4-40: Interim 12-Month E-FIVE Data

12 Month Outcomes	E-Five (N=1016)	ENDEAVOR Pooled (N=2132)
MACE	6.3% (61/970)	8.8%(115/1301)
Death	2.5% (24/970)	0.9%(12/1301)
Cardiac Death	1.6% (16/970)	0.6%(8/1301)
Non-cardiac Death	0.8% (8/970)	0.3%(4/1301)
Q Wave MI	0.4% (4/970)	0.2%(3/1301)
Non Q Wave MI	1.1% (11/970)	2.5%(32/1301)
TLR	3.3% (32/970)	5.9%(77/1301)
Stent Thrombosis (Protocol)		
30 days	0.8% (8/1011)	0.3%(7/2128)
12 months	1.0% (9/970)	0.3%(4/1301)

Finally, while late safety events have been the predominant focus recently for DES, Endeavor shows lower peri-procedural MACE rates as compared to both Cypher (in the ENDEAVOR III trial) and Taxus (in the ENDEAVOR IV trial). Although these trials were not designed to detect these differences, as shown in Table 4-41 and Table 4-42 below, the Endeavor stent produced a six-fold lower frequency of in-hospital MACE compared to the Cypher stent and a three-fold lower frequency compared to the Taxus stent.

Table 4-41: ENDEAVOR III Peri-Procedural MACE

	ENDEAVOR	CYPHER
In-Hospital MACE	0.6% (2/323)	3.5% (4/113)
MACE to 30 Days	0.6% (2/323)	3.5% (4/113)

Table 4-42: ENDEAVOR IV Peri-Procedural MACE

	ENDEAVOR	TAXUS
In-Hospital MACE	0.9% (7/773)	2.6% (20/775)
MACE to 30 Days	1.2% (9/770)	3.0% (23/771)

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In summary, the clinical program has shown that the Endeavor DES is both safe and effective and provides a net patient benefit:

Endeavor significantly reduces the need for repeat revascularization vs. the Driver BMS control and exhibits a long-term clinical efficacy rate that is similar to the currently available DES products.

In addition, the Endeavor stent exhibits an excellent safety profile: the pooled analysis shows low rates of cardiac death, MI, and stent thrombosis vs. the bare metal stent. In addition, the timing of these events has been similar with no apparent increase in these critical events after one year.

The collective evidence provides assurance that Endeavor is both safe and effective.

4.6 Conclusion

The Endeavor Zotarolimus-Eluting CSS pre-approval clinical trial program consists of multiple trials in which 2,133 patients were assigned to receive the Endeavor stent, and substantial follow up data is now available: 2,088 patients to 9 months, 1,301 patients to 12 months, 1,287 patients to 24 months, 675 patients to 36 months, and 97 patients to 48 months.

Endeavor's clinical results are complemented by a robust and comprehensive pre-clinical program which concluded that the stents performed as expected in the animal models, without evidence of increased toxicity due to the presence of the drug coating. During the vessel healing process post implant, the Endeavor stent allows for rapid and functional endothelialization with a low and acceptable inflammatory response as shown in pre-clinical studies.

Of the adverse events identified in the Endeavor studies, there was no evidence to suggest potential consequences of immunosuppression, and no laboratory abnormalities attributed to zotarolimus were identified. These results are consistent with excellent tolerability of zotarolimus demonstrated in early intravenous drug safety studies. Zotarolimus pharmacokinetics were characterized in two clinical studies of the Endeavor Zotarolimus-Eluting CSS by low maximum blood concentrations, rapid achievement of the blood maximum concentration, short half-life and rapid clearance of drug from the blood. There was no evidence of dose dumping. In the majority of patients, zotarolimus was not detectable in blood by approximately one to three days following stent placement.

In multiple clinical trials in the US and abroad, the Endeavor stent was shown to be highly deliverable even in patients with highly complex coronary lesions, with higher procedure success rates than the Cypher and Taxus stents in the ENDEAVOR III (99.4% vs. 95.6%) and ENDEAVOR IV trials (98.7% vs. 96.8%), respectively. Clinical performance as assessed by the primary endpoint of Target Vessel Failure was superior to the bare metal Driver stent in the randomized ENDEAVOR II trial and non-inferior to the Taxus stent in the ENDEAVOR IV trial. Based on angiographic endpoints, rates of restenosis were low and consistent across the trials of the Endeavor Zotarolimus-Eluting CSS, and angiographic endpoints for the Endeavor Zotarolimus-Eluting CSS were statistically lower in comparison to the Driver stent. The Endeavor Zotarolimus-Eluting CSS was shown to have a different angiographic profile compared to Cypher and Taxus; however, non-inferiority was clearly demonstrated in ENDEAVOR IV for the endpoint

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of 9 month TVF. In all studies, there was no evidence of distal or systemic adverse reactions to the Endeavor Zotarolimus-Eluting CSS, consistent with the minimal, transient systemic exposure to zotarolimus shown in the ENDEAVOR II PK subset and the ENDEAVOR US PK trial. Based on these data, the Endeavor Zotarolimus-Eluting CSS has been shown to consistently provide safe and effective coronary artery stenting, with superior rates of target vessel failure compared to a marketed bare metal stent and non-inferior rates compared to a marketed drug eluting stent.

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5.0 Product Description

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5.0 Product Description

The Endeavor Zotarolimus-Eluting Coronary Stent System (CSS) is a device / drug combination product comprised of device components (the Driver™ Coronary Stent and the Micro-Driver™ Coronary Stents and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus and phosphorylcholine polymer coating).

The Endeavor product has four main components:

- Stent - the Endeavor stent component (bare metal substrate) is identical to the Driver and the Micro-Driver Coronary Stents
- Delivery Systems – The Endeavor OTW, RX and MX^2 delivery systems.
- Polymer - the phosphorylcholine (PC) polymer is identical to that utilized in the Bio*divYsio*™ PC coated stent (P000011, approved September 29, 2000)
- Drug - the drug substance zotarolimus[1] (ABT-578), licensed from Abbott Laboratories.

The stent component of the Endeavor Zotarolimus-Eluting CSS is manufactured from a cobalt based alloy (MP35N) that has been successfully used in other implantable medical devices since 1985, including septal occluders, hip prostheses, aneurysm clips, pacing leads, vena cava filters, and bare metal coronary stents. The Endeavor stent is identical to the approved Driver (P030009, approved October 1, 2003) and the approved Micro-Driver (P030009/S002, approved April 21, 2006) coronary stents.

The Endeavor stent is mounted on one of three delivery systems. The three delivery systems offered with the Endeavor stent are the Over-The-Wire (OTW), Rapid Exchange (RX) and Multi Exchange II (MX^2) Delivery Systems. The delivery systems utilized for the Endeavor product are similar in materials, design and construction to the approved Driver OTW (P030009, approved October 1, 2003; Driver MX^2 P030009/S001, approved on August 4, 2004; Driver RX, P030009/S003, approved on December 22, 2005) and the approved Micro-Driver OTW and MX^2 (P030009/S002, approved on April 21, 2006) delivery systems.

The polymer coating on the Endeavor stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for the drug zotarolimus. PC polymer was originally developed by Biocompatibles UK, Ltd. to increase the biocompatibility and hemocompatibility of materials through biomembrane mimicry, as PC is the major lipid headgroup component found in the outer surface of biologic cell membranes. Reference Figure 5-1 below.

[1] The drug substance previously referred to as ABT-578 has been assigned the name Zotarolimus (Reference USAN [QQ-84] at www.ama-assn.org)

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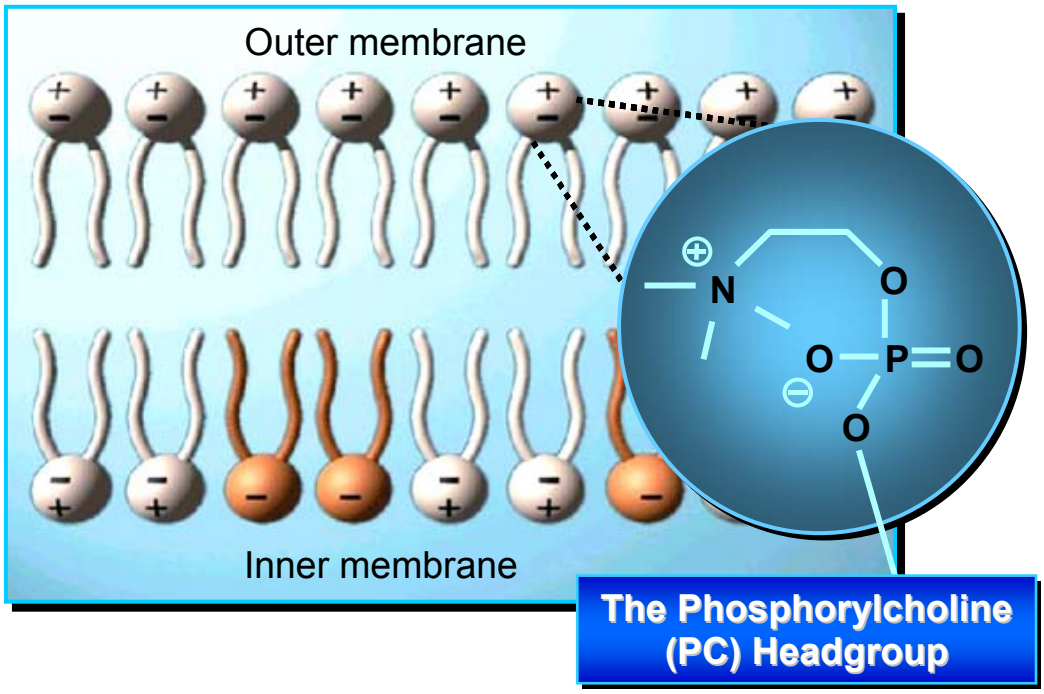

Figure 5-1: Graphical Depiction of Cell Membrane

PC polymer has been in use in Europe on coronary stents since 1997. The BiodivYsio PC coated stent was CE mark approved (Approval number: CE 02073) on September 4, 1998. PC coated stents have also been in use since 2000 in the United States, marketed as the BiodivYsio™ as PC coated stent and delivery system (P000011, approved September 29, 2000). The BiodivYsio™ PC coated stent has been successfully implanted worldwide in over 100,000 patients to date[2,3,4,5,6,7,8]. It has also been used in other medical implants where it has been shown to decrease thrombin formation on devices used for cardiac surgery [9] and to decrease platelet deposition when coated on arteriovenous (AV) grafts.[10]

[2] Cumberland DC, et al. Biomimicry 1:PC. Seminars in Interventional Cardiology 1998 Sep-Dec; 3(3-4): 149-50.
[3] Kuiper KK, Robinson KA, Chronos NAF, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated metallic stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J 1998; 32(5): 261-268.
[4] Zheng H, Barragan P, Corcos T, Simeoni JB, Favereau X, Roquebert PO, et al. Clinical experience with a new biocompatible phosphorylcholine-coated coronary stent. J Invasive Cardiol; 1999 Oct; 11(10): 608-614.
[5] Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart 2000 Mar; 83(3): 338-345.
[6] Boland JL, Corbeij HAM, van der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, et al. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. Int J Cardiovasc Intervent 2000 Dec; 3(4): 215-225.
[7] Atalar E, Haznedaroglu I, Aytemir K, Aksoyek S, Ovonc K, Oto A, et al. Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation. Clin Cardiol 2001 Feb; 24(2): 159-164.
[8] Malik N, Gunn J, Shepherd L, Crossman D, Cumberland DC, Holt CM. Phosphorylcholine-coated stents in porcine coronary arteries: In-vivo assessment of biocompatibility. J Invasive Cardiol 2001 Mar; 13(3): 193-201.
[9] F. Pappalardo, P. D. Valle, G. Crescenzi, C. Corno, A. Franco, L. Torracca, O. Alfieri, L. Galli, A. Zangrillo, and A. D'Angelo Phosphorylcholine Coating May Limit Thrombin Formation During High-Risk Cardiac Surgery: A Randomized Controlled Trial Ann. Thorac. Surg., March 1, 2006; 81(3): 886 - 891.
[10] Chen C, Ofenloch JC, Yianni YP, Hanson SR, Lumsden AB. Phosphorylcholine coating of ePTFE reduces platelet deposition and neointimal hyperplasia in arteriovenous grafts. J Surg Res 1998; 77: 119–125.

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The Endeavor drug component, zotarolimus is a tetrazole–containing macrocyclic immunosuppressant. [redacted] abluminal side of the stent. A representative schematic is shown in Figure 5-2 (not to scale).

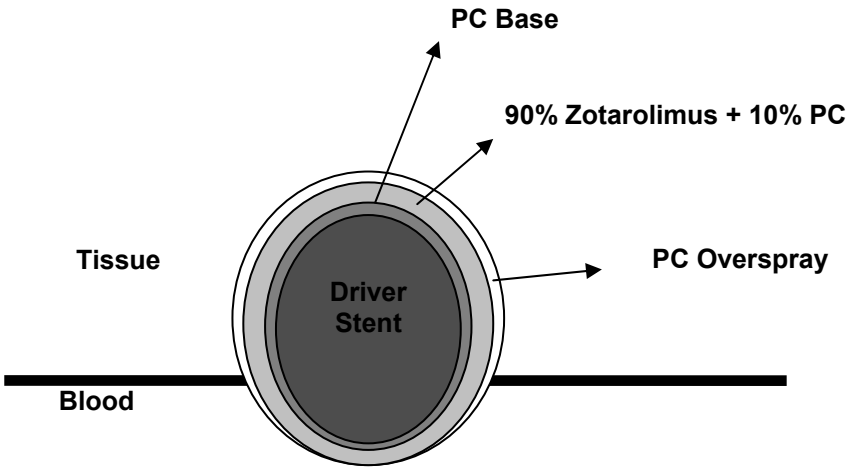

Figure 5-2: Cross Section of an Endeavor Stent Strut – a schematic (not to scale)

[redacted] A scaled schematic of the various coating layers is provided in Figure 5-3.

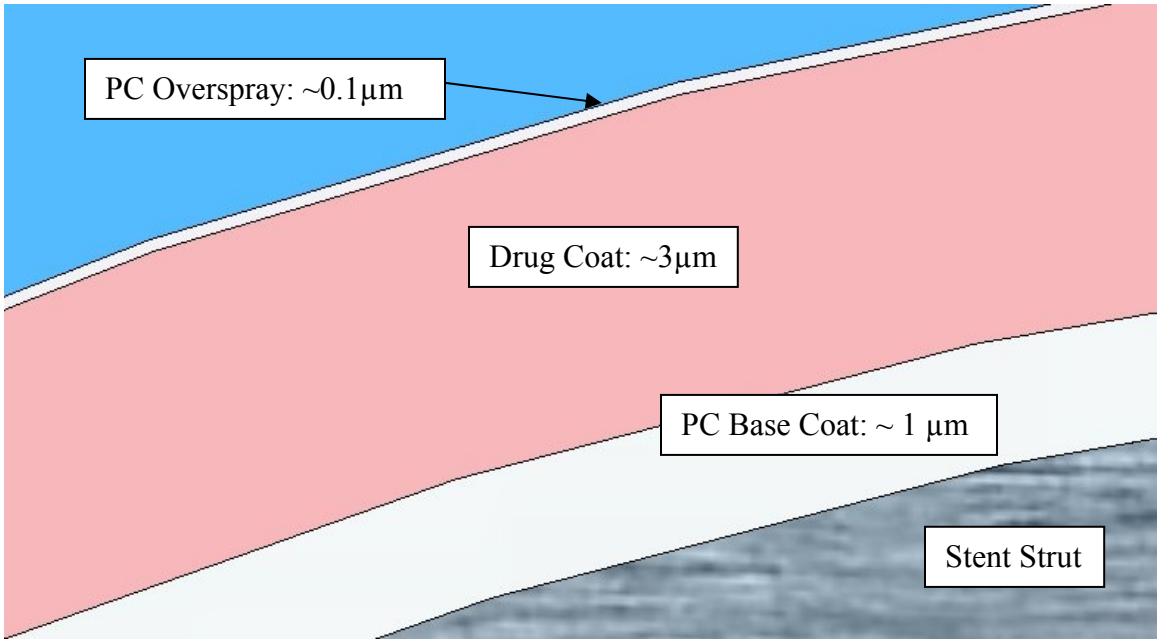

Figure 5-3: Schematic of Endeavor coatings, drawn to relative scale

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The product matrix associated with this PMA application for the Endeavor Zotarolimus-Eluting OTW, RX and MX[2] products is provided below in Table 5-1:

Table 5-1: The Endeavor Product Size Matrix

Diameter (mm)	Stent Length (mm)							
	8	9	12	14	15	18	24	30
2.5	✓	N/A	✓	✓	N/A	✓	✓	✓
3.0	N/A	✓	✓	N/A	✓	✓	✓	✓
3.5	N/A	✓	✓	N/A	✓	✓	✓	✓

The Endeavor Zotarolimus-Eluting CSS are manufactured in multiple steps.

The design characteristics across the three Endeavor delivery systems are provided in Table 5-2.

[11] Actual drug/ PC ratio is 90.9% drug / 9.1% PC (15mg/ml drug solution and 1.5mg/ml polymer solution).

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Table 5-2: Comparison of Design Characteristics between Endeavor Delivery Systems

Characteristic	Endeavor RX	Endeavor OTW	Endeavor MX[2]
Nominal balloon inflation pressure	9 ATM	9 ATM	9 ATM
Balloon Rated Burst Pressure	16 ATM	16 ATM	16 ATM
Balloon Bond Tensile	1.5 lbs minimum	1.5 lbs minimum	1.5 lbs minimum
Luer Bond Tensile	2.0 lbs minimum	2.0 lbs minimum	2.0 lbs minimum
Stent Crossing Profile	0.055" maximum	0.055" maximum	0.063"* maximum
Guide Wire Compatibility	0.014" maximum	0.014" maximum	0.014" maximum
Guide Catheter Compatibility	0.056" minimum (5F)	0.056" minimum (5F)	0.064" minimum (6F)
Distal Section OD	Distal = 2.7F	Distal = 2.7F	Distal = 2.7F
	Proximal = 3.0F	Proximal = 3.0F	Middle = 3.0F
			Proximal = 3.8F
Proximal OD	2.2F	3.3F	2.3F x 4.2F (Oval)

Table 5-2 identifies the areas of similarities and differences in design between the Endeavor OTW, Endeavor RX and the Endeavor MX² delivery systems. In addition, Table 5-3 identifies the components and materials used in all three delivery systems.

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#	Component	Device Comparison
Distal Section		
1	Stent	Identical across delivery systems
2	Balloon	Identical across delivery systems
3	Balloon Marker Bands	Identical across delivery systems
4	Distal Inner Shaft	Identical across delivery systems
5	Balloon Bond	Identical across delivery systems
6	Distal Outer Shaft	Identical across RX and OTW delivery systems [12]
Interface Section		
7	Proximal/Distal Bond	Specific to MX^2
8	Conversion Bond (wire insertion point)	Specific to RX
9	Transition bond	Specific to OTW
Proximal Section		
10	Stop Joint	Specific to MX^2
11	Dock Shaft	Specific to MX^2
12	Z-Component	Specific to MX^2
13	Proximal Shaft w/Hypotube	Specific to MX^2
14a	Strain relief	Identical across RX and MX^2 delivery systems
14b	Strain relief	
14c	Strain relief	Specific to OTW
15	Luer	Identical across RX and MX^2 delivery systems
16	Luer (Two-arm)	Specific to OTW
17	Jacketed Hypotube	RX specific hypotube

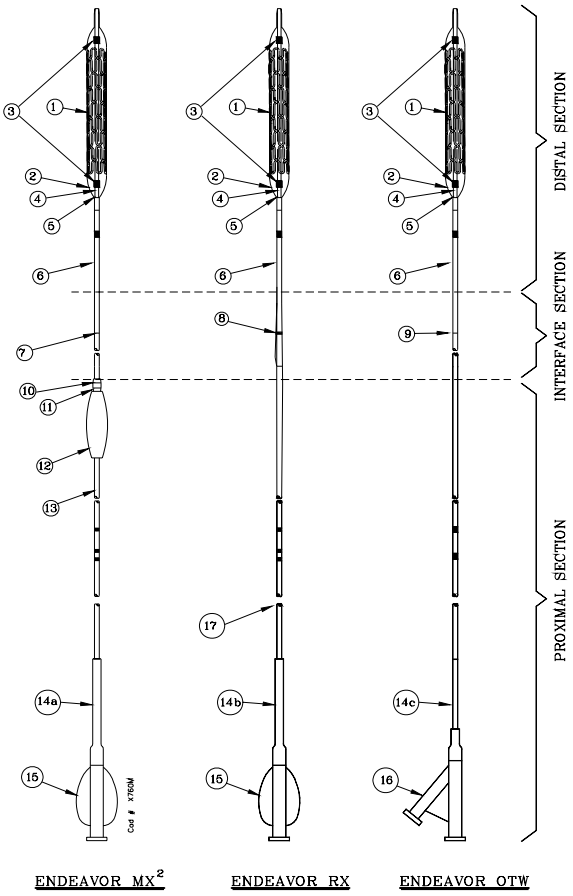

Figure 5-4: Comparison of the Endeavor OTW, RX and MX² delivery systems*

12 [redacted]

* [redacted]igure 5-7, Figure 5-8 and Figure 5-9 for further detail on the components of the Endeavor OTW, RX and MX^2 Delivery Systems respectively.

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Table 5-3: Comparison of Endeavor Delivery Systems Materials

System Component	Endeavor OTW	Endeavor RX	Endeavor MX[2]

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Table 5- 3: Comparison of Endeavor Delivery Systems Materials

System Component	Endeavor OTW	Endeavor RX	Endeavor MX[2]

* SurModics Inc. Device Master File #MAF-732

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5.1 Detailed Product Description

The following sections describe in greater detail each of the components of the Medtronic Vascular Endeavor Zotarolimus-Eluting CSS:

- The Endeavor Stent – a pre-mounted Cobalt alloy stent (Driver and Micro-Driver Coronary Stents)
- The three Delivery Systems (OTW, RX and MX^2)
- Phosphorylcholine (PC) Polymer Coating (drug carrier)
- Zotarolimus Drug Substance

5.2 Pictorial Representations

Schematic drawings and pictorial representations of the Endeavor stent and the Endeavor Zotarolimus-Eluting CSS (OTW, RX and MX^2) are provided below.

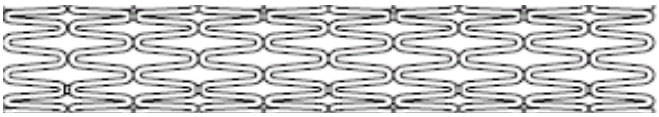

Figure 5-5: Endeavor Stent

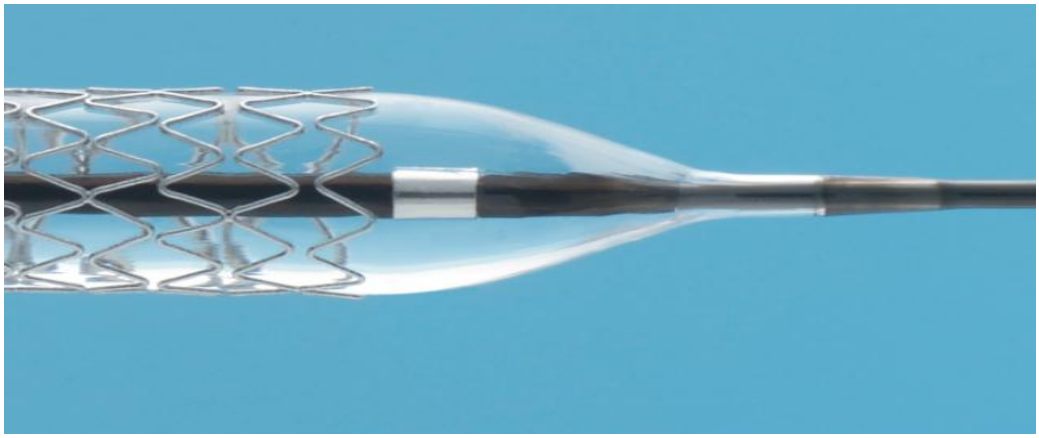

Figure 5-6: Pictorial Representative of Endeavor Stent

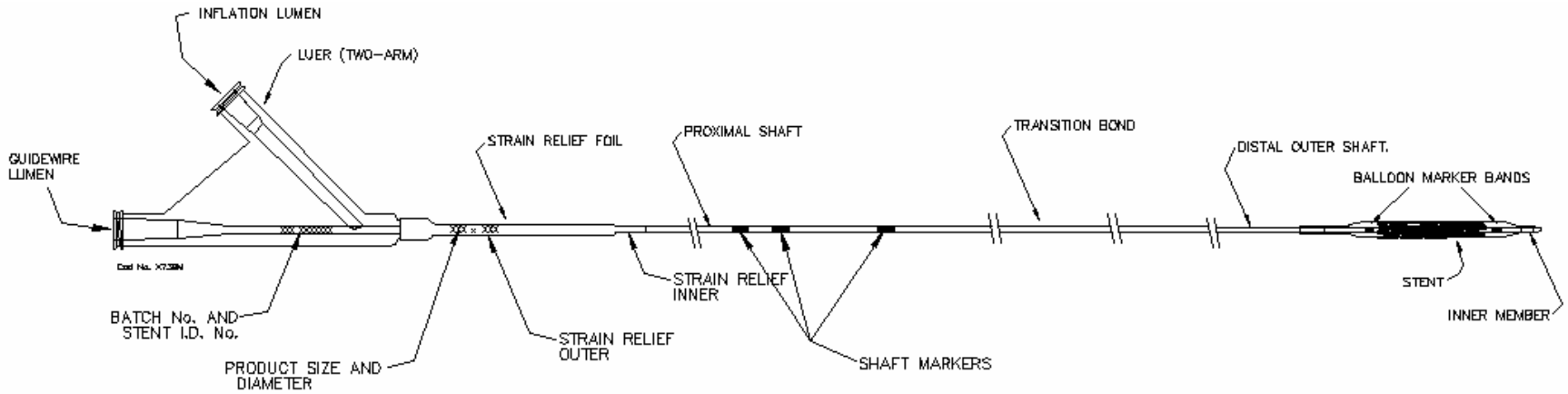

Figure 5-7: Endeavor OTW Delivery System

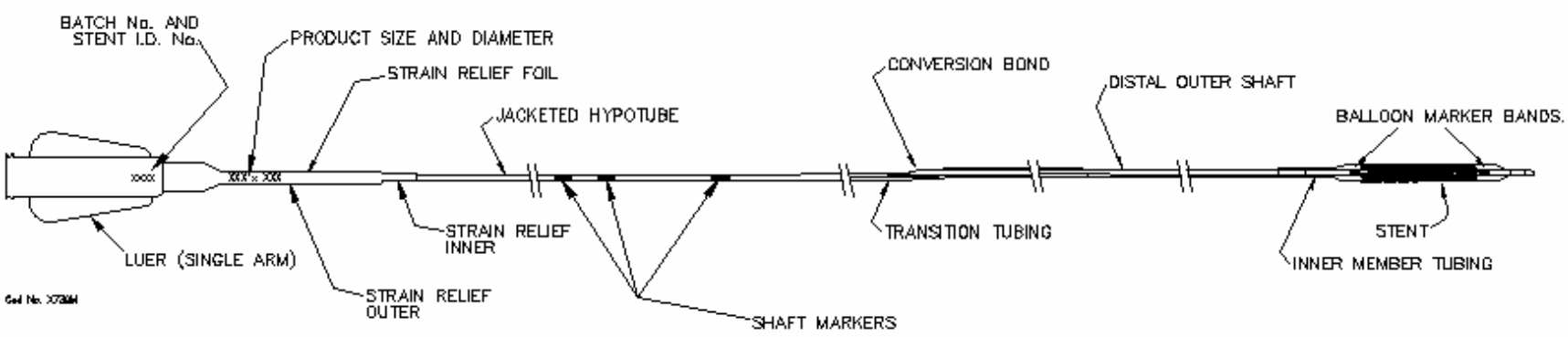

Figure 5-8: Endeavor RX Delivery System

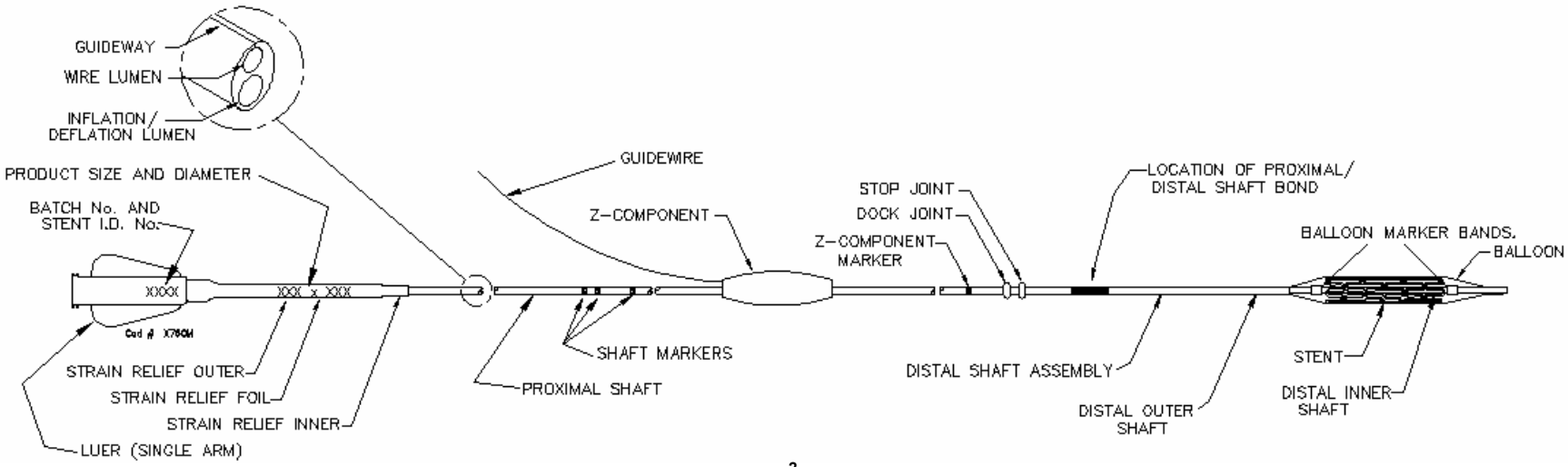

Figure 5-9: Endeavor MX^2 Stent Delivery System

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5.3 Functional Components

The following sections describe in greater detail each of the components of the Medtronic Vascular Endeavor Zotarolimus-Eluting CSS.

5.3.1 Endeavor Stent

The Endeavor stent is identical to the currently marketed Driver and the Micro-Driver coronary stents (P030009, approved October 1, 2003; P030009/S002, approved on April 21, 2006). The Endeavor coronary stent is made of a cobalt alloy conforming to ASTM F 562 – Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy. This material has been utilized to provide a combination of high strength and good ductility while demonstrating improved corrosion resistance and radiopacity when compared to stainless steel.

As described in the Driver and Micro-Driver PMA applications,

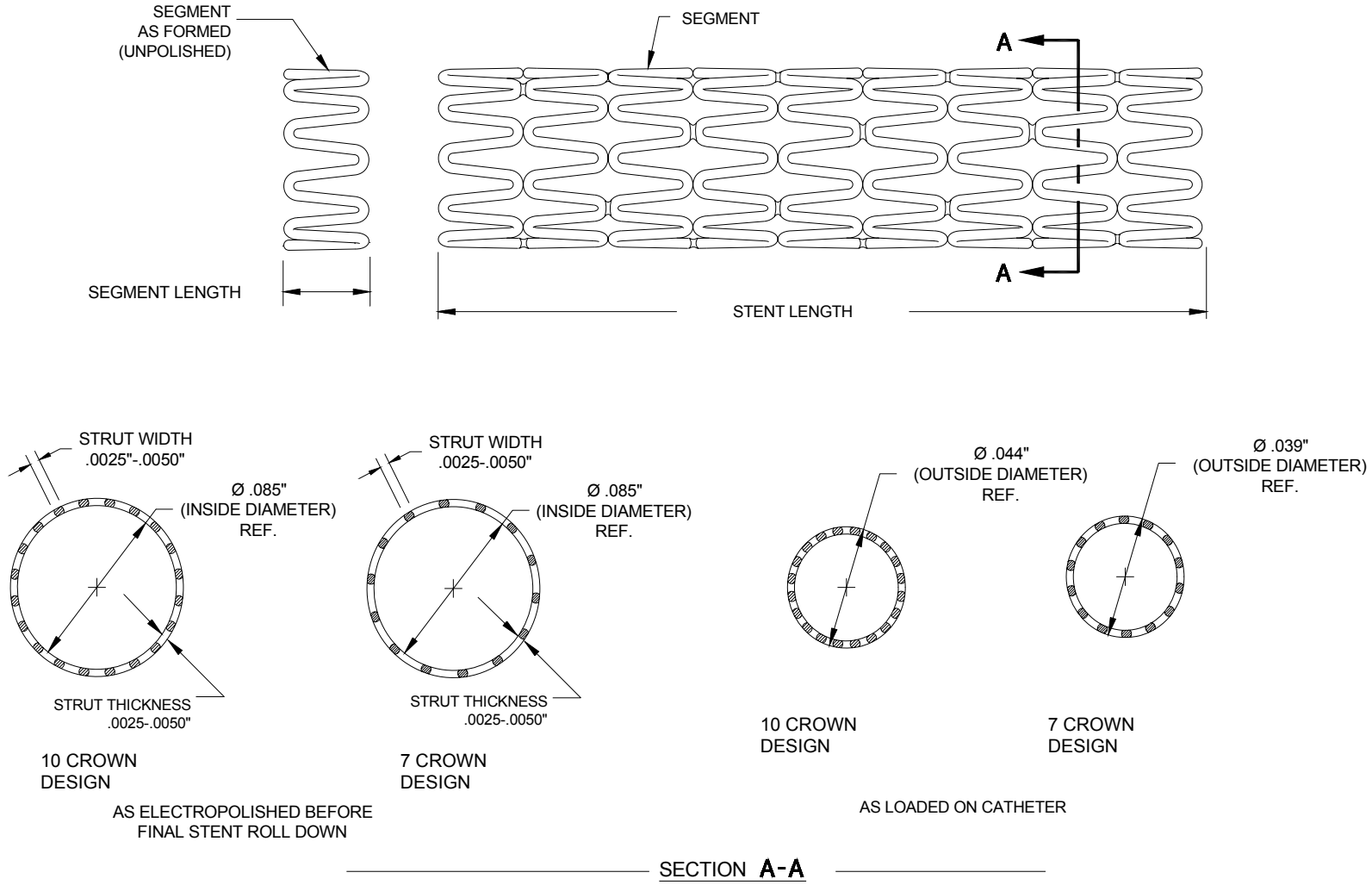

Figure 5-10: The Endeavor Coronary Stent

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The Endeavor Zotarolimus-Eluting CSS product matrix (subject of this application) is listed in Table 5-4.

Table 5-4: Endeavor Zotarolimus-Eluting CSS Stent Size Matrix

Diameter (mm)	Stent Length (mm)						Stent Design	
							Weld Pattern	Crown Pattern
2.50	8	12	14	18	24	30	Single Helix	7-Crown
3.00	9	12	15	18	24	30	U- Joint	10-Crown
3.50	-	12	15	18	24	30		
3.50[13]	9	-	-	-	-		Triple Helix	

The Endeavor stent contains a nominal drug dose of 10µg/mm of stent length as presented in Table 5-5 below.

Table 5-5: Nominal Total Drug per mm Stent Length

Stent Diameter (mm)	Nominal Total Drug per Stent Length (µg/mm)							
	8	**9**	**12**	**14**	**15**	**18**	**24**	**30**
2.50	10	N/A	10	10	N/A	10	10	10
3.00	N/A	10	10	N/A	10	10	10	10
3.50	N/A	10	10	N/A	10	10	10	10

The total nominal drug content (in units of µg) per nominal expanded stent diameter (ID) and length is provided in Table 5-6 below.

Table 5-6: Nominal Total Drug Content per Endeavor Zotarolimus-Eluting CSS

Stent Diameter (mm)	Stent lengths (mm)							
	8[14]	**9**	**12**	**14**[5]	**15**	**18**	**24**	**30**
2.50	84µg	N/A	120µg	144µg	N/A	180µg	240µg	300µg
3.00	N/A	90µg	120µg	N/A	150µg	180µg	240µg	300µg
3.50	N/A	90µg	120µg	N/A	150µg	180µg	240µg	300µg

[13] The 3.50 x 9 mm stent utilizes the Triple Helix weld pattern
[14] Note the 8 mm and 14 mm stent lengths have a total drug content of 84 µg and 144 µg respectively since the actual stent length for the 8 mm stent is 8.4 mm and the actual stent length for the 14 mm stent is 14.4 mm.

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Table 5-7 presents a summary of the stent surface area per stent size and stent design.

Table 5-7: Summary of Nominal Stent Surface Area per Stent Design and Stent Size

Surface Area per Stent Length (mm^2)										
Crown Design	**Weld Pattern**	**Diameter (mm)**	**8**	**9**	**12**	**14**	**15**	**18**	**24**	**30**
7 Crown	**Single Helix**	**2.50**	36	N/A	52	62	N/A	78	104	130
10 Crown	**U-Joint**	**3.00**	N/A	55	73	N/A	91	110	146	183
		3.50	N/A	N/A	73	N/A	91	110	146	183
	Triple Helix	**3.50**	N/A	55	N/A	N/A	N/A	N/A	N/A	N/A

Table 5-8 provides the nominal total drug dose per nominal stent surface area for information purposes.

Table 5-8: Nominal Total Drug per Nominal Stent Surface Area (µg/mm2)

Stent Diameter (mm)	**Stent lengths (mm)**							
	8	**9**	**12**	**14**	**15**	**18**	**24**	**30**
2.50	2.3	N/A	2.3	2.3	N/A	2.3	2.3	2.3
3.00	N/A	1.6	1.6	N/A	1.6	1.6	1.6	1.6
3.50	N/A	1.6	1.6	N/A	1.6	1.6	1.6	1.6

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5.3.2 Endeavor Delivery Systems

The Endeavor stent is mounted on one of three delivery systems. The three delivery systems offered with the Endeavor stent are Over-The-Wire (OTW), Rapid Exchange (RX) and Multi Exchange II (MX^2) Delivery Systems. The delivery systems utilized for the Endeavor product are similar in materials, design and construction to the delivery systems of Driver OTW P030009 approved October 1, 2003, Driver MX^2 P030009/S001, approved on August 4, 2004, Driver RX P030009/S003, approved on December 22, 2005 and the Micro-Driver OTW and MX^2 P030009/S002, approved on April 21, 2006.

Section 5.3.2.1 below contains a description of the components that are identical across all three delivery systems. This is followed by a description of each delivery system including a discussion of the functional components specific to each delivery system (Refer to Section 5.3.2.2 through Section 5.3.2.4 for detail).

5.3.2.1 Common Components of the Endeavor Delivery Systems (OTW, RX and MX^2)

As described in Table 5-3, a number of the device components are identical across the three Endeavor CSS delivery systems (OTW, RX and MX^2). With respect to the distal section of the product, these identical components include the following:

(a) The balloon
(b) The balloon radiopaque marker bands
(c) The tri-layer inner member

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Balloon

The balloon is identical for all three delivery systems of the Endeavor CSS and is mounted on the distal end of the catheter to provide a platform for, delivering and deploying the stent.

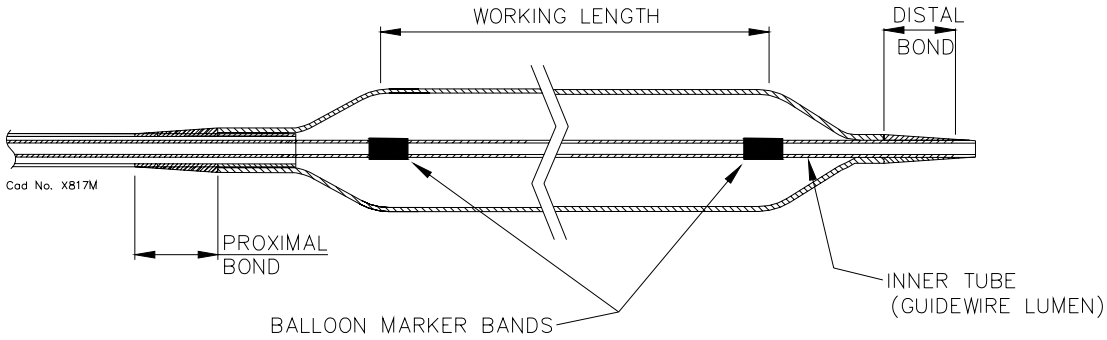

Figure 5-12: Distal End of Delivery System

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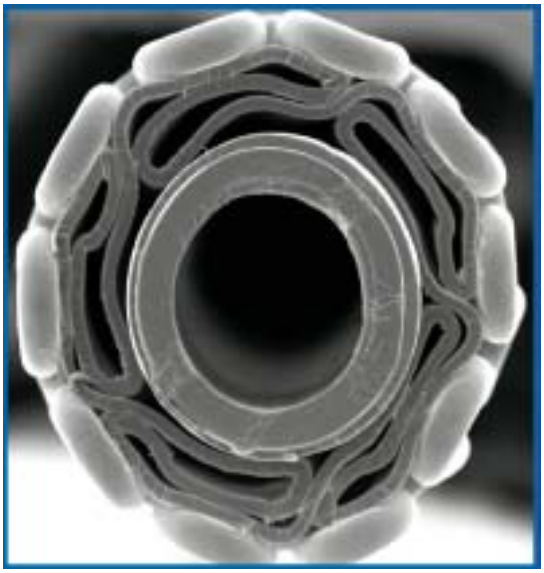

Figure 5-13: Representative Example of a Folded Balloon (for reference only)

Medtronic Vascular utilizes a proprietary process to create pillows, both proximal and distally to the stent. The pillows aid in holding the stent in position and gradually transition the distal and proximal tapers into the stent, see Figure 5-14.

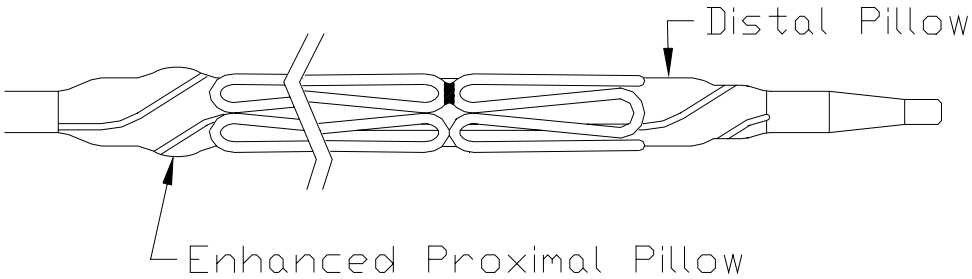

Figure 5-14: Balloon Pillows

Balloon Radiopaque Marker Bands

All Medtronic Vascular stent delivery systems have two radiopaque marker bands on the inner member underneath the balloon to aid in positioning the stent during delivery. Two Platinum/Iridium radiopaque marker bands, approximately 1 mm long, are mounted on the inner member of the catheter (one at each end of the balloon working length), as displayed in Figure 5-15.

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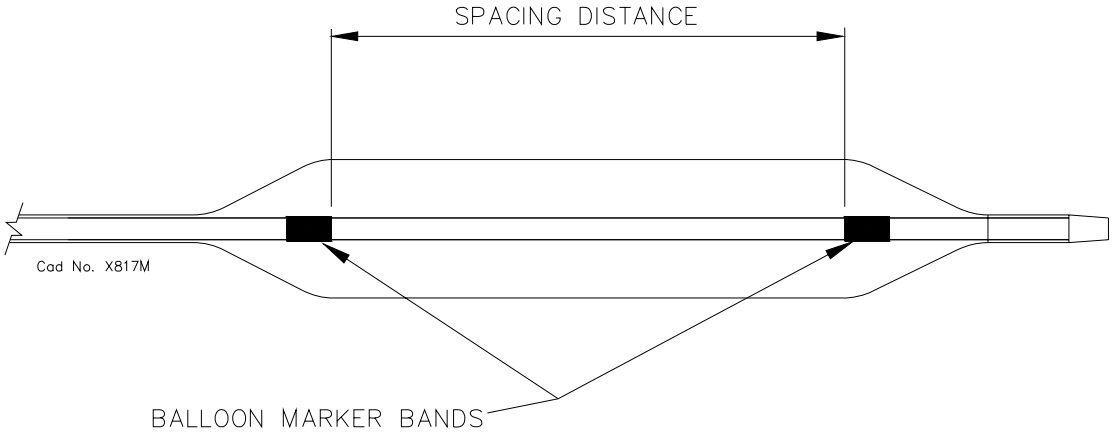

Figure 5-15: Balloon Radiopaque Marker Band Spacing

The Tri-layer Inner Member Tubing

The distal inner shaft is composed of a tri-layer co-extruded tubing.

Figure 5-16: Tri Layer Inner Member (not to scale)

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5.3.2.2 The Endeavor Over-The-Wire (OTW) Delivery System

The Endeavor OTW stent delivery system is similar in materials, design and construction to the Driver OTW Coronary Stent System, which was the subject of P030009 (approved October 1, 2003).

The OTW delivery system has a flexible, low profile distal portion for maneuvering through small, tortuous segments of the coronary vasculature. A semi-compliant balloon is mounted on the distal end of the catheter and provides a platform for mounting, delivering and deploying the stent. [redacted]. The hydrophilic coating is intended to reduce resistance and friction when advancing the delivery system through the vasculature. The OTW catheter is compatible with a 5 F (0.056″) guide catheter.

A guidewire lumen extends through the entire length of the catheter and is designed to be compatible with a 0.014” guidewire. A second lumen also extends along the entire length of the catheter and is used for inflation and deflation of the balloon. A two part strain relief is located on the proximal section of the catheter shaft for increased rigidity. The inner strain relief is positioned between the catheter shaft and two-arm luer, as the outer strain relief is secured over the nose of the two-arm luer.

The proximal end of the catheter contains a luer with two ports[15]; one port is for accessing the guidewire lumen while the second port facilitates inflation and deflation of the balloon. An engineering schematic of the Endeavor OTW stent delivery system is presented in Figure 5-17, followed by a discussion of the specific functional components of the OTW delivery system.

[15] The OTW luer is referred to as either a two-arm luer or a bifurcate throughout this PMA submission.

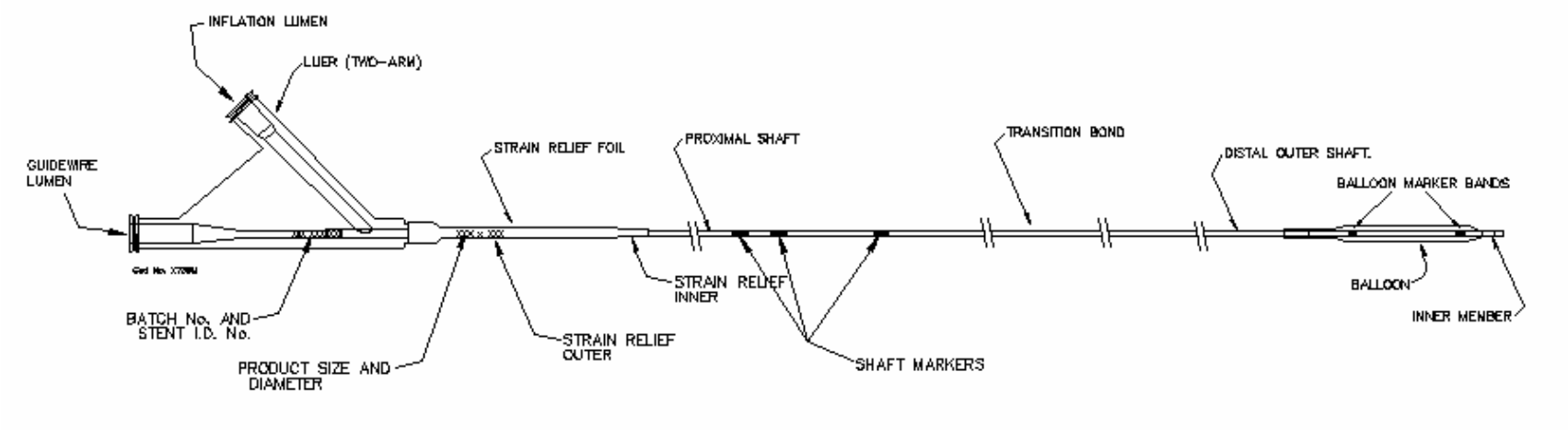

Figure 5-17: Endeavor OTW Delivery System

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OTW-Specific Functional Components

Shaft Markers

Consistent with most commercially available PTCA catheters and stent delivery systems, proximal shaft markers are provided on the shaft. The shaft markers provide a reference point for the physician when advancing the balloon/stent through the guide catheter, indicating when the balloon/stent is about to exit the guide catheter. The distal shaft marker is located 88 ± 5cm from the distal edge of the balloon bond and the proximal shaft markers are located 98 ± 5cm from the distal edge of the balloon bond. A third marker, located on the proximal end of the guidewire exit, indicates the location of the guidewire exit notch.

Guidewire Lumen

The guidewire lumen extends along the entire length of the catheter providing a conduit through which the guidewire travels when the catheter is advanced through the coronary vasculature. The guidewire lumen is formed by the inner member and begins at the distal tip of the balloon extending along the entire length of the catheter connecting to the two-arm luer.

Inflation/Deflation Lumen

As described above, the Endeavor OTW stent delivery system is comprised of a coaxially designed shaft with a semi-compliant balloon mounted near the distal tip. The coaxial shaft consists of a tubular inner and outer member. The annular space between the inner and outer members provides the "lumen" for the inflation and deflation of the balloon (see Figure 5-18) and extends along the entire length of the catheter.

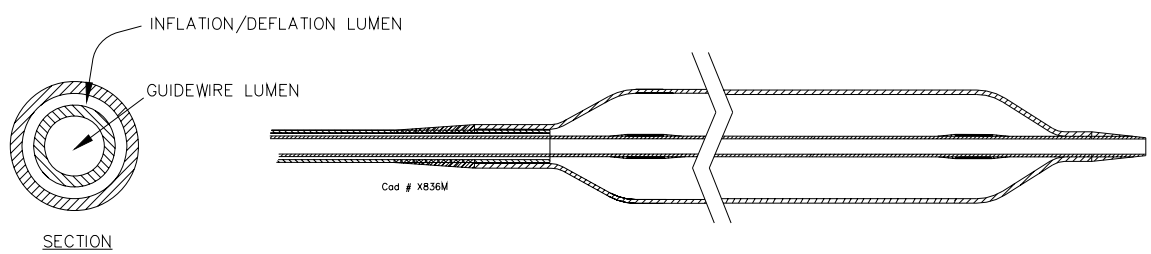

Figure 5-18: Endeavor OTW Balloon Inflation/Deflation Lumen

Catheter Coating

A hydrophilic coating is applied to the outside surface of the catheter. The coating runs from the proximal end of the transition bond to the proximal end of the balloon bond. The hydrophilic coating reduces resistance and friction when the catheter is advanced through the vasculature.

Strain Relief

As part of the two-arm luer assembly procedure, a two-component strain relief assembly is added to relieve kinking and enhance the proximal stiffness of the catheter.

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Two-Arm Luer

The proximal end of the catheter has a molded component to provide access to the inflation/deflation lumen and the en. Figure 5-19 shows the proximal assembly of Medtronic Vascular's Endeavor OTW stent delivery catheter.

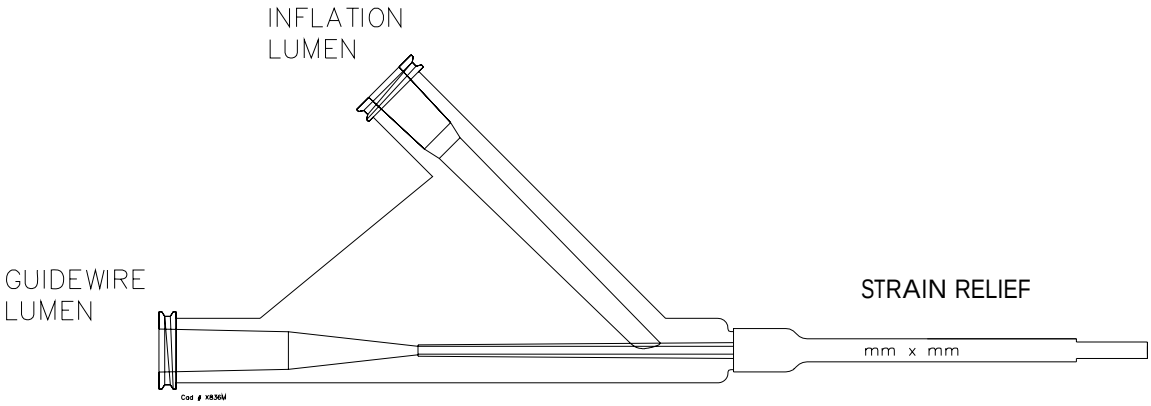

Figure 5-19: Endeavor OTW Proximal Assembly

In the final assembly, the guidewire access is provided through the straight port and the inflation/deflation lumen is provided through the angled port. Both ports have standard luer coupling. The guidewire port also provides access for flushing the wire lumen prior to use.

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5.3.2.3 The Endeavor Rapid Exchange (RX) Delivery System

The Endeavor RX stent delivery system is similar in materials, design and construction to the Driver RX Coronary Stent System, which was the subject of P030009/S003 (approved on December 22, 2005).

The Endeavor RX delivery system has a flexible, low profile distal portion for maneuvering through small, tortuous segments of the coronary vasculature. The Endeavor RX delivery system is equipped with a semi-compliant balloon mounted on the distal portion of the catheter to facilitate stent delivery and deployment.

Like other RX coronary stent systems and coronary dilatation catheters, the Endeavor Zotarolimus-Eluting RX delivery system combines a single lumen proximal shaft, conversion bond and a co-axial lumen distal shaft to create the rapid exchange cap The inner member permits the use of a guide wire with a diameter of 0.014 inches. The proximal end of the catheter contains a luer for balloon inflation and deflation. The Endeavor RX catheter is compatible with a 5 F (0.056 in.) guide catheter for all stent diameters.

An engineering schematic of the Endeavor RX stent delivery system is presented in Figure 5-20, followed by a detailed description of specific RX delivery system components.

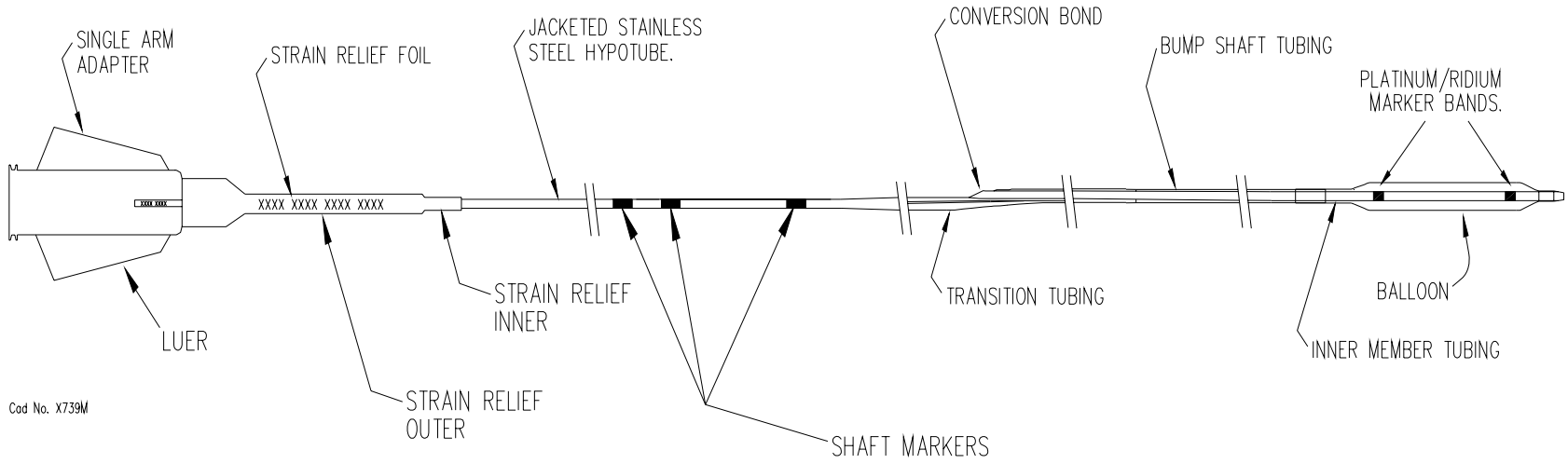

Figure 5-20: Endeavor RX Delivery System

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RX-Specific Functional Components

Shaft Markers

Consistent with most commercially available PTCA catheters and stent delivery systems, proximal shaft markers are provided on the shaft. The shaft markers provide a reference point for the physician when advancing the balloon/stent through the guide catheter, indicating when the balloon/stent is about to exit the guide catheter. The distal shaft marker is located 88 ± 5 cm from the distal edge of the balloon bond and the proximal shaft markers are located 98 ± 5 cm from the distal edge of the balloon bond. A third marker, located on the proximal end of the guidewire exit, indicates the location of the guidewire exit notch.

Guidewire Lumen

A second lumen also extends through the distal portion of the catheter providing a path through which the guidewire travels when the catheter is being traversed through the coronary vasculature. The design incorporates a guidewire lumen that begins at the distal tip and exits the catheter at the proximal end of the conversion bond, creating the Rapid Exchange feature (see Figure 5-22 for conversion bond illustration).

Inflation/Deflation Lumen

The balloon can be inflated and deflated via a lumen that extends along the entire length of the catheter from the balloon to the proximal single arm luer. The Rapid Exchange design, requires only the inflation/deflation lumen of the distal shaft to be coaxial, meaning the inner member tube resides inside an outer shaft tube leaving an annular space (inflation/deflation lumen) for fluid flow as displayed in Figure 5-21.

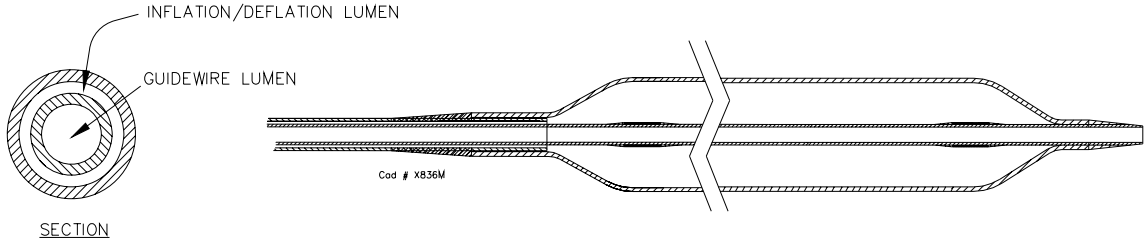

Figure 5-21: Endeavor RX Balloon Inflation/Deflation Lumen

The inflation/deflation lumen is coaxial from the balloon to the conversion bond, approximately 25 cm from the balloon.

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Figure 5-22: Conversion Bond

Catheter Coating

A hydrophilic coating is applied to the outside surface of the catheter. The hrough the vasculature.

Strain Relief

As part of the single-arm assembly procedure, a two-component strain relief assembly is added to relieve kinking and enhance the proximal stiffness of the catheter. The ity to the proximal portion of the catheter.

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Single Arm Luer

The final assembly has the inflation/deflation lumen access through the single port. The port has a standard luer coupling. A representative schematic of the single arm luer is displayed in Figure 5-23.

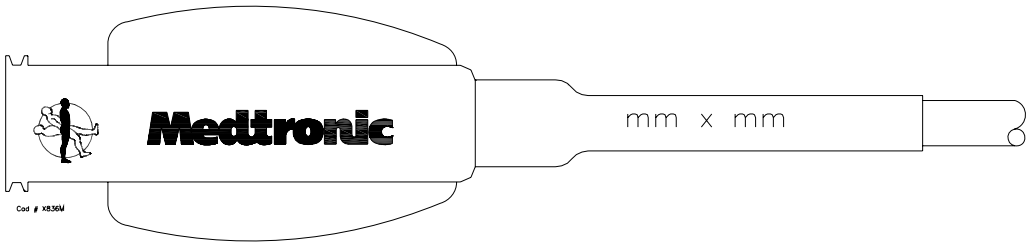

Figure 5-23: Endeavor RX Proximal Assembly

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5.3.2.4 Multi-Exchange II (MX2) Delivery System

The Endeavor MX^2 stent delivery system is similar in materials, design and construction to the approved Driver MX^2 Coronary Stent System, which was the subject of P030009/S001, approved on August 4, 2004.

The Endeavor MX^2 delivery system has a flexible, low profile distal portion for maneuvering through small, tortuous segments of the coronary vasculature. The distal portion of the MX^2 delivery system has identical design, materials and construction to both the Endeavor Rapid Exchange and Over-the-Wire Stent Delivery Systems except for a tri-layer distal shaft utilized in the Endeavor MX^2. The distal section of the catheter incorporates a coaxially arranged inner and outer shaft with a semi-compliant balloon mounted on the distal tip. The distal inner shaft acts as a guidewire lumen while the annular space between the shafts forms the balloon inflation/deflation lumen. The distal section of the outer shaft is coated with a hydrophilic coating to enhance lubricity and improve trackability through the coronary anatomy.

The proximal end of the MX^2 catheter consists of an extruded two-lumen shaft. One lumen serves as the balloon inflation/deflation lumen while the other acts as the guide wire lumen. The balloon inflation/deflation lumen is reinforced with a stainless steel, spiral cut hypotube. The guidewire lumen of the proximal shaft has a guideway along most of its length to facilitate interaction between it and the Z-component, which is mounted externally on the proximal shaft. The guideway is a closed track of finite length in the wire lumen that can be accessed by and facilitate movement of the Z-component.

The Z-component is seated over the proximal shaft and extends into the guideway. It can be placed at varying locations along the proximal shaft, facilitating the loading or unloading of the guidewire into or out of the wire lumen. This allows the device user to utilize a shorter guidewire than would be used in an OTW device, while still providing the option of wire interchange during device use. The inner lumen of the catheter is designed to accommodate a maximum guidewire diameter of 0.014 inches. The catheter is compatible with a 6 F (0.064) guide catheter for all diameters. A schematic of the Endeavor MX^2 Stent Delivery System is provided in Figure 5-24 on the following page.

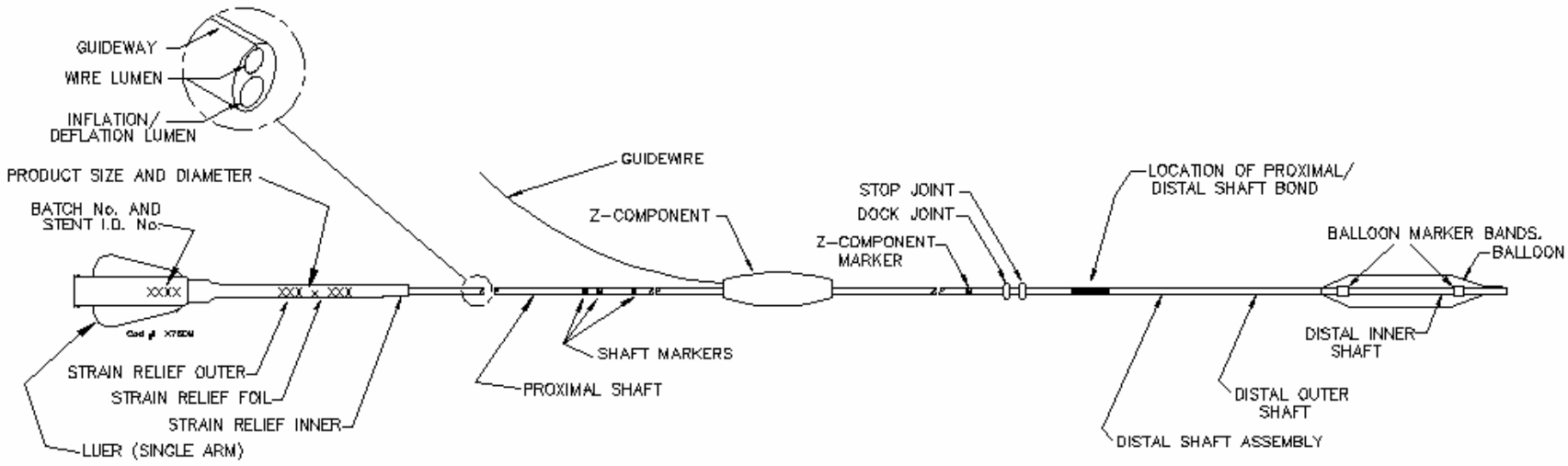

Figure 5-24: Endeavor MX^2 Stent Delivery System

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MX^2 Specific Functional Components

Z-Component

The Z-component functions as a conduit for the guidewire to enter and exit the proximal guidewire lumen.

Figure 5-25: MX^2 Z-Component

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Proximal Shaft

This creates a

Figure 5-27: MX^2 Proximal Shaft

The guidewire lumen has a guideway along most of its length to facilitate interaction between it and the Z-component, which is mounted externally on the proximal shaft. The guideway is a closed track of finite length in the wire lumen that can be accessed by and facilitate movement of the Z-component.

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Shaft Markers

Consistent with most commercially available PTCA and stent delivery catheters, proximal shaft markers are present on the shaft of MX^2 catheter to provide a reference point when advancing the balloon/stent through the guiding catheter indicating when the balloon/stent is about to exit the guiding catheter. The distal shaft marker is located 88 ± 5cm from the distal edge of the balloon bond and the proximal shaft markers are located 98 ± 5cm from the distal edge of the balloon bond. The MX^2 delivery system also has a third marker on the shaft indicating the distal position of the Z-Component.

Inflation/Deflation Lumen

The balloon is inflated and deflated by a lumen that extends along the entire length of the catheter from the balloon to the proximal single arm luer. The inflation/deflation lumen is coaxial in the distal section of the catheter from the balloon to the proximal/ distal joint bond, wherein the inner member (guidewire lumen) resides inside the outer distal shaft tubing leaving an annular space between the two for pressurized fluid to flow. The proximal/distal joint bond allows the coaxial distal section to transition into a side-by-side dual lumen design and permits the inner member to interface with the guidewire lumen of the proximal shaft.

Guidewire Lumen

A second lumen also extends along the entire length of the catheter providing a path through which the guidewire travels when the catheter is being traversed through the coronary vasculature. The design incorporates a guidewire lumen that begins at the distal tip and extends along the proximal shaft. The Z-Component, attached to the proximal shaft provides a passageway for the guidewire to travel into and out of the guidewire lumen.

Proximal /Distal Shaft Joint

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Figure 5-28: Endeavor MX Proximal / Distal Shaft Joint

Catheter Coating

A hydrophilic coating is applied to the outside surface of the catheter. The coating runs from the distal end of the stop joint to the proximal side/end of the balloon bond. The hydrophilic coating reduces resistance and friction when the catheter is advanced through the vasculature.

Strain Relief

As part of the single-arm assembly procedure, a two-component strain relief assembly is added to relieve kinking and enhance the proximal stiffness of the catheter.

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Single Arm Luer

The proximal end of the catheter has a [redacted] component that provides the means for accessing the inflation/d [redacted]

The final assembly has the inflation/deflation lumen access through the single port. The port has a standard luer coupling. A representative schematic of the single arm luer is displayed in Figure 5-29 below.

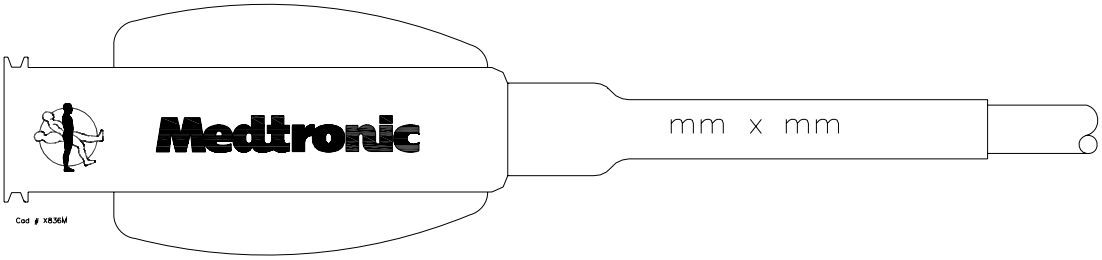

Figure 5-29: Endeavor MX^2 Proximal Assembly

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5.3.3 Phosphorylcholine (PC) Polymer

The polymer coating used on the Endeavor Zotarolimus-Eluting CSS is a Phosphorylcholine (PC) polymer licensed from Abbott Laboratories. PC coating is a biocompatible polymer, which acts as a carrier for the zotarolimus drug substance. The mechanism of drug release from the Endeavor stent is dissolution into its surrounding environment, i.e. in *vitro* elution testing demonstrates the PC polymer does not have a rate limiting effect on drug release. PC polymer has been in use in Europe on coronary stents since 1997. The Bio*divYsio* PC Coated stent was CE mark approved (CE 02073) on September 4, 1998. PC coated stents have also been in use since 2000 in the United States, marketed as the Bio*divYsio*™ AS PS (Phosphorylcholine) Coated Stent and Delivery System (P000011, approved September 29, 2000). The Bio*divYsio*™ PC coated stent has been successfully implanted worldwide in over 100,000 patients to date.[16,17,18,19,20,21,22] An authorization letter to reference the Bio*divYsio* PC Coated Stent PMA is provided in the PMA P060033.

The PC polymer consists of 2-Methacryloyloxyethyl phosphorylcholine that is synthesized and then used in the preparation of cross-linked polymer membranes with lauryl methacrylate, hydroxypropyl methacrylate and trimethoxysilylpropyl methacrylate (crosslinker) co-monomers. The PC polymer contains a biocompatible component which mimics the body's own chemistry, a hydrophobic component for adhesion and stability, and a crosslinking component for robustness.

[16] Cumberland DC, et al. Biomimicry 1:PC. Seminars in Interventional Cardiology 1998 Sep-Dec; 3(3-4): 149-50.
[17] Kuiper KK, Robinson KA, Chronos NAF, Cui J, Palmer SJ, Nordrehaug JE. Phosphorylcholine-coated metallic stents in rabbit iliac and porcine coronary arteries. Scand Cardiovasc J 1998; 32(5): 261-268.
[18] Zheng H, Barragan P, Corcos T, Simeoni JB, Favereau X, Roquebert PO, et al. Clinical experience with a new biocompatible phosphorylcholine-coated coronary stent. J Invasive Cardiol; 1999 Oct; 11(10): 608-614.
[19] Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, et al. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. Heart 2000 Mar; 83(3): 338-345.
[20] Boland JL, Corbeij HAM, van der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, et al. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short de novo coronary lesions: The SOPHOS study. Int J Cardiovasc Intervent 2000 Dec; 3(4): 215-225.
[21] Atalar E, Haznedaroglu I, Aytemir K, Aksoyek S, Ovonc K, Oto A, et al. Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation. Clin Cardiol 2001 Feb; 24(2): 159-164.
[22] Malik N, Gunn J, Shepherd L, Crossman D, Cumberland DC, Holt CM. Phosphorylcholine-coated stents in porcine coronary arteries: In-vivo assessment of biocompatibility. J Invasive Cardiol 2001 Mar; 13(3): 193-201.

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Chemical Structure

The chemical structure of the PC polymer is shown in Figure 5-30.

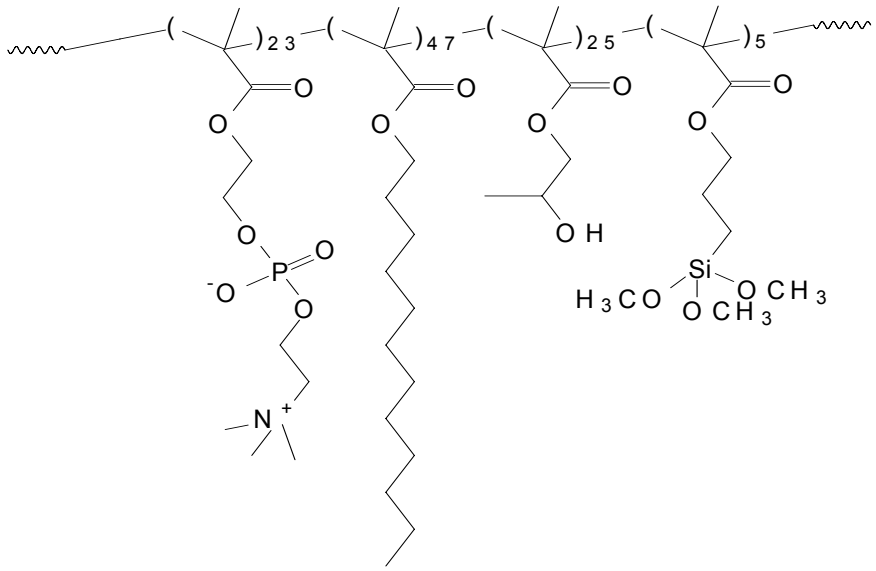

Figure 5-30: Chemical Structure of PC Polymer

Characteristics of PC

The PC coating exhibits a low coefficient of friction, is stable at physiological pH, and has been shown to produce a stable surface and a biocompatible layer on stents as well as other materials and devices. PC derivatives are polymerized with long chain monomers to produce a polymeric PC coating.

Molecular Weight[23]

The molecular weight of PC polymer was estimated using viscometry and resulted in values of M_w ranging from 160,000 to 270,000. These figures were supported by light scattering values of Mw (g/mol) ranging from 100,000 and 200,000.

Im [24]

-
-
-

[23] Andrew L. Lewis, Zoie L. Cumming, Hind H. Goreish, Laura C. Kirkwood, Lee A. Tolhurst, Peter W. Stratford, Crosslinkable coatings from phosphorylcholine-based polymers. Biomaterials. 2000 Mar; 22: 9

[24]

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Manufacturer
The PC polymer is supplied to Medtronic Vascular through a licensing agreement with Abbott Laboratories and is manufactured by:

5.3.4 Zotarolimus Drug Substance

The drug substance, zotarolimus, is utilized on the Endeavor Zotarolimus-Eluting Coronary Stent System (CSS) at a dose of 10µg/mm of stent length. Zotarolimus (also referred to as ABT-578) is supplied to Medtronic ng agreement with Abbott Laboratories and is manufactured by

Zotarolimus, which was originally developed in 1997 as an immunosuppressant to treat rheumatoid arthritis, is a semi-synthetic tetrazole-containing molecule of the limus family. In 1998, zotarolimus had been identified as a potent smooth muscle cell inhibitor and recognized its potential for use as an active ingredient on a drug eluting stent. By 2001, animal studies had been performed that showed potential for the anti-proliferative mechanism of zotarolimus to be used in coronary stent applications. On the basis of review of these studies, Medtronic Vascular licensed the use of zotarolimus from Abbott Laboratories in 2002 for use in Endeavor Zotarolimus-Eluting CSS and other development projects. There are currently no oral or intravenous formulations of zotarolimus available.

Chemical Name
[3S-[3R*[S*(1R*,3S*,4R*)],6S*,7E,9S*,10S*,12S*,14R*,15E,17E,19E,21R*, 23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazoyl-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

Abbreviation(s)
ABT-578

Chemical Structure

The chemical structure of zotarolimus is shown in Figure 5-31 below.

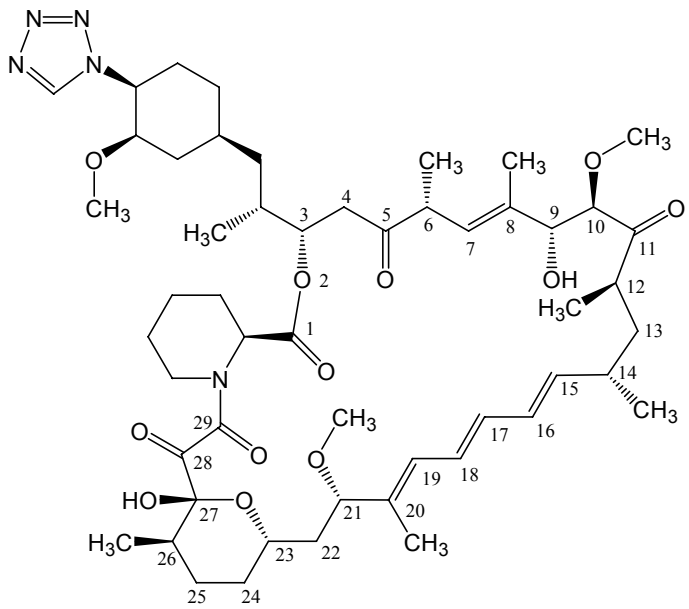

Figure 5-31: Chemical structure of zotarolimus.

Molecular Formula

The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

Physicochemical Properties

Zotarolimus has extremely low water solubility. The solubility of zotarolimus at 25°C is approximately 0.53 µg/mL in water, >100 mg/mL in ethanol, 22.4 ug/mL in 10% ethanol in water, and 1.34 mg/mL in 40% ethanol in water. The solubility of zotarolimus in 40% propylene glycol (PG) and 10% ethanol in water is about 300 µg/mL. Zotarolimus does not have any ionizable group(s) in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

Zotarolimus is a lipophilic compound as demonstrated by very high octanol: water partition coefficient (>4.5 at pH 6.5 and pH 7.4). The lipophilic properties of zotarolimus may enhance absorption across the cellular membrane of target tissues. Limited water solubility (0.47 µg/ml at pH 6.5 and 0.53 µg/ml at pH 7.4) is highly amenable to the design of a drug-coated stent, in that low water solubility may impede systemic distribution from the stent. In addition, its lipophilic character may favor an ability to cross cell membranes to inhibit neointimal proliferation of target tissue.

The physiochemical properties are summarized in Table 5-9.

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Table 5-9: Physicochemical Properties of zotarolimus[25]

Property	Observation
Appearance	White to yellow amorphous solid
Crystallinity	Amorphous by X-ray
Solubility/ Solution Stability	Medium — Solubility/ Stability 0.1N Hydrochloric acid pH1 — degrades 0.05M acetate buffer, pH 4 — 2.19 mcg/mL 0.05M phosphate buffer, pH 7.4 — degrades Solvent — Solubility (mg/mL)* [redacted]
Ionization Constants	No ionizable functional groups between pH 1-7
Lipophilicity	$\text{Log}_{10}D = \text{Log}_{10}P^{\text{octanol/pH 7.4 buffer}}$ = > 4.5, indicative of high lipophilicity.
Optical Rotation	-107 to -121 at 25 degrees C, 10mg/ml in methanol

* Not a saturated solubility. Zotarolimus is freely soluble in these solvents according to USP<26> definition (1-10 parts solvent required for 1 part solute) in these solvents.

Mechanism of Action

The mechanism of action of zotarolimus is to bind to the intracellular protein, FKBP12, leading to the formation of a trimeric complex with mTOR (mammalian target of rapamycin). The protein kinase activity of mTOR is thus inhibited which results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. The mechanism of action is graphically represented in Figure 5-32. *In vitro*, zotarolimus demonstrated binding affinity with FKBP-12 and potently inhibited growth factor-induced proliferation of human coronary artery smooth muscle cells.

[25] Reference DMF #16960

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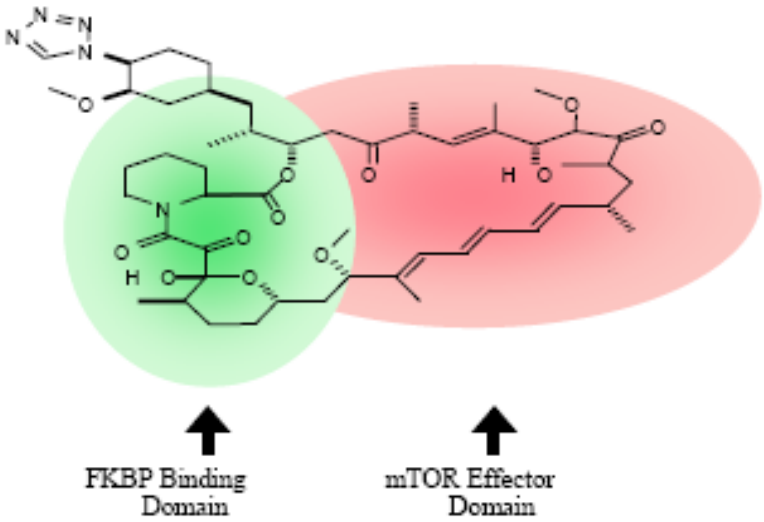

Figure 5-32: Suggested Mechanism of Action of Zotarolimus

Drugs of the limus family have been previously approved by FDA. For example, rapamycin (sirolimus) is the one limus drug approved for application on a drug eluting stent and is also approved as co-medication for renal transplant immunosuppression. Zotarolimus is a cytostatic cell cycle inhibitor that inhibits cells from entering the S phase of mitosis, as shown in Figure 5-33.

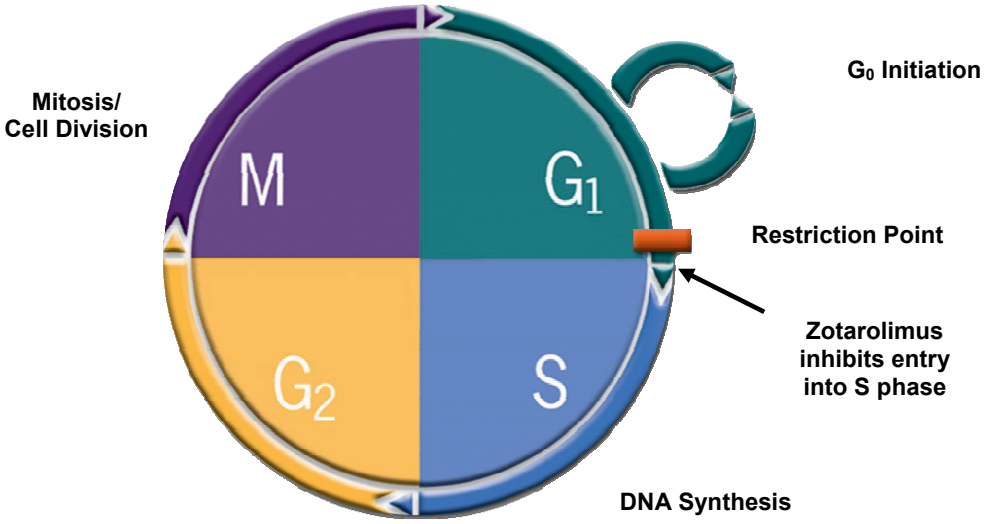

Figure 5-33: Cytostatic Cell Cycle Inhibition

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Table 5-10 below shows measures of lipophilicity and potency for the limus family of drugs involved in drug-eluting stent applications. The low nanomolar concentration in the tissue would indicate little anticipated difference in the tissue effect for the differences in IC50.. Also of note, zotarolimus is highly protein bound in man, distributed to the whole blood with a red blood cell-to-plasma appropriation of 20:1. The drug is not available as an oral formulation and when administered via stent or IV formulation, is metabolized and excreted primarily by the liver. Radiolabel studies in several species including man confirm approximately 84% excretion through the liver and gut, with only approximately 6% by renal excretion.

Table 5-10: Lipophilicity and Potency of Limus Family Drugs

	Rapamycin	Zotarolimus
Lipophilicity	logD 3.6	logD >4.5
Potency	IC50 0.4nM	IC50 0.3nM

By replacing the hydrophilic hydroxyl group with a lipophilic tetrazole group, the drug substance zotarolimus becomes substantially more lipophilic than sirolimus, thereby increasing its tissue retention time. Although there has been a lot of focus on the elution curves associated with many drug eluting stents, the important measure is time in tissue discussed below.

Lipophilicity is demonstrated by very high octanol: water partition coefficient (>4.5 at pH 6.5 and pH 7.4), represented as follows:

$$\mathrm{Log}_{10}D = \mathrm{Log}_{10}P_{\text{octanol/pH 7.4 buffer}}$$
$$= > 4.5\text{, indicative of high lipophilicity.}$$

The lipophilic properties of zotarolimus are thought to enhance absorption of the drug across the cellular membrane of target tissues. Limited water solubility (0.47 µg/ml at pH 6.5 and 0.53 µg/ml at pH7.4) is highly amenable to the design of a drug-coated stent, in that low water solubility may impede systemic distribution from the stent. In addition, the lipophilic character of zotarolimus may favor an ability to cross cell membranes to inhibit neointimal proliferation of target tissue and be retained in tissue longer than less lipophilic drugs. Consequently, despite the fact that zotarolimus elutes from the stent within 14 days, it remains in tissue at detectable levels up to 28 days. Reference Figure 5-34 and Figure 5-35 below for curves generated from studies of porcine drug elution kinetics and pharmacokinetics.

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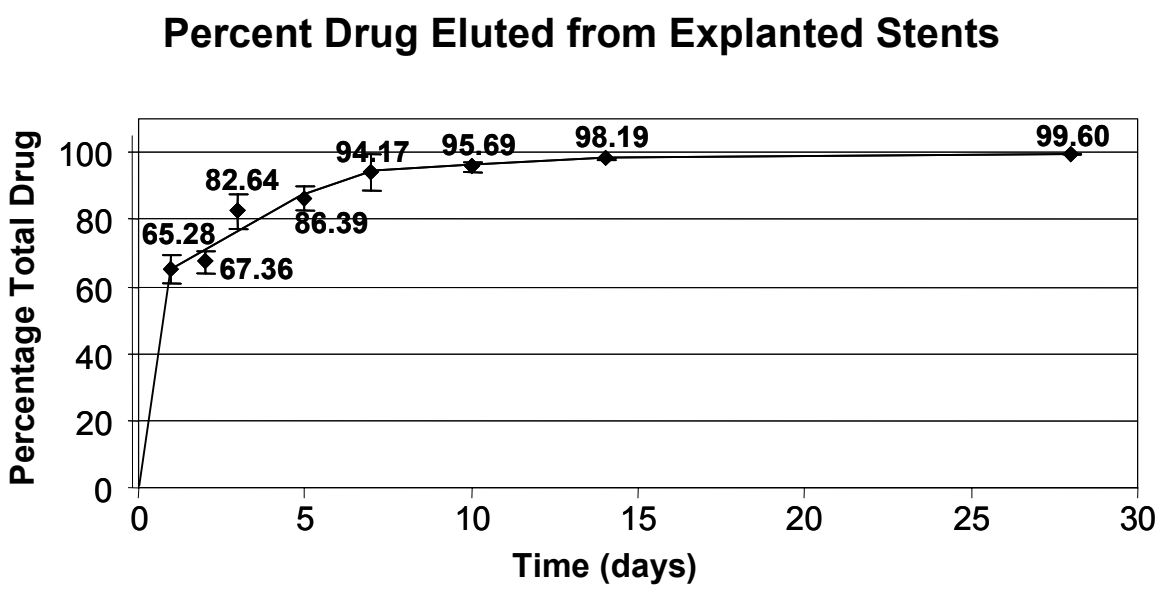

Figure 5-34: Percent Drug Eluted from Explanted Stents

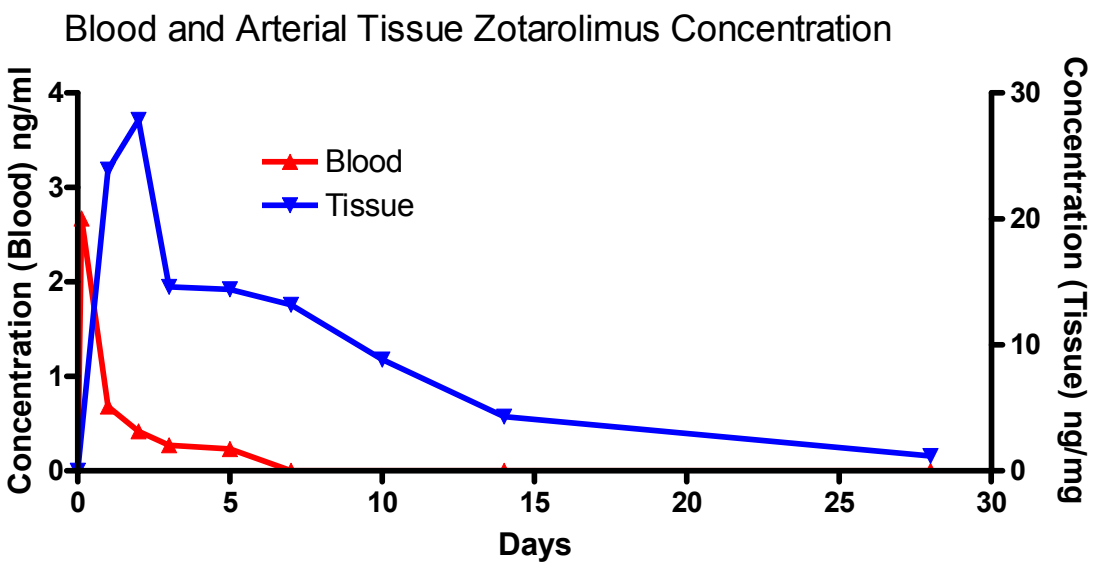

Figure 5-35: Blood and Arterial Tissue Zotarolimus Concentration

Stability

Macrolides like zotarolimus, which contain triene unsaturation (polyene macrolide), can be sensitive to oxidation. A pattern of degradation, consistent with triene oxidation, has been observed for amorphous zotarolimus when unprotected by an antioxidant.

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significantly protects zotarolimus from oxidation.

Note: Additional precautions taken to limit oxygen exposure to the Endeavor product include In addition, oxygen scavengers and desiccants are added to the packaging. The inner pouch provides a sterile barrier protection, while the outer pouch provides - a non-sterile barrier - which, protects the Endeavor product from light, oxygen and moisture.

Manufacturer

Zotarolimus is supplied to Medtronic Vascular through a licensing agreement with Abbott Laboratories and is manufactured by:

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6.0 Endeavor Clinical Experience – Individual Trial Summaries

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6.0 Endeavor Clinical Experience – Individual Trial Summaries

6.1 Introduction

The Endeavor Zotarolimus-Eluting Coronary Stent System clinical development program includes clinical safety and efficacy data from six multi-center trials conducted in the United States and abroad in support of PMA approval. Three of the six trials were randomized controlled studies and three were open-label trials. The randomized studies compared the safety and efficacy of the Endeavor stent to each of three marketed coronary stents: the uncoated bare metal Driver™ stent, the Cypher Sirolimus-Eluting Stent™, and the Taxus Paclitaxel-Eluting Coronary Stent System™. An additional registry was conducted in Japan to support regulatory approval in that country.

These studies provide extensive clinical safety and efficacy data for the Endeavor Zotarolimus-Eluting CSS. Among the PMA trials, 2,133 patients were assigned to receive the Endeavor stent and substantial follow up data is now available; 2,088 patients to 9 months, 1,301 patients to 12 months, 1,287 patients to 24 months, 675 patients to 36 months, and 97 patients to 48 months. Through randomized, controlled trials, the Endeavor stent was shown to be superior to a bare metal stent and non-inferior to a drug-eluting stent based on the composite endpoint of Target Vessel Failure (TVF). In addition, with substantial follow-up data available, there is no trend towards increased rates of cardiac death, MI, or stent thrombosis compared to the bare metal stent when assessed within the first year or in the critical post-one year time frame.

In addition to the data listed above the E-Five registry was conducted to monitor safety and performance in the commercial market place outside the US and enrolled over 8000 patients. Interim thirty-day data on the first 2015 patients and 12-month data on the first 1016 patients enrolled are available.
A summary for each of these studies is provided below and the study reports are provided in the following Appendices for reference:

Appendix 1: ENDEAVOR I 48-month report

Appendix 2: ENDEAVOR II 36-month report

Appendix 3: ENDEAVOR II CA 24-month report

Appendix 4: ENDEAVOR III 24-month report

Appendix 5: ENDEAVOR IV 9-month report

Appendix 6: ENDEAVOR PK 9-month report

Appendix 7: ENDEAVOR Japan 9-month report

Appendix 8: ENDEAVOR Five 30-day report

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6.2 ENDEAVOR I Clinical Study Summary

6.2.1 Clinical Study Description

ENDEAVOR I was a prospective, multi-center, non-randomized, single-arm study of the Medtronic Zotarolimus-Eluting Coronary Stent[1] in *De Novo* Native Coronary Artery Lesions.

6.2.1.1 Study Design

The study was designed as a prospective, multi-center, non-randomized, single-arm study.

6.2.1.2 Study Objectives

To demonstrate the safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries.

6.2.1.3 Primary Endpoints

The primary safety endpoint of this study was Major Adverse Cardiac Events (MACE) at 30 days. MACE was defined as the incidence of the combined clinical endpoints: death, myocardial infarction, emergent cardiac surgery, or clinically-driven repeat target lesion revascularization as determined by the Clinical Events Committee (CEC).

The primary efficacy endpoint was the angiographic late lumen loss at 4 months, defined as the difference between the post-index procedure minimal lumen diameter (MLD) and the 4-month follow-up angiography MLD.

6.2.1.4 Secondary Endpoints

- Target vessel failure (TVF) defined as a composite of cardiac death, MI (Q wave and non-Q wave), or target vessel revascularization at 9 months
- Target lesion revascularization (TLR) rate, defined as the incidence of clinically driven repeat revascularization of the target lesion at 9 months
- Late lumen loss at 12 months as measured by angiographic data
- Neointimal hyperplastic volume at 4 and 12 months as measured by IVUS.

6.2.1.5 Patient/Study Population

<u>General Inclusion Criteria</u>
Candidates were considered for inclusion if the following conditions were met:

1. The subject was ≥18 years of age.
2. The subject was an acceptable candidate for PTCA, stenting, and emergent CABG surgery.
3. The subject had clinical evidence of ischemic heart disease <u>or</u> a positive functional study.
4. The target lesion / vessel met the following criteria:

[1] Endeavor Zotarolimus-Eluting Coronary Stent System was previously known as the Medtronic AVE ABT-578 Coated Driver Coronary Stent

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a) The target lesion was a single *de novo* lesion that was not previously treated with any interventional procedure. Only one lesion was treated per subject.
b) The target vessel was a native coronary artery with a stenosis of ≥50% and <100%.
c) The target lesion was ≤15 mm in length.
d) The target vessel reference diameter was ≥3.0 mm and ≤3.5 mm. (Measurements were made by careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound.)

5. Female subjects of childbearing potential had a negative pregnancy test within seven (7) days before the procedure.
6. The subject or the subject's legal representative was informed of the nature of the study and agreed to its provisions and provided written informed consent as approved by the Human Research Ethics Committee of the respective clinical site.
7. The subject and the treating physician agreed that the subject would return for all required post-index procedure follow-up visits.

General Exclusion Criteria

1. A documented left ventricular ejection fraction <30%.
2. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, cobalt, nickel, chromium, molybdenum, or a sensitivity to contrast media, which could not be adequately pre-medicated.
3. History of an allergic reaction or significant sensitivity to drugs similar to Zotarolimus (rapamycin or analogue).
4. A platelet count <100,000 cells/mm³ or >700,000 cells/mm³, or a WBC <3,000 cells/mm³.
5. Evidence of an acute myocardial infarction within 72 hours of the intended treatment (defined as: Q wave or non-Q wave infarction having CK enzymes >2X the upper laboratory normal with the presence of a CK-MB elevated above the Institution's upper limit of normal).
6. Creatinine >170 micromol/L.
7. A previous coronary interventional procedure of any kind within the 30 days prior to the procedure.
8. The subject required planned interventional treatment of either the target or any non-target vessel within 30 days post-index procedure.
9. The target lesion required treatment with a device other than PTCA prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
10. Previous stenting anywhere in the target vessel.
11. The target vessel had evidence of thrombus or was excessively tortuous (2 bends >90° to reach the target lesion).
12. The target lesion had any of the following characteristics:
    a) Lesion location was aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the LAD, LCX, or RCA.
    b) Involved a side branch >2.0 mm in diameter.
    c) Was at or distal to a 45º bend in the vessel.
    d) Was moderately to severely calcified.

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13. Unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery).
14. History of a stroke or transient ischemic attack within the prior 6 months.
15. Active peptic ulcer or upper GI bleeding within the prior 6 months.
16. The subject had a history of bleeding diathesis or coagulopathy or would refuse blood transfusions.
17. Concurrent medical condition with a life expectancy of less than 12 months.
18. Any previous or planned treatment with anti-restenotic therapies including, but not limited to, drug-eluting stents and brachytherapy.
19. Currently participating in any investigational drug or another device study, per Nation Health and Medical Research Council (NHMRC) guideline.

Key Baseline Characteristics

The key baseline characteristics are provided below.

Table 6.2-1: Key Baseline Variables

Key Baseline Variables	Endeavor I	
	N	%
Age (years)	100	
Mean (SD*)	58.7 ± 10.08	
Range	35-76	
Gender	100	
Male	79	(79.0%)
Female	21	(21.0%)
Race	100	
White/Caucasian	93	(93.0%)
Clinical Characteristics	N	%
History of diabetes mellitus	16/100	(16.0%)
History of hypertension	52/98	(53.1%)
Lesion Characteristics	N	Mean (SD*)
Reference Vessel Diameter (mm)	100	2.96 ± 0.47
Lesion length (mm)	100	10.94 ± 3.13
	N	%
Discreet (< 10mm)	43/100	43.0%
Tubular (10-19.9 mm)	56/100	56.0%
Diffuse (≥20mm)	1/100	1.0%
ACC/AHA lesion class	N	%
A	17/100	17.0%
B1	34/100	34.0%
B2	44/100	44.0%
C	5/100	5.0%

* SD = Standard Deviation.

Enrollment/ Randomization

Study Period (enrollment): 7 January 2003 to 29 April 2003

This was a non-randomized study and all patients were treated with the Endeavor stent.

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Antiplatelet Medications

All subjects received aspirin (at least 300-325 mg daily) and clopidogrel (300 mg loading dose 6 hours prior to procedure when possible or 300 mg at procedure) prior to coronary stent implantation. If the subject was currently taking clopidogrel, the patient continued with 75 mg daily. The ACT was monitored and recorded on source documentation during the procedure and adjusted to keep the subject's ACT ≥250 sec., or 200-250 sec. if a glycoprotein IIb/IIIa receptor blocker was administered.

All subjects received aspirin 300-325 mg for 12 weeks followed by at least 100 mg daily indefinitely per the physician's discretion, and clopidogrel 75 mg daily for at least 12 weeks. A summary is provided below.

Table 6.2-2: Summary of Concomitant Medical Therapy

Medication	Pre-Procedure	During Catheterization	Post-Index Procedure	Follow-up
IV Heparin	PRN	To maintain elevated ACT per site's standard practice	PRN	No
Intracoronary Nitroglycerin	No	100 – 200 mcg prior to baseline and post intervention angiograms	No	No
Aspirin	300-325 mg QD	No	300-325 mg QD	300-325 mg QD for 12 weeks, then ≥100 mg per physician discretion
Clopidogrel	300 mg po 6 hours prior to procedure, or 300 mg po at procedure (if not given prior to procedure) Note: If subject currently taking clopidogrel, continue 75 mg QD		75 mg po QD	75 mg po QD for 12 weeks

Patient Follow-up

Clinical follow-up for all subjects was performed at: 30 days (telephone contact); 4 months (angiographic and IVUS measurements); 9 months (telephone contact); 12 months (angiographic and IVUS measurements); and at 2, 3 and 4 years (telephone contact). In addition, subjects have telephone follow-up contact up to 5 years from the date of procedure to assess for adverse events and angina status (Canadian Cardiovascular Society Classification of angina). The primary analysis subset was the Intent-to-Treat (ITT) population for MACE (Major Adverse Cardiac Events) at 30 days and late lumen loss at 4 months defined as the difference between the post-index procedure minimal lumen diameter (MLD) and the 4-month follow-up angiography MLD. MACE is defined as the incidence of the combined clinical endpoints of death, myocardial infarction, emergent cardiac bypass surgery, or clinically-driven repeat target lesion revascularization as determined by the Clinical Events Committee (CEC) that adjudicates all clinical endpoint events. An independent Angiographic Core Laboratory

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and an independent IVUS (Intravascular Ultrasound) Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. A Data Safety Monitoring Board (DSMB) reviews the study on a regular basis.

Schedule of Treatments and Assessments

A summary of treatments and assessments is provided below.

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Table 6.2-3: Schedule of Treatments and Assessments

Index Hospitalization				Follow-up			
				30 Day	4 Month	9 Month	12 months – 5 years
Event	Screen	Procedure	Post-index procedure	Telephone	Angiography IVUS	Telephone	12 months – Angiography IVUS 2 years- 5 years - Telephone
Informed Consent Signed	X						
Inclusion/Exclusion Criteria	X						
Medical and Cardiac History	X						
Angina Status	X		X	X	X	X	X
Pregnancy test	X [1,2]						
Liver Function test	X[2]						
CBC with differential [3], platelet count & serum urea, creatinine, electrolytes	X [2]		X [4, 5]				
12-Lead Electrocardiogram	X [2]		X [4]				
CK & CK-MB	X [6]		X [7]				
ACT Measurements		X					
Medication Regimen [8]	X	X	X	X			
Adverse Event Monitoring			X	X	X	X	X
Angiography (QCA)	X	X			X		X
IVUS		X			X		X

[1] For women of childbearing potential only.
[2] Within 7 days prior to procedure.
[3] If WBC was within normal limits, a differential was not required.
[4] Within 24 hours post-index procedure or at discharge, which ever came first.
[5] CBC with differential was not drawn post-index procedure.
[6] Within 72 hours prior to procedure.
[7] Within 6-8, 12-16, and 18-24 hour post-index procedure or prior to hospital discharge, which ever came first.
[8] It was expected that clopidogrel be used, unless the patient was allergic or sensitive to this medication. For patients unable to take clopidogrel, or at the discretion of the physician, ticlopidine was used.

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6.2.1.6 Patient Accountability

ENDEAVOR I enrolled a total of 100 patients at eight clinical research sites in Australia and New Zealand from January 7, 2003 through April 29, 2003. A summary of the sites, investigators, and number of patients enrolled is provided in the report (Appendix 1).

All enrolled study patients were scheduled to undergo an angiogram and IVUS at four and 12 months post procedure.

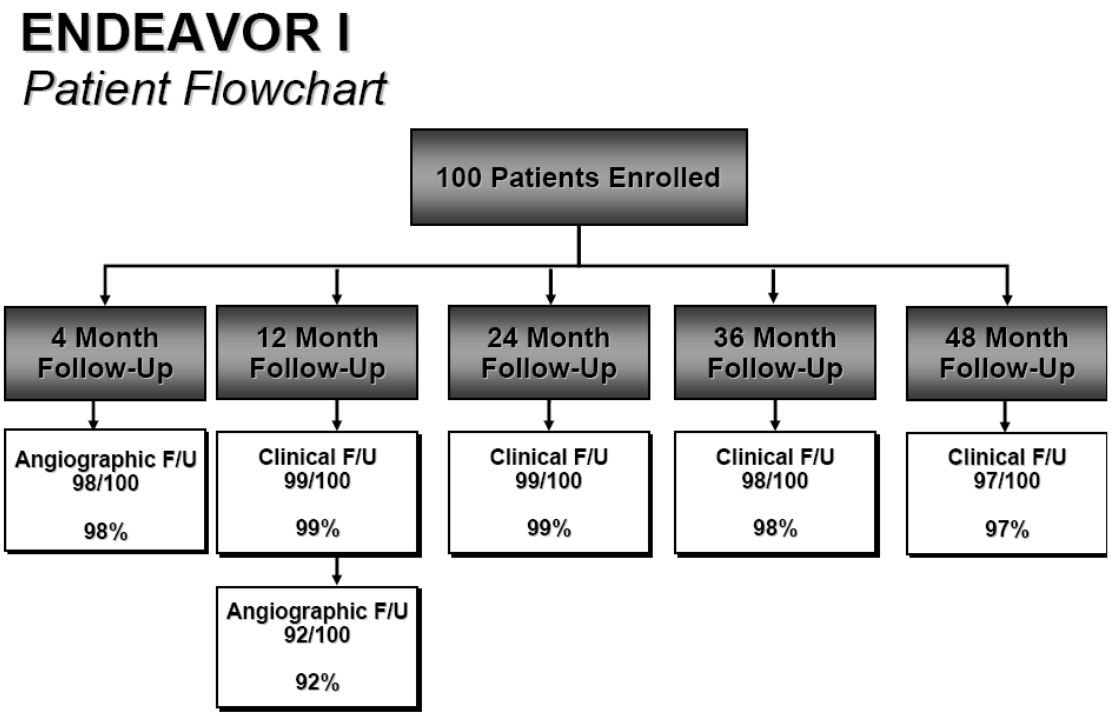

Figure 6.2-1: Patient flowchart for ENDEAVOR I at 48 months

6.2.2 Statistical Methodology

6.2.2.1 Clinical Trial Objectives and Hypotheses

ENDEAVOR I was a non-randomized study and all patients were treated with the Endeavor stent. ENDEAVOR I enrolled a total of 100 patients at eight clinical research sites in Australia and New Zealand.

Data collected in this study were documented using summary tables. Demographic and background characteristics, safety and efficacy data were summarized. Descriptive statistics were provided. The statistics for continuous variables included mean, standard deviation, minimum, maximum, and sample size. Categorical variables were described with counts and percentages. Percentages were rounded to one decimal place. Computations for all results were performed using SAS Version 6.12 or higher computer software package.

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Analysis Samples

The primary analytical subset is the intent-to-treat (ITT) population and the secondary analytical subset is the per protocol (PP) subset.

Intent to Treat (ITT): All patients enrolled in the study.

IVUS Analysis Set: All patients enrolled in the study had IVUS performed immediately post-stent procedure and at the 4- and 12-month follow-up.

Angiography Analysis Set: For each time point (baseline, post-index procedure, 4- and 12-month) the analysis set included all subjects enrolled in the study who had the angiogram required for the analysis at that time point (any subject with an angiogram within 30 days of the scheduled angiogram was included in the analysis at that time point). If an analysis involved more than one time point, subjects must have had all required angiograms in order to be included in the analysis.

For the primary endpoint analyses, subjects were analyzed regardless of the sequence of events. Those subjects who met eligibility requirements for primary endpoint ascertainment included all subjects enrolled who did not withdraw their consent. The per-protocol analytical subset is the secondary analytical subset.

Primary Endpoint

The primary safety endpoint of this study was Major Adverse Cardiac Events (MACE) at 30 days. MACE was defined as the incidence of the combined clinical endpoints: death, myocardial infarction, emergent cardiac surgery, or clinically-driven repeat target lesion revascularization as determined by the Clinical Events Committee (CEC).

The expected incidence of MACE at 30 days in contemporary stenting trials was approximately 4%. Using this base rate of 4% as the expected complication rate, this would correspond to a true event rate of four or fewer subjects with major adverse cardiac events in this pilot study. However, the random error of estimating a true 4% rate with 95 subjects (assuming 5% lost to follow-up at 30 days) was relatively large, and a statistical test designed to test the probability of a true rate greater than 4% allowed for sufficient alpha (type I) error. The upper 95% confidence bound for a 4% rate with n=95 is 7.9%. Thus, the test for demonstration of acute safety and feasibility was observation of a 30-day MACE rate ≤ 7.9%, or observation of MACE in ≤ 8 subjects.

The primary efficacy endpoint was the angiographic late lumen loss at 4 months, defined as the difference between the post-index procedure minimal lumen diameter (MLD) and the 4-month follow-up angiography MLD.

In contemporary stenting trials, late loss of approximately 0.8 mm was observed with a standard deviation of 0.55 mm. If 20% lost to follow-up is assumed (80 evaluable subjects), this trial had 89% power to detect a late loss difference of 0.2 mm. These estimates were derived using a one group t-test with a two tailed alpha value of 0.05.

Secondary Endpoints

The secondary endpoints for this study were: 1) Target vessel failure (TVF) defined as a composite of cardiac death, MI (Q wave and non-Q wave), or target vessel revascularization at 9 months; 2) Target lesion revascularization (TLR) rate, defined as the incidence of clinically driven repeat revascularization of the target lesion at 9 months;

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3) Late lumen loss at 12 months as measured by angiographic data; and 4) Neointimal hyperplastic volume at 4 and 12 months as measured by IVUS. An independent Clinical Events Committee adjudicated all major clinical endpoints. All endpoints were analyzed on intent-to-treat and per-protocol bases. The intent-to-treat subset is the primary analytical subset.

Analysis on Baseline Characteristics
All clinically relevant baseline and follow-up variables were tabulated. Means, standard deviations and ranges were reported for continuous variables, and percentages were reported for categorical variables. Comparisons of angiographic and IVUS data collected at baseline and at 4 and 12 months were analyzed as follows: categorical variables will be tested using contingency tables analyses (exact or chi-square approximations), and continuous variables will be tested using unpaired Student's t-test or Wilcoxon rank-sum test, depending on variable distribution. In addition, where appropriate, cumulative frequency distribution plots of angiographic and IVUS variables will be performed. Kaplan-Meier techniques will be utilized to assess survival free of MACE, TVR and TLR.

6.2.3 Results

The principal effectiveness and safety results for the Endeavor Zotarolimus-Eluting Coronary Stent System are presented in the tables below. The primary safety endpoint of the trial, incidence of major adverse cardiac events (MACE) at 30 days, was 1% (1/100). In-hospital incidence of MACE was 0%. At both 270 and 360 days, the incidence of MACE was 2% (2/100 and 2/99, respectively). At 720 days post-procedure, the incidence of MACE was 3.0% (3/99). The cumulative incidence of MACE at Day 1080 was 6.1% (6/98) and 7.2% (7/97) at 1440 days. The Kaplan-Meier estimate of freedom from MACE at 1440 days was 92.9%. The cumulative incidence of TVF at 1440 days was 5.2% (5/97). The Kaplan-Meier estimate of freedom from TVF at 1440 days was 94.9%. The Kaplan-Meier estimates are based on the full enrollment of 100 patients. Patients with follow-up less than 48 months are censored at time of dropout (and at time of death for all non-death endpoints).

The primary efficacy endpoint of the trial was late loss at 4 months. Of the one hundred (100) patients, ninety-eight returned for protocol specified angiography at 4 months and had qualified films for the 4-month analysis. Late lumen loss as measured in-segment (defined as the difference between the in-segment MLD at the post-index procedure and the in-segment MLD at follow up) was 0.22 ± 0.43 mm (98) and late lumen loss as measured in-stent (defined as the difference between the in-stent MLD at the post-index procedure and the in-stent MLD at follow-up) was 0.32 ± 0.37 mm (98). Of the ninety-eight (98) patients with qualified angiographic films, 3.1% (3/98) had binary angiographic restenosis (defined as ≥50% diameter stenosis by quantitative angiographic analysis).

Ninety-two patients returned for protocol specified angiography at 12 months and had qualified films for the 12-month analysis. Of the ninety-two qualified patients, 5.4% (5/92) had binary angiographic restenosis (defined as ≥50% diameter stenosis by

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quantitative angiographic analysis). Late lumen loss as measured in-segment was 0.43 ± 0.44 mm (92) and late lumen loss as measured in-stent was 0.58 ± 0.44 mm (92).

Eight (8/100, 8%) patients had at least two Endeavor stents implanted during the index procedure. Five patients (5/100, 5%) experienced a post-index procedure dissection. Of these five patients, one (234-009) had two stents implanted.

Table 6.2-4: Principal Effectiveness and Safety Results through 1440 days for ENDEAVOR I

Safety and Effectiveness Measures	ENDEAVOR I (N=100 Patients)
Lesion Success	100.0% (100/100)
Procedure Success	100.0% (100/100)
Device Success	100.0% (100/100)
4 Month results	
Four-Month Follow-up Percent Diameter Stenosis (% DS)	
In-Stent	14.40±13.10 (98)
In-Segment	22.36±12.08 (98)
Four-Month Follow-up Late Loss (mm)	
In-Stent	0.32±0.37 (98)
In-Segment	0.22±0.43 (98)
Four-Month Binary Restenosis	
In-Stent	2.0% (2/98)
In-Segment	3.1% (3/98)
Volume Obstruction (%)	4.46±6.05 (94)
Minimal Lumen Area (mm^2)	5.96±1.66 (95)
Neointimal Hyperplastic Volume (mm^3)	6.10±7.39 (94)
12 Month Results	
Twelve-Month Follow-up Percent Diameter Stenosis (% DS)	
In-Stent	21.75±15.35 (92)
In-Segment	28.00±13.41 (92)
Twelve-Month Follow-up Late Loss (mm)	
In-Stent	0.58±0.44 (92)
In-Segment	0.43±0.44 (92)
Twelve-Month Follow-up Binary Restenosis	
In-Stent	4.3% (4/92)
In-Segment	5.4% (5/92)
Volume Obstruction (%)	9.73±8.50 (86)
Minimal Lumen Area (mm^2)	5.69±1.74 (86)
Neointimal Hyperplastic Volume (mm^3)	14.15±11.82 (86)

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Table 6.2-4: Principal Effectiveness and Safety Results through 1440 days for ENDEAVOR I

Safety and Effectiveness Measures	ENDEAVOR I (N=100 Patients)
Safety Measures	
In-Hospital MACE	0.0% (0/100)
MACE to 30 Days	1.0% (1/100)
MACE to 270 Days	2.0% (2/100)
MACE to 360 Days	2.0% (2/99)
MACE to 720 Days	3.0% (3/99)
MACE to 1080 Days	6.1% (6/98)
MACE to 1440 Days	7.2% (7/97)
Death to 1440 Days	4.1% (4/97)
Vascular Complications to 1440 Days	3.1% (3/97)
Major Bleeding to 1440 Days	1% (1/97)
Early Stent Thrombosis	2.1% (2/97)
Late Thrombosis to 270 days	0.0% (0/100)
Late Thrombosis to 360 days	0.0% (0/99)
Late Thrombosis to 720 days	0.0% (0/99)
Late Thrombosis to 1080 days	0.0% (0/98)
Late Thrombosis to 1440 days	0.0% (0/97)
Cerebrovascular Accident (CVA)	1.0% (1/97)
Perforation	0.0% (0/97)
Target Vessel Revascularization to 30 days	1.0% (1/100)
Target Vessel Revascularization to 270 days	2.0% (2/100)
Target Vessel Revascularization to 360 days	2.0% (2/99)
Target Vessel Revascularization to 720 days	4.0% (4/99)
Target Vessel Revascularization to 1080 days	5.1% (5/98)
Target Vessel Revascularization to 1440 days	5.2% (5/97)
Target Vessel Failure to 30 days	1.0% (1/100)
Target Vessel Failure to 270 days	2.0% (2/100)
Target Vessel Failure to 360 days	2.0% (2/99)
Target Vessel Failure to 720 days	4.0% (4/99)
Target Vessel Failure to 1080 days	5.1% (5/98)
Target Vessel Failure to 1440 days	5.2% (5/97)

Table 6.2-5: Major Adverse Events (to 1440 days)

Hierarchial Complications to 1440 days	ENDEAVOR I (N=100 Patients)
Any MACE (Death, MI, Emergent CABG, TLR)	7.2% (7/97)
Death	4.1% (5/97)
Non-fatal Q Wave MI	0.0% (0/97)
Non-fatal Non-Q Wave MI without Q Wave MI	1.0% (1/97)
Emergent CABG without Death or MI	0.0% (0/97)
TL-CABG without Death or MI	0.0% (0/97)
TL-PTCA without Death, MI, or TL-CABG	2.1% (2/97)

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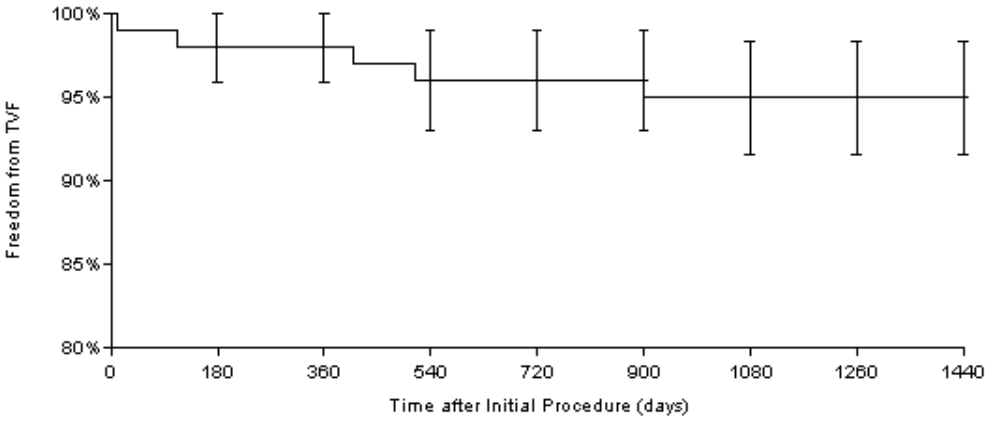
Table 6.2-6: Combined Complications to 1440 Days	ENDEAVOR I (N=100 Patients)
MACE (Death, MI, Emergent CABG, TLR)	7.2% (7/97)
Death	4.1% (4/97)
Myocardial Infarction (Q Wave or Non-Q Wave)	1.0% (1/97)
Q Wave MI	0.0% (0/97)
Non-Q Wave MI	1.0% (1/97)
Emergent CABG	0.0% (0/97)
Target Lesion Revascularization	3.1% (3/97)
TL-CABG	1.0% (1/97)
TL-PTCA	3.1% (3/97)
Target Vessel Revascularization not involving the Target Lesion	2.1% (2/97)
TV/non-TL-CABG	1.0% (1/97)
TV/non-TL-PTCA	1.0% (1/97)
Target Vessel Revascularization	5.2% (5/97)
Target Vessel Failure	5.2% (5/97)
Perforation	0.0% (0/97)
Early Stent Thrombosis	1.0% (1/97)
Late Stent Thrombosis	0.0% (0/97)
Vascular Complications	3.1% (3/97)
Cerebrovascular Accident (CVA)	1.0% (1/97)
Major Bleeding	2.1% (2/97)



TVF	0	180	360	540	720	900	1080	1260	1440
# Entered	100	100	98	97	94	94	92	90	90
# Censored	0	0	1	1	0	2	1	0	2
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	0	2	0	2	0	0	1	0	0
% Survived	100.0%	98.0%	98.0%	96.0%	96.0%	96.0%	94.9%	94.9%	94.9%
SE	0.0%	1.4%	1.4%	2.0%	2.0%	2.0%	2.3%	2.3%	2.3%
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Figure 6.2-2: Survival Free from Target Vessel Failure at 1440 days (ITT)

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6.2.4 Conclusions

The acute clinical results demonstrate 100.0% (100/100) lesion, device, procedure and device-specific procedure success rates with MACE rates of 1.0% (1/100) at 30 days and 7.2% (7/97) at 48 months post-index procedure. The survival estimate free from the secondary endpoint TVF at 9 months post-index procedure was 98.0%. The survival estimate free from the endpoint of TVF at 48 months post-index procedure was 94.9%. The cumulative incidence of TVF at 48 months was 5.2% (5/97). The survival estimate free from TLR at 48 months post-index procedure was 96.9%, and the cumulative incidence of TLR at 48 months was 3.1% (3/97). Four-month angiographic late loss was 0.22 $\pm$ 0.43 in-segment and 0.32 $\pm$ 0.37 in-stent. Twelve-month angiographic late loss was 0.43 $\pm$ 0.44 in-segment and 0.58 $\pm$ 0.44 in-stent for the 92 evaluable patients.

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6.3 ENDEAVOR II Clinical Study Summary

6.3.1 Clinical Study Description

ENDEAVOR II was a Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic Zotarolimus-Eluting Coronary Stent in *De novo* Native Coronary Artery Lesions.

6.3.1.1 Study Design

The study was designed as a prospective, multi-center, double-blind, two-arm randomized controlled trial.

6.3.1.2 Study Objectives

To demonstrate the safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System coated with 10 µg/mm zotarolimus compared to the Driver stent for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter

6.3.1.3 Primary Endpoints

Target vessel failure (TVF) rate, defined as a composite of target vessel revascularization (TVR), recurrent Q or non-Q wave myocardial infarction (MI), or cardiac death that could not be clearly attributed to a vessel other than the target vessel at 270 days post index procedure

6.3.1.4 Secondary Endpoints

- MACE defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) at 30 days and 6, 9, and 12 months
- Lesion success defined as attainment of <50% residual stenosis of the target lesion using any percutaneous method
- Device success defined as attainment of <50% residual stenosis of the target lesion using only the assigned device
- Procedure success defined as attainment of <50% residual stenosis of the target lesion and no in-hospital MACE
- Device-specific procedure success defined as device success and no in-hospital MACE
- Late loss at 8 months as measured by QCA, defined as the difference between the post-index procedure minimal lumen diameter (MLD) and the 8 month follow-up MLD
- Angiographic in-stent and in-segment binary restenosis rate (≥50% diameter stenosis) at 8 months post-index procedure
- In-stent and in-segment minimum lumen diameter (MLD) at 8 months post-index procedure
- Neointimal hyperplastic volume at 8 months as measured by intravascular ultrasound (IVUS)
- TLR at 270 days post-index procedure
- TVR at 270 days post-index procedure

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- Pharmacokinetic assessment in a subset of subjects
- Safety and tolerance.

6.3.1.5 Patient/Study Population

General Inclusion Criteria

Candidates were considered for inclusion if the following conditions were met:

Note: Subjects could only be included in the study once.

1. The subject was ≥18 years of age (or minimum age dictated by local regulations).
2. The subject was an acceptable candidate for PTCA, stenting, and emergent CABG.
3. The subject had clinical evidence of ischemic heart disease or a positive functional study.
4. The subject had single vessel disease or had multi-vessel disease with only moderate stenosis (max 50-60% or total occlusion (100%) for which no interventions were planned at the time of study inclusion).
5. The target lesion / vessel must have met the following criteria:
    a. The target lesion was a single *de novo* lesion that had not been previously treated with any interventional procedure. Only one lesion may have been treated per subject.
    b. The target vessel was a native coronary artery with a stenosis of ≥50% and <100%.
    c. The target lesion was ≥14 mm and ≥27 mm in length.
    d. The target vessel reference diameter was ≥2.25 mm and ≥3.5 mm. (Measurements were made by careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound.)
6. Female subjects of childbearing potential had a negative pregnancy test within seven (7) days before the procedure.
7. The subject or the subject's legal representative had been informed of the nature of the study and agreed to its provisions and provided written informed consent as approved by the Institutional Review Board/Ethics Committee of the respective clinical site.
8. The subject and the treating physician agreed that the subject would comply with all required post-index procedure follow-up.

General Exclusion Criteria

1. A documented left ventricular ejection fraction <30%.
2. A known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, cobalt, nickel, chromium, or a sensitivity to contrast media, which could not have been adequately pre-medicated.
3. Had a history of an allergic reaction or significant sensitivity or received drugs similar to/or synergistic to Zotarolimus (rapamycin, tacrolimus, sirolimus, CCI-779 or other analogues).
4. A platelet count <100,000 cells/mm³ or >700,000 cells/mm³, or a WBC <3,000 cells/mm³.

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5. Had evidence of an acute myocardial infarction within 72 hours of the intended treatment (defined as: Q wave or non-Q wave infarction having CK enzymes ≥2X the upper laboratory normal with the presence of a CK-MB elevated above the Institution's upper limit of normal).
6. Creatinine >2.0 mg/dl.
7. A previous coronary interventional procedure of any kind within the 30 days prior to the procedure.
8. The subject required planned interventional treatment of either the target or any non-target vessel within 30 days post-index procedure.
9. The target lesion required treatment with a device other than PTCA prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
10. Had previous stenting anywhere in the target vessel.
11. The target vessel had evidence of thrombus or was excessively tortuous (2 bends >90° to reach the target lesion).
12. Had significant (>50%) stenosis proximal or distal to the target lesion that may have required revascularization or impede run off.
13. Target lesion located in native vessel distally to anastomosis with vein graft or LIMA.
14. The target lesion had any of the following characteristics:
    a. Lesion location was aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the LAD, LCX, or RCA.
    b. Involved a side branch >2.0 mm in diameter.
    c. Was at or distal to a 45º bend in the vessel.
    d. Was severely calcified.
15. Had an unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery).
16. Had a history of a stroke or transient ischaemic attack within the prior 6 months.
17. Had an active peptic ulcer or upper GI bleeding within the prior 6 months.
18. The subject had a history of bleeding diathesis or coagulopathy or would have refused blood transfusions.
19. Had a concurrent medical condition with a life expectancy of less than 12 months.
20. Had any previous or planned treatment with anti-restenotic therapies including, but not limited to, drug-eluting stents and brachytherapy.
21. Was currently participating in an investigational drug or another device study that had not completed the primary endpoint or that clinically interfered with the current study endpoints. [Note: Trials requiring extended follow-up for products that were investigational, but had since become commercially available, were not considered investigational trials.]

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Key Baseline Characteristics

The key baseline characteristics are provided in the following table.

Table 6.3-1: Key Baseline Variables

Baseline Variables	Endeavor		Driver	
	N	%	N	%
Age (years)	597		596	
Mean (SD*)	61.58 ± 10.53		61.89 ± 10.45	
Range	30-87		28-90	
Gender	597		596	
Male	461	(77.2%)	449	(75.3%)
Race	597		596	
White/Caucasian	562	(94.1%)	561	(94.1%)
Clinical Characteristics	N	%	N	%
History of diabetes mellitus	108/595	(18.2%)	132/595	(22.2%)
History of hypertension	378/596	(63.4%)	403/591	(68.2%)
Lesion Characteristics	N	Mean (SD*)	N	Mean (SD*)
Reference Vessel Diameter	590	2.73 ± 0.48	591	2.76 ± 0.49
Lesion length	582	14.04 ± 5.56	588	14.38 ±5.73
	N	%	N	%
Discrete (< 10mm)	157/582	27.0%	139/588	23.6%
Tubular (10-19.9 mm)	344/582	59.1%	358/588	60.9%
Diffuse (≥20mm)	81/582	13.9%	91/588	15.5%
ACC/AHA lesion class	N	%	N	%
A	17/590	2.9%	24/591	4.1%
B1	110/590	18.6%	100/591	16.9%
B2	300/590	50.8%	323/591	54.7%
C	163/590	27.6%	144/591	24.4%

Enrollment/ Randomization

Study Period (enrollment): 14 July 2003 to 13 January 2004

Subjects were randomized in a double-blind fashion (1:1 randomization) to one of two treatments: Uncoated Driver CSS or Endeavor Zotarolimus-Eluting CSS.

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Randomization was achieved using an Interactive Voice Response System (IVRS). A randomization block size of eight was used at each site. At each site, the system generated eight randomization numbers starting with the first patient enrolled and then every ninth patient.

Antiplatelet Medications

It was strongly recommended that all subjects received the medication regimen listed below. All medications administered were to have been recorded in the subject's medical record. All concomitant medications taken by the patient for 30 days post-index procedure were to have been reported on the study case report form. All anti-platelet and anti-coagulant medication taken throughout the study was to have been reported on the study case report form.

Prior to Procedure	IV Heparin	PRN
	Aspirin	At least 75 mg QD
	Clopidogrel [a, b]	300 mg loading dose (if patient not currently taking clopidogrel)
During Procedure	IV Heparin	To maintain ACT ≥250 sec., or 200-250 sec. if GP IIb/IIIa blocker is used
	Intracoronary Nitroglycerin	100-200 μg *prior to baseline* and post intervention angiograms
Post-Index Procedure	IV Heparin	PRN
	Aspirin	At least 75 mg QD indefinitely
	Clopidogrel[a]	75 mg po QD (for 12 weeks)

Patient Follow-up

Clinical evaluations occurred during hospitalization and at 30 days and 9 months. Telephone follow-up for safety at 6, 12 and 24 months and annually thereafter for 5 years. Adverse events were reported up to 9 months. Subsequently, SAEs (including MACE) and device-related adverse events are reported to 5 years. The first 600 subjects enrolled had 8 month angiography performed. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. A sub-study using IVUS from these 600 subjects as well as subjects implanted with two or more study stents had a baseline and 8 month IVUS. A Clinical Events Committee (CEC) adjudicates all clinical endpoint events. Annual follow-up is for assessment of angina status (Canadian Cardiovascular Society Classification of angina), serious adverse events (including MACE), concomitant

[a] It was expected that clopidogrel was used, unless the patient was allergic or sensitive to this medication. For patients unable to take clopidogrel, or at the discretion of the physician, ticlopidine was used. For patients on ticlopidine, CBCs were to be performed as per the drug labeling.
[b] If the patient had been on clopidogrel for at least 48 hours prior to the procedure, the daily dose was continued and no additional loading dose given prior to the procedure.

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medications and any interventional treatments occurring since the previous contact. A subset of patients was evaluated for pharmacokinetics (*See Other Analysis under the Results section below*). A Kaplan-Meier technique was used to assess survival free of MACE, TVF, TVR, and TLR. A Data Safety Monitoring Board (DSMB) reviews the study on a regular basis.

Schedule of Treatments and Assessments

A summary of treatments and assessments is provided below.

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Table 6.3-2: Schedule of Treatments and Assessments

Index Hospitalization				Follow-up						
Event	Screen	Proce -dure	Post-Index Proce-dure	7 Day	14 Day	30 Day	6 Month	8 Month	9 Month	12 months-5 years
						Office visit	Tele-phone	Angio[1]/ IVUS [2]	Office visit	Tele-phone
Informed Consent Signed	X									
Inclusion/ Exclusion Criteria	X									
Medical and Cardiac History	X									
Angina Status	X		X			X	X	X	X	X
Pregnancy test	X [3,4]									
CBC with differential, platelet count Chemistry Panel [5]	X [4]		X [6]			X			X	
PK Sample	X [7]		X [7]	X [7]	X [7]	X [7]				
CRP	X [2]		X [2]							
CK & CK-MB	X [8]		X [9]							
Troponin	X [10]		X [10]							
12-Lead Electrocardiog-ram	X [8]		X [6]							
ACT Measurements [11]		X								
Medication Regimen [12]	X	X	X			X	X		X	X
Adverse Event Monitoring			X	X	X	X	X	X	X	X (SAE)
Angiography (QCA)	X	X						X [1]		
IVUS		X [2]						X [2]		

[1] A subset including the first 600 consecutive study subjects enrolled had angiographic follow-up at 8 months.
[2] Selected clinical sites only.
[3] For women of childbearing potential only.
[4] Within 7 days prior to procedure.
[5] Please see complete list in definitions section.
[6] Within 24 hours post-index procedure or at discharge, which ever came first.
[7] Up to 120 subjects had blood samples taken prior to procedure and at 0.25hr, 0.5hr, 1hr, 2hr, 4hr, 6hr, 12hr, 24hr (or discharge, whichever came first) and at 7, 14 and 30 days post-index procedure for pharmacokinetic (PK) analysis as a sub-study at selected sites.
[8] Within 72 hours prior to procedure.
[9] Within 6-8, 12-16, and 20-24 hours post-index procedure or prior to hospital discharge, whichever came first.
[10] Optional – Measurement was recommended if the lab had the capability.
[11] Optional – per hospital practice.
[12] It was expected that clopidogrel was used, unless the patient was allergic or sensitive to this medication. For patients unable to take clopidogrel, or at the discretion of the physician, ticlopidine was used.

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6.3.1.6 Patient Accountability

ENDEAVOR II enrolled a total of 1,197 patients at 72 clinical research sites in Europe, Asia Pacific, Israel, Australia, and New Zealand from July 14, 2003 through January 13, 2004. There were four sites that received approval but did not enroll any patients.

One hundred and six (106) subjects at selected sites were part of the pharmacokinetic (PK) substudy and had blood samples taken for PK analysis. Sites were selected based on the ability to conduct the follow-up PK draws over the 30-day period as well as the availability of a -70 °C storage freezer. Of the 106 patients, 54 were randomized to receive the Endeavor Zotarolimus-Eluting CSS and blood data necessary for PK analysis was available for 53 of the 54 patients.

The first 600 consecutively enrolled patients (300 per treatment assignment) were scheduled for follow-up angiography at eight months.

The first 300 consecutively enrolled patients (150 per treatment assignment) were scheduled for follow-up IVUS at eight months at selected sites.

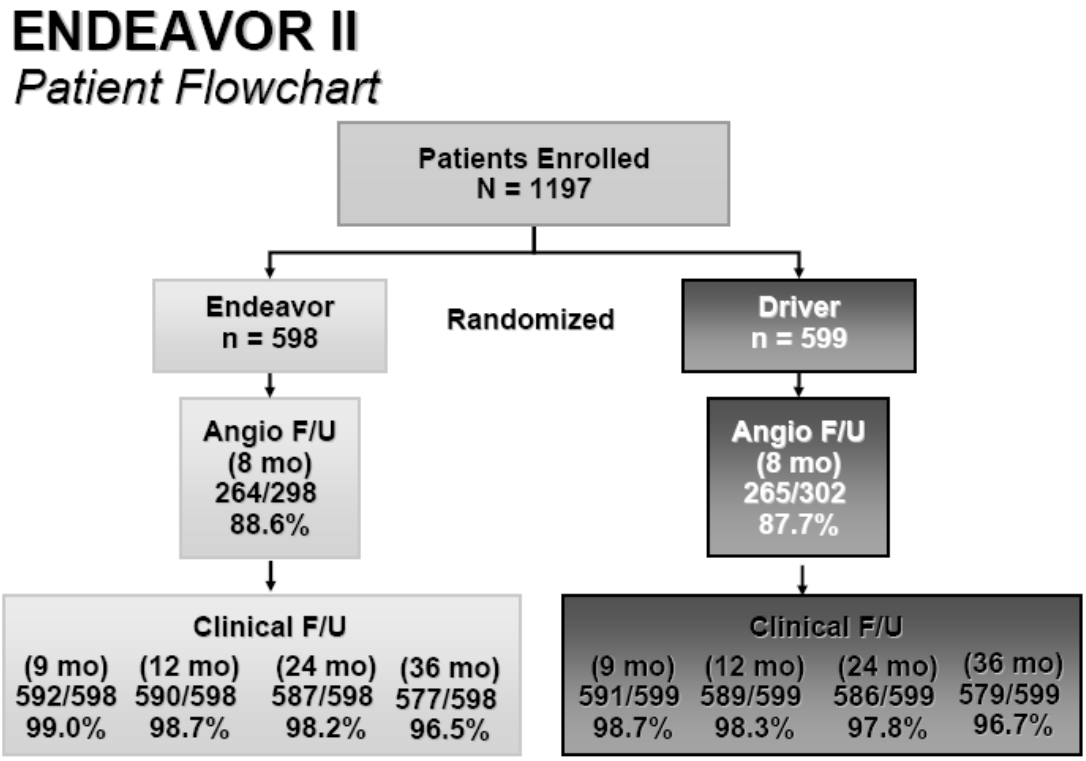

Figure 6.3-1: Patient flowchart for ENDEAVOR II at 36 months

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6.3.2 Statistical Methodology

6.3.2.1 Clinical Trial Objectives and Hypotheses

The ENDEAVOR II clinical trial was a randomized, controlled, prospective, multi-center two-arm trial designed to assess the safety and effectiveness of the Endeavor Zotarolimus-Eluting Coronary Stent System compared to the Driver bare metal stent. The primary endpoint evaluated in this study was target vessel failure, defined as the composite of cardiac death, recurrent myocardial infarction, or target vessel revascularization at 270 days post-index procedure.

The study enrolled a total of 1,197 patients at 72 clinical research sites in Europe, Asia Pacific, Israel, Australia, and New Zealand.

Analysis Samples
The primary analysis sample was based on the principle of intention-to-treat. For this study, all subjects who met the study entry criteria, signed the written informed consent and were randomized to a treatment arm were counted in the primary analysis.

The secondary analysis sample was based on the principle of per-protocol.

All statistical analyses were performed using SAS for Windows (version 6.12 or higher) or other widely accepted statistical or graphical software. Patient data listings and tabular and graphical presentations of results were provided.

All clinically relevant baseline variables were tabulated and compared between subjects assigned the Endeavor Zotarolimus-Eluting Coronary Stent System and the control arm of the trial. Categorical variables were tested using appropriate contingency table analyses (exact or chi-square approximations), and continuous variables were tested using unpaired Student's t-test. Multivariable regression and multivariable survival analysis was utilized to examine alternative hypotheses, such as exploration of outcome determinants. Multi-variable testing used linear regression for continuous response variables and logistic regression for dichotomous response variables. The time-sensitive nature of any response variable was displayed by using a Kaplan-Meier plot, with differences between groups for such variables tested by log rank tests.

A statistical significance was declared if the two-sided P-value is <0.05.

Secondary endpoint testing and subgroup hypothesis testing proceeded using identical statistical techniques as in the primary endpoint analysis.

Primary Endpoint
The primary endpoint evaluated in this study was Target Vessel Failure (TVF), defined as the composite of cardiac death, recurrent myocardial infarction, or target vessel revascularization at nine months post-procedure. The null hypothesis for this study is that the Endeavor Zotarolimus-Eluting Stent will have a primary endpoint rate equal to that of the control (Driver stent). The alternative hypothesis is that the Endeavor Zotarolimus-Eluting Stent will have a primary endpoint rate less than, or greater than, the control stent.

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H_o: $\pi_{DE} = \pi_{CS}$
H_a: $\pi_{DE} < \pi_{CS}$
H_a: $\pi_{DE} > \pi_{CS}$

Where π_{DE} is the primary endpoint rate estimate for the Endeavor Zotarolimus-Eluting Stent and π_{CS} is the primary endpoint rate estimate for the control Driver Stent. Rejection of the null hypothesis signifies that the Endeavor Zotarolimus-Eluting Stent is *superior or inferior* compared to the control stent with regard to nine-month target vessel failure. The parameters/assumptions for this analysis are:

- The nine-month target vessel failure rate of the subjects treated with the control stent (π_{CS}) is assumed to be 16.0%.
- The nine-month target vessel failure rate of the subjects treated with the Endeavor Zotarolimus-Eluting Stent (π_{DE}) is assumed to be 9.5 %. This implies a treatment effect of approximately 40%.
- The power of the study is 90%.
- The two-sided alpha error is 5%.

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

Secondary Endpoints

The endpoint to be evaluated is angiographic Late Loss as determined by core lab measurement of the difference between the MLD after follow-up and post stent implantation. The objective is to prove that with respect to this endpoint, the Endeavor Zotarolimus-Eluting Stent performs better than the control Driver stent. The null-hypothesis that was tested is that the mean Late Loss at eight months in patients treated with the Endeavor Zotarolimus-Eluting Stent is equal to the mean Late Loss at eight months in patients treated with the control Driver stent. The alternative hypothesis is that the mean MLD at eight months in patients treated with the drug-eluting stent is greater than or less than that of patients treated with the control stent.

H_o : $m_{CS} = m_{DE}$
H_a : $m_{CS} < m_{DE}$
H_a : $m_{CS} > m_{DE}$

Where m_{CS} is the mean Late Loss at eight months for the Endeavor Zotarolimus-Eluting Stent and m_{DE} is the mean Late Loss at eight months for the control Driver stent.

A minimally required sample size has been calculated based on the following assumptions:

The mean MLD at eight months in the Endeavor Zotarolimus-Eluting Stent arm is 0.21 mm larger than the mean Late Loss at eight months in the control arm.

The standard deviation of the Late Loss is 0.70 mm in both arms.

The power is 90%.

The two-sided alpha error is 5%

The loss to follow up will be approximately 20%.

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The calculated sample size under these assumptions is 234 per arm, so 468 in total. The number is increased to 600 in order to account for patients who could be lost to follow-up.

Analysis on Baseline Characteristics
All clinically relevant baseline variables are tabulated and compared between subjects assigned the Medtronic AVE Zotarolimus-Eluting Driver Stent and the control arm of the trial. Categorical variables were tested using appropriate contingency table analyses (exact or chi-square approximations), and continuous variables were tested using unpaired Student's t-test or Wilcoxon rank-sum test, depending on variable distribution. Multivariable regression and multivariable survival analysis were utilized to examine alternative hypotheses, such as exploration of outcome determinants. Multi-variable testing used linear regression for continuous response variables and logistic regression for dichotomous response variables. The time-sensitive nature of any response variables are displayed by using a Kaplan-Meier plot, with differences between groups for such variables tested by log rank tests.

6.3.3 Results

In selected patients, elective Endeavor stent placement in native coronary artery *de novo* lesions resulted in reduction of the incidence of TVF at 1080 days compared to control (12.8% vs. 21.4 %). The table below summarizes the results of the primary endpoint of target vessel failure (TVF) at 270 days post index procedure. Overall Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) were reduced in the Endeavor stent group at 1080 days compared to control (9.5% vs. 18.7%). The rate of early stent thrombosis was lower in the Endeavor stent arm when compared to the control (0.5% vs. 1.2%).

Table 6.3-3: Primary Endpoint from Endeavor II Trial

Study	Primary Endpoint	Test/ Control	Parameter in % or Mean ± SD	Difference [95% CI]	p-value
Endeavor II	Target Vessel Failure at 9 months post-procedure	Endeavor	7.9% (47/592)	-7.1% [-10.7%,-3.5%]	< 0.001
		Driver	15.1% (89/591)		

By follow-up angiography at 8-months, there was significantly lower in-stent late loss (0.62 vs. 1.03) and in-segment late loss (0.36 vs. 0.72). Mean in-stent percent diameter stenosis was significantly reduced (27.9% vs. 42.2%). Additionally, in-stent and in-segment binary angiographic restenosis were significantly reduced (9.5% vs. 33.2% and 13.3% vs. 34.7%).

Examination by IVUS at 8 months showed that neointimal hyperplasia (NIH) volume was significantly reduced in the Endeavor stent arm (30.2 mm^3 vs. 53.5 mm^3). There was no evidence of late stent incomplete apposition in either treatment arm at 8 months.

The table below summarizes the principal effectiveness and safety results of the ENDEAVOR II trial through 1080 days. The figure following the table provides the cumulative percent of patients who are TVF-free through 1080 days.

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6.3.3.1 Hypothesis Test

Primary Endpoint

The primary endpoint evaluated in this study was target vessel failure (TVF), defined as the composite of cardiac death, recurrent myocardial infarction, or target vessel revascularization at 270 days post-index procedure. The null hypothesis for this study was that the Endeavor Zotarolimus-Eluting Coronary Stent System had a primary endpoint rate equal to that of the control (Driver bare metal stent). The alternative hypothesis was that the Endeavor Zotarolimus-Eluting Coronary Stent System had a primary endpoint rate not equal to the control stent. Specifically, the null and alternative hypotheses were

$$H_o: \pi_{DE} = \pi_{CS}$$
$$H_a: \pi_{DE} \neq \pi_{CS}$$

where π_{DE} was the primary endpoint rate estimate for the Endeavor Zotarolimus-Eluting Coronary Stent System and π_{CS} was the primary endpoint rate estimate for the control (Driver bare metal stent).

The results were as follows:

- The 270-day target vessel failure rate of the subjects treated with the control strategy (π_{CS}) was observed to be 15.1% (89/591).
- The 270-day target vessel failure rate of the subjects treated with the Endeavor Zotarolimus-Eluting Coronary Stent System (π_{DE}) was 7.9% (47/592).

The p-value for the two-sided significance test was <0.001 using the Fisher's Exact test, therefore rejecting the null hypothesis. This fact and the fact that the observed 270-day TVF rates were less for Endeavor Zotarolimus-Eluting Coronary Stent System than for the control group signified that the Endeavor Zotarolimus-Eluting Coronary Stent System was *superior* compared to the control strategy with respect to 270-day TVF.

Supportive Analysis on 270-day TVF (Primary Endpoint)

Stepwise logistic regression, using a 0.10 level of entry and 0.10 level of stay, was conducted to find the subset of the baseline characteristics related to 270-day TVF. This was performed for both treatments combined. The subset of characteristics related to 270-day TVF (hereafter referred to as *baseline predictors*) were then used as covariates in comparing treatments on 270-day TVF as discussed below, using logistic regression. Region was included as a candidate for entry in these stepwise logistic models; treatment was included as a candidate for entry in the model for both treatment groups combined.

Significant baseline predictors entering the stepwise model were treatment group, post-procedure MLD, number of total stents implanted, ACC/AHA lesion morphology class, pre-procedure thrombus. Region and diabetes did not enter as candidates for entry into the stepwise model. However, for completeness, a treatment comparison on 270-day TVF was carried out first using logistic regression *adjusting for geographic region only*, yielding a treatment comparison p-value of <0.001. The Hosmer-Lemeshow Goodness of Fit test p-value was 0.936 and the c-statistic was 0.681 indicating good calibration but

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poor discriminatory ability of the logistic regression model. The treatment comparison on 270-day TVF was then carried out using logistic regression adjusting for geographic region and the set of baseline predictors found to be significantly related to 270-day TVF above, yielding a significant p-value of <0.001. The Hosmer-Lemeshow Goodness of Fit test p-value was 0.916 and the c-statistic was 0.733 indicating good calibration but below average discriminatory ability of the logistic regression model. Both logistic models support the efficacy of Endeavor over the control strategy.

Secondary Endpoint Analysis

The endpoint evaluated was the angiographic Late Loss at 8 months as determined by core lab measurement of the difference between the MLD after follow-up and post stent implantation. The objective was to prove that with respect to this endpoint, the Endeavor Zotarolimus-Eluting Coronary Stent System performed better than the control Driver bare metal stent. The null-hypothesis tested was that the mean Late Loss at 8 months in patients treated with the Endeavor Zotarolimus-Eluting Coronary Stent System was equal to the mean Late Loss at 8 months in patients treated with the control Driver bare metal stent. The alternative hypothesis was that the mean Late Loss at 8 months in patients treated with the drug-eluting stent was not equal to that in patients treated with the control stent. Specifically, the null and alternative hypotheses were

$$Ho: \mu CS = \mu DE$$
$$Ha: \mu CS \neq \mu DE$$

where μDE was the mean Late Loss at 8 months for the Endeavor Zotarolimus-Eluting Coronary Stent System and μCS was the mean Late Loss at 8 months for the control Driver bare metal stent. The results were as follows:

- The mean Late Loss at 8 months in the Endeavor Zotarolimus-Eluting Coronary Stent System arm was 0.62 mm±0.46 mm in-stent and 0.36 mm±0.46 mm in-segment (N=262).
- The mean Late Loss at 8 months in the control arm was 1.03 mm±0.59 mm in-stent and 0.72 mm ±0.61 mm in-segment (N=263).

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Table 6.3-4: Principal Effectiveness and Safety Results through 1080 Days for Endeavor II

Safety and Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]*
Lesion Success	99.7% (587/589)	100.0% (590/590)	--
Device Success	98.8% (585/592)	99.2% (586/591)	--
Procedure Success	97.3% (573/589)	97.1% (573/590)	--
Device-Specific Procedure Success	96.5% (571/592)	96.4% (570/591)	--
Post-Procedure Minimal Lumen Diameter (MLD, in mm)			
In-Stent	2.59±0.43 (588)	2.61±0.44 (589)	--
In-Segment	2.21±0.49 (589)	2.24±0.49 (590)	--
Post-Procedure Percent Diameter Stenosis (% DS)			
In-Stent	6.04±10.43 (588)	6.23±10.03 (589)	--
In-Segment	20.39±10.26 (589)	20.11±9.38 (590)	--
Eight-Month Follow-up Minimal Lumen Diameter (MLD, in mm)			
In-Stent	1.99±0.56 (264)	1.62±0.70 (265)	--
In-Segment	1.86±0.55 (264)	1.56±0.67 (265)	--
Eight-Month Follow-up Percent Diameter Stenosis (% DS)			
In-Stent	27.91±17.30 (264)	42.24±21.73 (265)	--
In-Segment	32.67±16.27 (264)	44.33±20.45 (265)	--
Eight-Month Follow-up Late Loss (mm)			
In-Stent	0.62±0.46 (264)	1.03±0.59 (263)	--
In-Segment	0.36±0.46 (264)	0.72±0.61 (263)	-0.36 [-0.45,-0.27]
Eight-Month Binary Restenosis			
In-Stent	9.5% (25/264)	33.2% (88/265)	--
In-Segment	13.3% (35/264)	34.7% (92/265)	--
Safety Measures (1080 Days)			
Out-of-Hospital MACE to 1080 Days	9.5% (55/577)	18.7% (108/579)	--
MACE to 1080 Days	12.0% (69/577)	20.7% (120/579)	--
Death	3.3% (19/577)	4.5% (26/579)	-1.2% [-3.4%,1.0%]
Vascular Complications	0.5% (3/577)	1.2% (7/579)	--
Early Stent Thrombosis	0.5% (3/577)	1.2% (7/579)	--
Late Stent Thrombosis	0.0% (0/577)	0.0% (0/579)	--
Cerebrovascular Accident (CVA)	1.0% (6/577)	1.2% (7/579)	--

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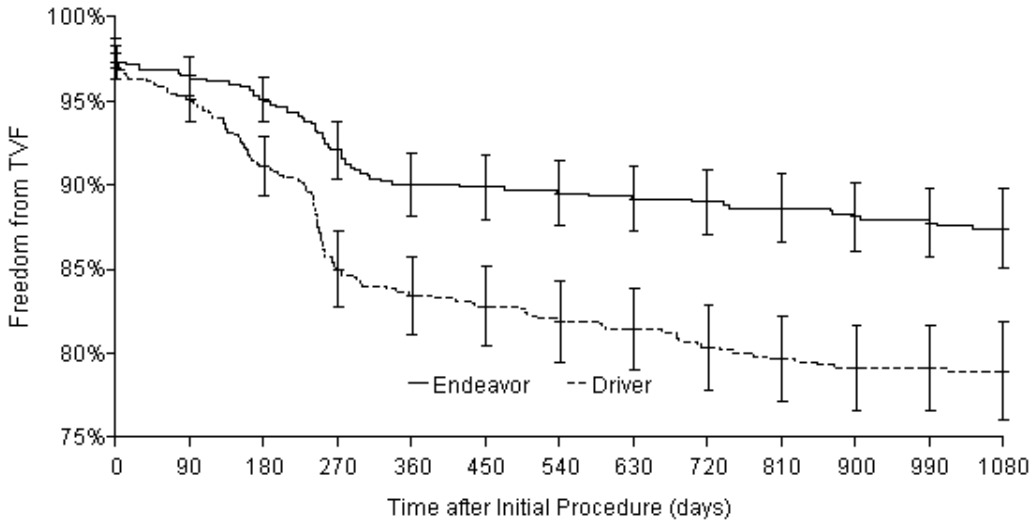
Table 6.3-4: Principal Effectiveness and Safety Results through 1080 Days for Endeavor II

Safety and Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]*
Perforation	0.5% (3/577)	0.3% (2/579)	--
Target Vessel Revascularization	9.5% (55/577)	17.6% (102/579)	-8.1% [-12.0%,-4.2%]
Target Lesion Revascularization	7.3% (42/577)	14.7% (85/579)	-7.4% [-11.0%,-3.8%]
Target Vessel Failure	12.8% (74/577)	21.4% (124/579)	-8.6% [-12.9%,-4.3%]

* Confidence Intervals are provided only for components of powered endpoints.

Kaplan-Meier Estimate	Endeavor (N=598 patients)	Driver (N=599 patients)
MACE-Free at 1080 days	88.3%	79.6%
TLR-Free at 1080 days	92.8%	85.4%
TVR-Free at 1080 days	90.6%	82.6%
TVF-Free at 1080 days	87.4%	78.9%



TVF	0	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor													
# Entered	597	584	570	561	541	525	522	519	515	512	503	500	497
# Censored	0	6	1	2	4	2	1	2	2	7	0	1	108
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	13	8	8	18	12	1	2	2	1	2	3	2	2
% Survived	97.8%	96.5%	95.1%	92.1%	90.0%	89.9%	89.5%	89.2%	89.0%	88.6%	88.1%	87.8%	87.4%
SE	0.6%	0.8%	0.9%	1.1%	1.2%	1.3%	1.3%	1.3%	1.3%	1.3%	1.4%	1.4%	1.6%
Driver													
# Entered	596	580	565	540	500	485	478	473	470	460	453	450	448
# Censored	0	2	1	4	6	3	0	0	4	3	0	2	109
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	16	13	24	36	9	4	5	3	6	4	3	0	1
% Survived	97.3%	95.1%	91.1%	85.0%	83.5%	82.8%	81.9%	81.4%	80.3%	79.6%	79.1%	79.1%	78.9%
SE	0.7%	0.9%	1.2%	1.5%	1.5%	1.6%	1.6%	1.6%	1.7%	1.7%	1.7%	1.7%	2.0%

Figure 6.3-2: Survival Free from Target Vessel Failure (at 1080 days)

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6.3.3.2 Other Analyses

Pharmacokinetic Sampling Sub-study
Up to 120 subjects had blood samples taken pre-procedure and at 0.25 hr, 0.5 hr, 1 hr, 2 hr, 4 hr, 6 hr, 12 hr and 24 hr (or discharge, whichever came first) and at 7, 14 and 30 days post-index procedure for a sub-study PK analysis at selected sites. The analysis, the result of this sub-study and comparison with other ENDEAVOR PK results is presented in ENDEAVOR US PK and ENDEAVOR Japan study reports.

Assessment of Data Poolability Across Regions
The ENDEAVOR II study was a multi-center, double-blind, two-arm randomized controlled trial conducted at sites in Asia, Australia, Europe, Israel and New Zealand.

To account for the pooling of results across geographic regions, the following analyses were performed.

Assessment of Region Differences in Baseline Characteristics
The baseline demographics of diabetes and major coronary stenosis, and lesion characteristics of lesion length, reference vessel diameter (RVD), in-segment minimum lumen diameter (MLD) and location of left anterior descending (LAD) were tabulated for each region. Descriptive statistics (sample size, mean, median, standard deviation, minimum, maximum) were computed for continuous variables and counts and percentages were computed for categorical variables.

Assessment of differences in baseline characteristics across regions was performed using one-way analysis of variance for continuous parameters and the logistic regression for categorical parameters.

This analysis showed that for all the baseline characteristics identified above, there are significant differences across the sites in baseline characteristics. However, this does not prevent sites from being pooled for analysis if the treatment effect on 270-day TVF is similar across regions. An assessment of rates of 270-day TVF by geographic region and treatment group was made. For most regions, the Driver 270-day TVF rate was higher than the Endeavor 270-day TVF rate. A formal assessment of the treatment-by-region interaction was carried out using logistic regression. This regression model included terms for region, treatment and treatment-by-region interaction. This non-significant interaction result supports the similarity of treatment effect on 270-day TVF across the regions.

6.3.4 Conclusions

Randomized patients had a mean age of 61.7 years, 24% were women, 20% had diabetes, 36% had multivessel coronary artery disease, and mean left ventricular ejection fraction was 61%. Baseline lesion characteristics and quantitative angiographic data are shown in Tables 4 and 6 of the report (Appendix 2). The ACC/AHA lesion classification was B2 or C for 79% of lesions. The mean reference diameter was 2.75 ± 0.48 mm and the mean lesion length was 14.21 ± 5.64 mm. There were no statistically significant differences between the randomized groups for any of the baseline clinical or lesion characteristics. These baseline characteristics are representative of moderate risk for development of

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restenosis and 9-month clinical events. Compared with the published SIRIUS[1] and TAXUS IV[2] studies the proportion of patients with diabetes is slightly less (24% in TAXUS IV and 26% in SIRIUS), and reference diameter (2.76 mm in TAXUS IV and 2.81 mm in SIRIUS) and lesion length are about the same (13.4 mm and 14.4 mm in TAXUS IV and SIRIUS, respectively).

Device success was achieved in nearly 99% of patients in each group. In-hospital MACE occurred in 2.5% (15/597) of patients in the Endeavor arm and 2.9% (17/596) of patients in the Driver arm, yielding acute procedure success of 97.3% and 97.1%, respectively. The acute quantitative angiographic results are shown in Table 6 of the report (Appendix 2). The final angiographic results showed overall post-procedure mean in-stent percent diameter stenosis of 6.04 ± 10.43% and mean in-segment percent diameter stenosis of 20.39 ± 10.26%. There were no acute angiographic result differences between groups.

By 30 days, MACE had occurred in 2.9% (17/596) of patients in the Endeavor arm and 3.7% (22/594) of patients in the Driver arm. These rates are not significantly different and are consistent with other contemporary stent trials. Review of the individual safety components demonstrates early stent thrombosis occurred in 0.8% of patients (0.5% Endeavor vs. 1.2% Driver). Of the seven (7) Q wave MIs in the overall population, five (5) were associated with stent thrombosis. Early repeat revascularization was infrequent and nearly identical in both groups, and the 30-day non-Q wave MI rate (2.5% in the overall population; 2.3% in the Endeavor group vs. 2.7% in the Driver group) was similar to contemporary stent trials without a statistical difference between groups.

Of the 1,197 randomized patients, 600 (298 Endeavor and 302 Driver) were prospectively enrolled in a routine angiographic follow-up subset. Qualifying follow-up angiography was available for 529 (88.2%) patients (88.6% in the Endeavor arm and 87.7% in the Driver arm) and is reported in Tables 6 and 8 of the report (Appendix 2). The angiographic in-stent late loss was significantly lower for Endeavor (0.62 ± 0.46 vs 1.03 ± 0.59 mm). This translated into significantly lower in-stent (9.5% vs. 33.2%) and in-segment (13.3% vs. 34.7%) BAR. Of note, there was no significant increase in proximal or distal edge late loss or BAR for Endeavor.

Nine-month clinical follow-up was available for 1,183 (98.8%) patients. The primary endpoint of 9-month TVF was significantly lower for Endeavor 7.9% vs. 15.1%, $p<0.001$, (KM estimate 7.9% vs. 15.0%). TLR occurred in 4.6% vs. 11.8%, (KM estimate 4.6% vs. 11.9%) and TVR occurred in 5.6% vs. 12.5%, (KM estimate 5.6% vs. 12.5%). The overall rate of 9-month MACE was 7.3% vs. 14.4%, (KM estimate 7.2% vs. 14.3%).

Twelve-month clinical follow-up was available for 1,179 (98.5%) patients. The rate of 12-month TVF was significantly lower for Endeavor 10.0% vs. 16.6%, (KM estimate 10.0% vs. 16.5%). TLR occurred in 5.9% vs. 13.1%, (KM estimate 6.0% vs. 13.2%) and

[1] Moses, JW; Leon, MB; Popma, JJ; Fitzgerald, PJ; Holmes, DR; O'Shaughnessy, C; Caputo, RP; Kereiakes, DJ; Williams, DO; Teirstein, PS, Jaeger, JL; Kuntz, RD. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. The New England Journal of Medicine 2003; 349:1315-1323.

[2] Stone, GW; Ellis, SG; Cox, DA; Hermiller, J; O'Shaughnessy, C; Mann, JT; Turco, M; Caputo, R; Bergin, P; Greenberg, J; Popma, JJ; Russell, ME. A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease. The New England Journal of Medicine 2004; 350:221-331.

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TVR occurred in 7.5% vs. 14.1%, (KM estimate 7.5 % vs. 14.1%). The overall rate of 12-month MACE was 8.8% vs. 15.6%, (KM estimate 8.8% vs. 15.5%).

Twenty-four month clinical follow-up was available for 1,173 (98.0%) patients. The rate of 24-month TVF was significantly lower for Endeavor 11.1% vs. 19.8%, (KM estimate 11.0% vs. 19.7%). TLR occurred in 6.5% vs. 14.2%, (KM estimate 6.5% vs. 14.3%) and TVR occurred in 8.3% vs. 16.4%, (KM estimate 8.3 % vs. 16.4%). The overall rate of 24-month MACE was 9.9% vs. 18.1%, (KM estimate 9.8% vs. 17.9%).

Thirty-six month clinical follow-up was available for 1,156 (96.6%) patients. The rate of 36-month TVF was significantly lower for Endeavor 12.8% vs. 21.4%, (KM estimate 12.6% vs. 21.1%). TLR occurred in 7.3% vs. 14.7%, (KM estimate 7.2% vs. 14.6%) and TVR occurred in 9.5% vs. 17.6%, (KM estimate 9.4 % vs. 17.4%). The overall rate of 36-month MACE was 12.0% vs. 20.7%, (KM estimate 11.7% vs. 20.4%).

In Summary:

(1) The Endeavor Zotarolimus-Eluting Coronary Stent System demonstrates safety based on the following:
   - A. Device success is nearly 100% and compares favorably with the Driver bare metal stent.
   - B. The 30-day MACE rate is low and similar to the rate in the Driver bare metal stent.
   - C. The long term MACE rates are significantly favorable to the Endeavor stent.
   - D. There was no evidence of increased early or late stent thrombosis in the Endeavor stent compared with the Driver bare metal stent.

(2) The Endeavor Zotarolimus-Eluting Coronary Stent System demonstrated efficacy with significantly lower rate of the primary clinical endpoint of TVF, sustained in long term follow-up.

(3) The secondary angiographic efficacy endpoints of late loss and BAR (in-stent and in-segment) were significantly lower for the Endeavor Zotarolimus-Eluting Coronary Stent System.

(4) The secondary clinical efficacy endpoints of TLR and TVR were significantly lower for the Endeavor Zotarolimus-Eluting Coronary Stent System and remain significantly lower in long term follow-up.

Based on acute procedural results, 8-month angiographic, and 9-month and long-term clinical follow-up the Endeavor Zotarolimus-Eluting Coronary Stent System has demonstrated similar safety and superior efficacy compared with the Driver bare metal stent.

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6.4 ENDEAVOR II-CA Clinical Study Summary

6.4.1 Clinical Study Description

ENDEAVOR II Continued Access was a substudy of ENDEAVOR II which was a Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic Zotarolimus-Eluting Coronary Stent in *De Novo* Native Coronary Artery Lesions. In addition, this study also allowed for direct stenting of lesions < 20 mm in length at physicians' discretion.

6.4.1.1 Study Design

The study was designed as a prospective, multi-center, single-arm, open-label substudy.

6.4.1.2 Study Objectives

To expand the acute safety information and performance data of the Endeavor Drug Eluting Stent (Medtronic Zotarolimus-Eluting Coronary Stent System) for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter.

6.4.1.3 Primary Endpoints

Major Adverse Cardiac Events (MACE) rate at 30 days post-procedure, defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (repeat PTCA or CABG).

6.4.1.4 Secondary Endpoints

- Device success defined as attainment of <50% in-stent residual stenosis using only the assigned device
- Lesion success defined as attainment of <50% in-stent residual stenosis using any percutaneous method
- Procedure success defined as attainment of <50% in-stent residual stenosis using any percutaneous method and no in-hospital MACE (Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent bypass surgery, or target lesion revascularization (TLR))
- MACE at 6, 9 and 12 months and annually thereafter out to 5 years
- Late loss at 8 months as measured by QCA, defined as the difference between the post-index procedure minimal lumen diameter (MLD) and the follow-up MLD
- Angiographic in-stent and in-lesion binary restenosis rate (≥ 50% diameter stenosis) at 8 months post-index procedure
- In-stent and in-lesion minimum lumen diameter (MLD) at 8 months post-index procedure
- Neointimal hyperplastic volume at 8 months as measured by intravascular ultrasound (IVUS)
- Target Lesion Revascularization (TLR) at 270 days post-procedure
- Target Vessel Revascularization (TVR) at 270 days post-procedure
- Target Vessel Failure (TVF) at 270 days post-procedure.

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6.4.1.5 Patient/Study Population

General Inclusion Criteria

Candidates were considered for inclusion if the following conditions were met:

Note: Subjects could only be included in the study once.

1. The subject was ≥18 years of age (or minimum age dictated by local regulations).
2. The subject was an acceptable candidate for PTCA, stenting, and emergent CABG.
3. The subject had clinical evidence of ischemic heart disease or a positive functional study.
4. The subject had single vessel disease or had multi-vessel disease with only moderate stenosis (max 50-60% or total occlusion (100%) for which no interventions were planned at the time of study inclusion).
5. The target lesion / vessel must have met the following criteria:
    a. The target lesion was a single *de novo* lesion that had not been previously treated with any interventional procedure. Only one lesion was treated per subject.
    b. The target vessel was a native coronary artery with a stenosis of ≥ 50% and <100%.
    c. The target lesion was ≥ 14 mm and ≤ 27 mm in length.
    d. The target vessel reference diameter was ≥ 2.25 mm and ≤ 3.5 mm. (Measurements were made by careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound.)
6. Female subjects of childbearing potential had a negative pregnancy test within seven (7) days before the procedure.
7. The subject or the subject's legal representative had been informed of the nature of the study and agreed to its provisions and provided written informed consent as approved by the Institutional Review Board/Ethics Committee of the respective clinical site.
8. The subject and the treating physician agreed that the subject would comply with all required post-index procedure follow-up.

General Exclusion Criteria

1. A documented left ventricular ejection fraction < 30%.
2. A known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, cobalt, nickel, chromium, or a sensitivity to contrast media, which could not be adequately pre-medicated.
3. Had a history of an allergic reaction or significant sensitivity or receiving drugs similar to/or synergistic to Zotarolimus (rapamycin, tacrolimus, sirolimus, CCI-779 or other analogues).
4. A platelet count <100,000 cells/mm³ or >700,000 cells/mm³, or a WBC <3,000 cells/mm³.
5. Had evidence of an acute myocardial infarction within 72 hours of the intended treatment (defined as: Q wave or non-Q wave infarction having CK enzymes ≥ 2X the upper laboratory normal with the presence of a CK-MB elevated above the Institution's upper limit of normal).

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6. Creatinine > 2.0 mg/dl
7. A previous coronary interventional procedure of any kind within the 30 days prior to the procedure.
8. The subject required planned interventional treatment of either the target or any non-target vessel within 30 days post-index procedure.
9. The target lesion required treatment with a device other than PTCA prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
10. Had previous stenting anywhere in the target vessel.
11. The target vessel had evidence of thrombus or was excessively tortuous (2 bends > 90° to reach the target lesion).
12. Had significant (>50%) stenosis proximal or distal to the target lesion that might have required revascularization or impede run off.
13. Target lesion located in native vessel distally to anastomosis with vein graft or LIMA.
14. The target lesion had any of the following characteristics:
    a. Lesion location was aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the LAD, LCX, or RCA.
    b. Involved a side branch >2.0 mm in diameter.
    c. Was at or distal to a 45º bend in the vessel.
    d. Was severely calcified.
15. Had an unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery).
16. Had a history of a stroke or transient ischemic attack within the prior 6 months.
17. Had an active peptic ulcer or upper GI bleeding within the prior 6 months.
18. The subject had a history of bleeding diathesis or coagulopathy or would refuse blood transfusions.
19. Had a concurrent medical condition with a life expectancy of less than 12 months.
20. Had any previous or planned treatment with anti-restenotic therapies including, but not limited to, drug-eluting stents and brachytherapy.
21. Was currently participating in an investigational drug or another device study that had not completed the primary endpoint or that clinically interfered with the current study endpoints. [Note: Trials requiring extended follow-up for products that were investigational, but had since become commercially available, were not considered investigational trials.]

Key Baseline Characteristics

The key baseline characteristics are provided below.

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Table 6.4-1: Key Baseline Characteristics

Key Baseline Variables	Endeavor	
	N	%
Age (years)	296	
Mean (SD*)	64.25 ± 9.69	
Range	37-87	
Gender	296	
Male	222	(75.0%)
Female	74	(25.0%)
Race	296	
White/Caucasian	294	(99.3%)
Clinical Characteristics	N	%
History of diabetes mellitus	76/295	(25.8%)
History of hypertension	241/295	(81.7%)
Lesion Characteristics	N	Mean (SD*)
Reference Vessel Diameter (mm)	297**	2.63 ± 0.45
Lesion length (mm)	293	16.49 ± 7.86
	N	%
Discreet (< 10mm)	56/293	19.1%
Tubular (10-19.9 mm)	159/293	54.3%
Diffuse (≥20mm)	78/293	26.6%
ACC/AHA lesion class	N	%
A	17/297	5.7%
B1	59/297	19.9%
B2	91/297	30.6%
C	130/297	43.8%

* SD = Standard Deviation.
** One patient had 2 lesions.

Enrollment/ Randomization
Study Period (enrollment): 18 March 2004 to 21 June 2004

ENDEAVOR II Continued Access was a non-randomized study, and all eligible patients were planned to be treated with the Endeavor stent.

Two hundred ninety seven (297) subjects from fifteen (15) study sites in Europe enrolled subjects into this trial. Patients with symptomatic ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters between 2.25 mm and 3.5 mm and lesion lengths of ≥ 14 mm and ≤ 27 mm that were amenable to percutaneous treatment with stenting were enrolled in this trial. In addition, this study also allowed for direct stenting of lesions < 20 mm in length at physicians' discretion.

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Antiplatelet Medications

It was strongly recommended that all subjects received the medication regimen listed below. All medications administered were to have been recorded in the subject's medical record. All concomitant medications taken by the patient for 30 days post-index procedure were to have been reported on the study case report form. All anti-platelet and anti-coagulant medication taken throughout the study was to have been reported on the study case report form.

Prior to Procedure	IV Heparin	PRN
	Aspirin	At least 75 mg QD
	Clopidogrel [1, 2]	300 mg loading dose (if patient not currently taking clopidogrel)
During Procedure	IV Heparin	To maintain ACT ≥250 sec., or 200-250 sec. if GP IIb/IIIa blocker is used
	Intracoronary Nitroglycerin	100-200 µg *prior to baseline* and post intervention angiograms
Post-Index Procedure	IV Heparin	PRN
	Aspirin	At least 75 mg QD indefinitely
	Clopidogrel[1]	75 mg po QD (for 12 weeks)

All subjects were to have received at least 75 mg aspirin indefinitely and clopidogrel 75mg daily for at least 12 weeks. The ACT or other appropriate laboratory testing was to have been monitored and recorded on source documents while being maintained at therapeutic levels. All patients except for one were discharged on aspirin/clopidogrel.

Patient Follow-up

The follow-up schedules are the same as that of the ENDEAVOR II trial with substitution of a telephone call for a clinic visit at 9 months. Clinical evaluations occurred during hospitalization and at 30 days. Telephone follow-up for safety occurred at 6, 9, 12 and 24 months and occurs annually thereafter for 5 years. Adverse events were reported up to 9 months. Subsequently, SAEs (including MACE) and device-related adverse events were reported to 5 years. Follow-up angiography was scheduled at 8 months for the first 150 consecutive patients enrolled. IVUS evaluation occurred at 8 months post-index procedure as a sub-study at selected sites for approximately 100 patients. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all

[1] It was expected that clopidogrel was used, unless the patient was allergic or sensitive to this medication. For patients unable to take clopidogrel, or at the discretion of the physician, ticlopidine was used. For patients on ticlopidine, CBCs were to be performed as per the drug labeling.
[2] If the patient had been on clopidogrel for at least 48 hours prior to the procedure, the daily dose was continued and no additional loading dose given prior to the procedure.

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baseline and follow-up angiograms and IVUS images. A Clinical Events Committee (CEC) adjudicates all clinical endpoint events. Annual follow-up is for assessment of angina status, serious adverse events (including MACE), concomitant medications and any interventional treatments occurring since the previous contact. A Data Safety Monitoring Board (DSMB) reviews the study on a regular basis. The primary analytical subset for this trial is the Intent-to-Treat (ITT) population, defined as all patients who signed the written informed consent and for whom the study device was introduced through the guide catheter. Two further secondary analyses were performed, on the subset of the ITT sample that was directly stented and on the subset of the ITT sample for whom pre-dilatation was performed. Kaplan-Meier techniques are used to assess survival free of MACE, TVR, and TLR.

Schedule of Treatments and Assessments

A summary of treatments and assessments is provided below.

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Table 6.4-2: Schedule of Treatments and Assessments

Index Hospitalization				Follow-up				
Event	**Screen**	**Proce-dure**	**Post Proce-dure**	**30 Day**	**6 Month**	**8 Month**	**9 Month**	**12 month to 5 year**
				Office visit	**Tele-phone**	**Angio[7] /IVUS[8]**	**Tele-phone**	**Tele-phone**
Informed Consent Signed	X							
Inclusion/ Exclusion Criteria	X							
Medical and Cardiac History	X							
Angina Status	X		X	X	X	X	X	X
Pregnancy test	X [1,2]							
CBC with differential, platelet count	X [2]			X				
CK & CK-MB	X [4]		X [5]					
Troponin	X [9]		X [9]					
12-Lead Electrocardiogram	X [4]		X [3]					
ACT Measurements [10]		X						
Medication Regimen[6]	X	X	X	X	X		X	X
Adverse Event Monitoring			X	X	X	X	X	X
Angiography (QCA)	X	X				X [7]		
IVUS		X [8]				X [8]		

1. For women of childbearing potential only
2. Within 7 days prior to procedure
3. Within 24 hours post-procedure or at discharge, which ever comes first
4. Within 72 hours prior to procedure
5. Within 6-8, 12-16, and 20-24 hours post-procedure or prior to hospital discharge, whichever comes first
6. It is expected that clopidogrel will be used, unless the patient is allergic or sensitive to this medication. For patients unable to take clopidogrel, or at the discretion of the physician, ticlopidine will be used
7. The first 150 consecutive study subjects enrolled will have angiographic follow-up at 8 months as well as patients implanted with two or more stents from the second 150 consecutive patients.
8. Selected clinical sites only for IVUS sub study of approx. 100 patients and patients from all sites implanted with two or more stents
9. Optional- Measurement is recommended if the lab has the capability.
10. ACT measurements should be performed during the procedure.

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Patient Accountability

The ENDEAVOR II Continued Access study enrolled 297[1] patients at 15 clinical research sites in Germany and the Netherlands from March 18, 2004 to June 21, 2004.

The first 150 patients enrolled were scheduled to undergo repeat angiography at eight-months follow-up. IVUS at baseline and at the eight month follow-up was scheduled to be performed in a subset of approximately 100 patients.

Pre-dilatation was performed at the physician's discretion for lesions that were readily accessible and ≤ 20 mm in length. This resulted in 170 patients where pre-dilatation was performed. Another subgroup of 126 patients had direct stenting.

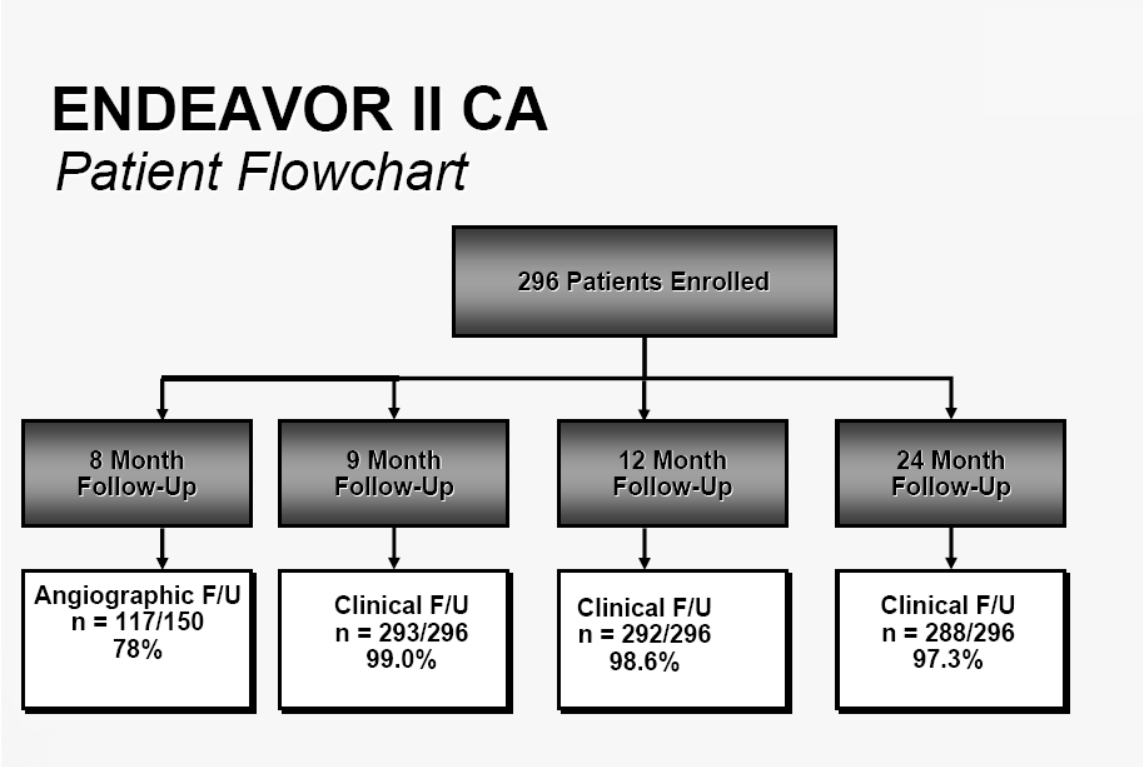

Figure 6.4-1 Patient Flowchart for ENDEAVOR II-CA at 24 Months

[1] One (1) patient (603-35) with two lesions treated with Endeavor stents

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6.4.2 Statistical Methodology

6.4.2.1 Clinical Trial Objectives and Hypotheses

ENDEAVOR II Continued Access was a prospective, multi-center, single-arm, open-label study to expand the acute safety information and performance data of the Endeavor Zotarolimus-Eluting CSS. Endeavor stent sizes evaluated in this study were 2.25, 2.5, 3.0 and 3.5 mm in diameter and 8 or 9, 18, 24, and 30 mm in length on an RX delivery system. The ENDEAVOR II Continued Access substudy enrolled 297 patients at 15 clinical research sites in Germany and the Netherlands.

Analysis Samples
The primary analysis sample was based on the principle of intent-to-treat (ITT). For this study, all patients who signed the written informed consent and where the study device was introduced in the guide catheter were counted in the primary analysis. The primary endpoint analysis is also performed for the Per-Protocol (PP) subset.

Two further secondary analyses were performed, on the subset of the ITT sample that was directly stented and on the subset of the ITT sample on whom pre-dilatation was performed.

A total of 296 patients were included in the intent to treat (ITT) analysis. A total number of 287 patients were included in the per protocol (PP) analysis.

The data in this summary report is based on the data available as of 15 September 2006

Primary Endpoint
The primary endpoint, Major Adverse Cardiac Events (MACE) rate at 30 days post-procedure, are estimated and reported along with the 95% confidence interval for the estimate.

Secondary Endpoints
The dichotomous secondary endpoints of device success, lesion success, procedure success, MACE rate (at 6, 9, and 12 months post-procedure and annually thereafter out to 5 years), target lesion revascularization (TLR) rates, target vessel revascularization (TVR) rates, target vessel failure (TVF) rates, and 8-month binary restenosis rate are reported in tables which includes frequency and percent of each outcome.

The secondary endpoints of in-stent and in-segment late lumen loss, in-stent and in-segment minimum luminal diameter (MLD), and neointimal hyperplastic volume are reported by giving the number of known values, the mean, standard deviation, and minimum and maximum values. These endpoints were measured on the subset of subjects undergoing the relevant procedure.

Analysis on Baseline Characteristics
All clinically relevant baseline variables in this sub-study are tabulated. Categorical variables are reported using contingency tables, and continuous variables are reported by giving the number of known values, the mean, standard deviation, and minimum and maximum values.

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6.4.3 Results

The table below summarizes the principal effectiveness and safety results of the ENDEAVOR II-CA trial through 24 months

Table 6.4-3: Principal Effectiveness and Safety Results through 720 days for Endeavor II CA

Safety and Effectiveness Measures	Endeavor Continued Access (Number of Patients =296 Number of Lesions =297*)
Lesion Success % (#/n)	99.7%(295/296)
Device Success % (#/n)	98.3%(292/297)
Procedure Success % (#/n)	94.9%(280/295)
Device-Specific Procedure Success % (#/n)	93.6%(277/296)
Post-index Procedure Minimal Lumen Diameter (MLD, in mm)	
In-Stent	2.56±0.43 (296)
In-Segment	2.24±0.46 (296)
Post-index Procedure Percent Diameter Stenosis (%DS)	
In-Stent	5.27±9.45 (296)
In-Segment	17.76±9.57 (296)
Eight-Month Follow-up Minimal Lumen Diameter (MLD, in mm)	
In-Stent	1.92±0.65 (117)
In-Segment	1.81±0.61 (117)
Eight-Month Follow-up Percent Diameter Stenosis (%DS)	
In-Stent	27.67±21.95 (117)
In-Segment	31.93±20.54 (117)
Eight-Month Late Loss (mm)	
In-Stent	0.58±0.58 (117)
In-Segment	0.39±0.56 (117)
Eight-Month Binary Restenosis	
In-Stent	15.4%(18/117)
In-Segment	17.1%(20/117)
TLR-Free at 720 days	92.7%
TVR-Free at 720 days	87.6%
TVF-Free at 720 days	83.9%
MACE-Free at 720 days	87.4%
Safety Measures (to 30 days) % (#/n)	
In-Hospital MACE	4.7%(14/296)
Out-of-Hospital MACE to 30 days	0.7%(2/296)
MACE to 30 days	5.4%(16/296)
Death	0%(0/296)
Vascular Complications	0.3%(1/296)
Stent Thrombosis	0%(0/296)
Acute Stent Thrombosis	0%(0/296)
Sub-Acute Stent Thrombosis	0%(0/296)
Late Stent Thrombosis	0%(0/296)
Cerebrovascular Accident (CVA)	0%(0/296)
Perforation	0.3%(1/296)
Target Vessel Revascularization	1.4%(4/296)
Target Lesion Revascularization	0.3%(1/296)
Target Vessel Failure	5.7%(17/296)
Safety Measures (to 270 days) % (#/n)	
Out-of-Hospital MACE to 270 days	6.5%(19/293)
MACE to 270 days	10.6%(31/293)

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Table 6.4-3: Principal Effectiveness and Safety Results through 720 days for Endeavor II CA

Safety and Effectiveness Measures	Endeavor Continued Access (Number of Patients =296 Number of Lesions =297*)
Death	0.7%(2/293)
Vascular Complications	0.3%(1/293)
Stent Thrombosis	0%(0/293)
Acute Stent Thrombosis	0%(0/293)
Sub-Acute Stent Thrombosis	0%(0/293)
Late Stent Thrombosis	0%(0/293)
Cerebrovascular Accident (CVA)	0.3%(1/293)
Target Vessel Revascularization	8.9%(26/293)
Target Lesion Revascularization	5.1%(15/293)
Target Vessel Failure	13.0%(38/293)
Safety Measures (to 360 days) % (#/n)	
Out-of-Hospital MACE to 360 days	8.2%(24/292)
MACE to 360 days	12.3%(36/292)
Death	0.7%(2/292)
Vascular Complications	0.3%(1/292)
Stent Thrombosis	0%(0/292)
Acute Stent Thrombosis	0%(0/292)
Sub-Acute Stent Thrombosis	0%(0/292)
Late Stent Thrombosis	0%(0/292)
Cerebrovascular Accident (CVA)	0.3%(1/292)
Target Vessel Revascularization	11.6%(34/292)
Target Lesion Revascularization	6.5%(19/292)
Target Vessel Failure	15.8%(46/292)
Safety Measures (to 720 days) % (#/n)	
Out-of-Hospital MACE to 720 days	9.0%(26/288)
MACE to 720 days	12.8%(37/288)
Death	1.4%(4/288)
Vascular Complications	0.3%(1/288)
Stent Thrombosis	0%(0/288)
Acute Stent Thrombosis	0%(0/288)
Sub-Acute Stent Thrombosis	0%(0/288)
Late Stent Thrombosis	0%(0/288)
Cerebrovascular Accident (CVA)	0.3%(1/288)
Target Vessel Revascularization	12.5%(36/288)
Target Lesion Revascularization	7.3%(21/288)
Target Vessel Failure	16.3%(47/288)

*One (1) patient (603-35) with two lesions treated with Endeavor stents

6.4.3.1 Other Analysis

Eight-month follow-up angiographic and IVUS results:

The 8 months in-stent late loss was 0.58±0.58mm. At 8 months the binary in-stent restenosis rate was 15.4% and the binary in-segment restenosis rate was 17.1% .The in-stent MLD at 8 months was 1.92mm and the in-segment MLD 1.81mm. Approximately 100 patients at selected centers were enrolled for routine IVUS follow-up. A qualifying follow-up IVUS was available for 43 patients. The neointimal hyperplastic volume at 8 months was 29.66mm^3.

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Nine, twelve and twenty-four month clinical outcomes:
The 720 days clinical follow-up was available for 288 patients. At 270 days the TLR rate was 5.1%, the TVR rate 8.9% and the TVF rate 13.0%. The incidence of MACE was 6.8% (20/295) at 180 days, 10.6% (31/293) at 270 days, 12.3% (36/292) at 360 days and 12.8% (37/288) at 720 days. Review of the individual safety components shows that the rates of stent thrombosis at 720 days was 0%. The rate of 270-day Q-wave MI was 0.3%, the percentage of Target Lesion Revascularization was 5.1% and the percentage of non Q wave MI was 4.8%. At 360 days the rate of Q-wave MI was 0.3%, the Target Lesion Revascularization 6.5% and the percentage of non Q-wave MI 5.1%. At 720 days the rate of Q-wave MI was 0.3%, the Target Lesion Revascularization 7.3% and the percentage of non Q-wave MI 5.6%. The Kaplan-Meier estimate of freedom from MACE was 89.5% at 270 days, 87.8% at 360 days and 87.4% at 720 days post procedure.

Safety and efficacy outcomes for the direct stenting and pre-dilatation subgroups:
Of the 296 patients enrolled, 126 patients (127 lesions) were treated with direct stenting and for 170 patients pre-dilatation was performed. Baseline patient characteristics were comparable for both subgroups except for age, which was significantly higher in the pre-dilatation subgroup (65.3 years vs 62.9 years). The lesion characteristics showed some differences between both subgroups as expected per protocol, as only lesions with a length <20mm could be treated by direct stenting. The lesion length was smaller in the direct stenting subgroup as compared to the pre-dilatation subgroup (14.29+6.41mm vs 18.16+8.46mm). The MLD was smaller in the pre-dilatation subgroup as compared to the direct stenting subgroup (0.71±0.29mm vs 0.89±0.36mm) and the % diameter stenosis pre procedure was smaller in the direct stenting subgroup as compared to the pre-dilatation subgroup (66.5±12.0% vs 72.7±11.0%). In addition, the lesion location between both subgroups also showed a difference (proximal 34.1% in the pre-dilatation subgroup vs 53.5% in the direct stenting subgroup, mid 57.6% in the pre-dilatation subgroup vs 40.9% in the direct stenting subgroup, distal 7.6% in the pre-dilatation subgroup vs 4.7% in the direct stenting subgroup and ostial 0.6% in the pre-dilatation subgroup vs 0.8% in the direct stenting subgroup). Overall, the patient populations for the subgroups were comparable for most baseline demographic or lesion characteristics except for the age, lesion location, and several pre-procedure angiographic parameters (lesion length, MLD, lesion location and % diameter stenosis).

The in-hospital MACE and the MACE at 30, 180, 270 and 360 days were comparable for both subgroups. In-hospital incidences of MACE were 5.6% for the direct stenting subset and 4.1% for the pre-dilatation subset. The MACE rate at 30 days, 270 days, 360 days and 720 days in the direct-stenting subgroup was 6.3%, 10.3%, 11.2% and 11.4% respectively. The MACE rate at 30 days, 270 days, 360 days and 720 days for the pre-dilatation subgroup was 4.7%, 10.8%, 13.2% and 13.9% respectively.

The lesion, device, procedure and device-specific procedure success rates were also comparable for both subgroups. The lesion success rate was 99.4% for the pre-dilatation subset and 100% for the direct stenting subset. The device success rate was 98.2% for the pre-dilatation subset and 98.4% for the direct stenting subset. The procedure success rate was 95.3% for the pre-dilatation subset and 94.4% for the direct stenting subset. The device-specific procedure success rate was 94.1% for the pre-dilatation subset and 92.9% for the direct stenting subset.

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At 8 months the in-stent binary restenosis rate for the direct stenting subgroup was 10.4% and for the pre-dilatation subgroup 18.8%. The in-stent acute gain was 1.75±0.46mm for the direct stenting subset and 1.79±0.48mm for the pre-dilatation subset. The 8 month in-stent late loss was 0.56±0.56mm for the direct stenting subset and 0.59±0.60mm for the pre-dilatation subset. Therefore, the angiographic parameters were comparable between both subgroups.

6.4.4 Conclusions

This analysis reports the final 24-months results of the ENDEAVOR II Continued Access study in the areas including the baseline characteristics, procedural device performance, the 9, 12 and 24-month safety outcomes, the 8-month angiographic and IVUS outcomes and the 9, 12 and 24-month secondary clinical outcomes.

In summary the 720-day results of the ENDEAVOR II Continued Access study show that the Endeavor stent is safe and effective. The lesion, device and procedure success rates were high. No stent thrombosis was observed up to 720 days. The 30 day, 180 day, 270 day, 360 day and 720 day MACE rates were comparable to the MACE rates in similar studies, taken into account the relatively high patient age, high percentage of diabetes patients and long lesion length. The safety and efficacy outcomes in the direct stenting subgroup and in the pre-dilatation subgroup were comparable, indicating that the good safety and effectiveness data for the Endeavor stent were maintained with direct stenting for lesions <20mm.

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6.5 ENDEAVOR III Clinical Study Summary

6.5.1 Clinical Study Description

ENDEAVOR III was a Randomized Controlled Trial of the Medtronic Endeavor Zotarolimus-Eluting Coronary Stent System versus the Cypher Sirolimus-Eluting Coronary Stent System in *De Novo* Native Coronary Artery Lesions.

6.5.1.1 Study Design

The study was designed as a prospective, multi-center, single-blind, parallel, two-arm, randomized, controlled trial.

6.5.1.2 Study Objectives

To demonstrate the equivalency in in-segment late lumen loss at 8 months between the Endeavor Zotarolimus-Eluting Coronary Stent System coated with zotarolimus (10 μg/mm) and the Cypher Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter.

6.5.1.3 Primary Endpoints

In-segment late lumen loss at 8 months post-procedure

6.5.1.4 Secondary Endpoints

- In-stent late lumen loss at 8 months
- Device Success
- Lesion Success
- Procedure Success
- Major Adverse Cardiac Event (MACE) rate at 30 days, 6, 9, and 12 months post-procedure
- Target Site Revascularization (TSR) rate and clinically-driven TSR rate at 9 months post-procedure
- Target Vessel Revascularization (TVR) rate and clinically-driven TVR rate at 9 months post-procedure
- Target Vessel Failure (TVF) rate at 9 months post-procedure
- Angiographic binary restenosis (> 50% diameter stenosis) rate at 8 months post-procedure
- In-stent and in-segment minimum lumen diameter (MLD) at 8 months post-procedure
- Neointimal hyperplastic volume at 8 months as measured by IVUS

6.5.1.5 Patient/Study Population

General Inclusion Criteria

Candidates were considered for inclusion if the following conditions were met:

1. The patient was ≥18 years of age.
2. The patient had clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, or a positive functional study.

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3. The patient was an acceptable candidate for percutaneous transluminal coronary angioplasty (PTCA), stenting, and emergent coronary artery bypass graft (CABG) surgery.
4. Female patients of childbearing potential had a negative pregnancy test within seven (7) days before the procedure.
5. The patient was informed of the nature of the study and agreed to its provisions and has provided written informed consent as approved by the Institutional Review Board of the respective clinical site.
6. The patient and the treating physician agreed that the patient will return to the treating research center, or an affiliated institution under the same IRB jurisdiction, for all required post-procedure follow-up visits. A research staff member who has been properly trained to the ENDEAVOR III protocol must have conducted all follow-up evaluations.

Angiographic Inclusion Criteria

The target lesion / vessel met the following criteria:

1. The target lesion was a single *de novo* lesion that had not been previously treated with any interventional procedure.
2. The target vessel was a native coronary artery with a stenosis of ≥50% and <100%.
3. The target vessel had a TIMI flow 2 or greater.
4. The target lesion was ≥14 mm and ≤27 mm in length.
5. The target vessel reference diameter was ≥2.5 mm and ≤3.5 mm.

   Note: Measurements were made by careful visual estimate, on-line QCA, or intravascular ultrasound (IVUS).

General Exclusion Criteria

1. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, cobalt, nickel, chromium, molybdenum, or a sensitivity to contrast media, which could not be adequately pre-medicated.
2. History of an allergic reaction or significant sensitivity to drugs similar to Zotarolimus (rapamycin or rapamycin analog).
3. A platelet count <100,000 cells/mm³ or > 700,000 cells/mm³, or a WBC < 3,000 cells/mm³.
4. A creatinine level >2.0 mg/dL.
5. Evidence of an acute myocardial infarction within 72 hours of the intended treatment (defined as: Q wave or non-Q wave myocardial infarction having creatine kinase (CK) enzymes ≥2X the upper laboratory normal with the presence of a creatine kinase myocardial-band isoenzyme (CK-MB) elevated above the Institution's upper limit of normal).
6. Any previous or planned treatment of any vessel with a drug eluting stent.
7. Previous or planned percutaneous coronary intervention of any vessel within 30 days pre or post procedure.
8. Previous stenting anywhere in the target vessel.

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9. During the index procedure, the target lesion required treatment with a device other than PTCA prior to stent placement (such as, but not limited to, cutting balloon, directional coronary atherectomy, excimer laser, rotational atherectomy, thrombectomy, etc.).
10. History of a stroke or transient ischemic attack within the prior 6 months.
11. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months.
12. History of bleeding diathesis or coagulopathy or refused blood transfusions.
13. Concurrent medical condition with a life expectancy of less than 12 months.
14. Any previous or planned treatment of the target vessel with anti-restenotic therapies including, but not limited to brachytherapy.
15. Currently participating in an investigational drug or another device study that had not completed the primary endpoint or that clinically interfered with the current study endpoints; or required coronary angiography, intravascular ultrasound (IVUS) or other coronary artery imaging procedures. [Note: Trials that required extended follow-up for products that were investigational, but have since become commercially available, were not considered investigational trials.]

Angiographic Exclusion Criteria

1. A documented left ventricular ejection fraction <30% at any time prior to index procedure.
2. Target lesion was located in a native vessel distal to anastomosis with a saphenous vein graft or LIMA/RIMA bypass.
3. Target vessel had other lesions with greater than 40% diameter stenosis based on visual estimate or on-line QCA.
4. The target vessel had evidence of thrombus.
5. The target vessel was excessively tortuous.
6. The target lesion had any of the following characteristics:
   a) Lesion location was aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the LAD, LCX, or RCA,
   b) Involved a side branch >2.0 mm in diameter,
   c) Was at or distal to a >45º bend in the vessel,
   d) Was severely calcified.
7. Unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery).
8. The target lesion involved a bifurcation.

Key Baseline Characteristics

The key baseline characteristics are provided below.

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Table 6.5-1: Key Baseline Characteristics

Baseline Variables	Endeavor		Cypher	
	N	%	N	%
Age (years)	323		113	
Mean (SD*)	61.42 ± 10.58		61.73 ± 11.59	
Range	34-86		37-83	
Gender	323		113	
Male	211	(65.3%)	92	(81.4%)
Race	323		113	
White/ Caucasian	298	(92.3%)	102	(90.3%)
Clinical Characteristics	N	%	N	%
History of diabetes mellitus	96/323	(29.7%)	32/113	(28.3%)
History of hypertension	227/321	(70.7%)	84/113	(74.3%)
Lesion Characteristics	N	Mean (SD*)	N	Mean (SD*)
Reference Vessel Diameter	323	2.75 ± 0.46	113	2.79 ± 0.46
Lesion length	322	14.96 ± 6.20	112	14.95 ± 7.28
	N	%	N	%
Discreet (< 10mm)	67/322	20.8%	33/112	29.5%
Tubular (10-19.9 mm)	191/322	59.3%	56/112	50.0%
Diffuse (≥20mm)	64/322	19.9%	23/112	20.5%
ACC/AHA lesion class	N	%	N	%
A	12/323	3.7%	8/113	7.1%
B1	94/323	29.1%	41/113	36.3%
B2	125/323	38.7%	37/113	32.7%
C	92/323	28.5%	27/113	23.9%

Enrollment/ Randomization

Study Period (enrollment): 19 February 2004 to 18 September 2004

Eligible patients were randomized to receive either the Endeavor Zotarolimus-Eluting CSS or the Cypher Sirolimus-Eluting CSS in a ratio of 3:1, respectively. Patients who participated in the ENDEAVOR III clinical trial remained blinded to their treatment assignments through the 12-month follow-up visit.

Randomization was achieved using an Interactive Voice Response System (IVRS). A randomization block size of eight was used at each site. The IVRS was programmed to generated eight randomization numbers starting with the first patient enrolled and then every ninth patient at each site.

Antiplatelet Medications

All patients were to receive a minimum of 75 mg of aspirin daily indefinitely, and 75 mg daily of clopidogrel (> 300 mg loading dose immediately post procedure if not administered prior to the procedure) for at least 3 months. If a patient was to develop a sensitivity or intolerance to clopidogrel subsequent to randomization and enrollment, the patient may be given ticlopidine (250 mg BID). Patients with a known hypersensitivity or contraindication to aspirin, clopidogrel, or ticlopidine are excluded from the study.

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All patients were to receive aspirin (a minimum of 75 mg daily, starting at least 24 hours prior to the procedure). During the procedure, heparin could be administered. Activated clotting time (ACT) was to be monitored and adjusted to keep the patient's ACT $\geq$ 250 seconds, or 200-250 seconds

Patient Follow-up

Clinical follow-up was performed during an office visit for all patients at 30 days and 8 months and included assessment for angina status (Canadian Cardiovascular Society Classification of angina), all adverse events and concomitant medications, any interventional treatment that occurred since the previous contact (e.g. repeat revascularization), laboratory tests (30 days) and angiography/IVUS (8 months). A telephone assessment, consisting of the collection of angina status, all adverse events, all concomitant medications, and any interventional treatment that occurred since the previous contact (e.g., repeat revascularization) for all patients, was performed at 6, 9 and 12 months and annually thereafter out to 5 years post-procedure. Adverse events were reported up to 9 months. Subsequently, SAEs (including MACE) and device-related adverse events are reported to 5 years. All study patients enrolled were scheduled to have angiographic and intravascular ultrasound (IVUS) follow-up at 8 months post-index procedure. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. A Clinical Events Committee (CEC) adjudicates all clinical endpoint events. A Data Safety Monitoring Board (DSMB) reviews the study on a regular basis. The primary analysis subset was the Intent-to-treat (ITT) population for the primary endpoint of in-segment late lumen loss at 8 months post-procedure. Kaplan-Meier techniques were be used to assess survival free of MACE, TVR, and TLR.

Schedule of Treatments and Assessments

A summary of treatments and assessments is provided below.

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Table 6.5-2: Schedule of Treatments and Assessments

Index Hospitalization				Follow-up				
Event	Screen	Proce-dure	Post Proce-dure	30 Day Clinic Visit	6 Month Patient Contact [1]	8 Month Clinic Visit Angio & IVUS	9 Month Patient Contact [12]	1-5 Years Annually Patient Contact[1]
Informed Consent Signed	X							
Inclusion/Exclusion Criteria	X							
Medical and Cardiac History	X							
Angina Status	X		X	X	X	X	X	X
Pregnancy test	X [3,4]							
Liver Function test	X [4]							
CBC with differential, chemistry panel (including serum urea, creatinine, electrolytes)	X [4]			X [5]				
CK & CK-MB	X [6]		X [7]					
12-Lead Electrocardiogram	X [4]		X [8]					
ACT Measurements		X						
Medication Regimen [9]	X	X	X	X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X	X
Angiography (QCA)	X	X				X		
IVUS		X				X		

[1] Patient contact includes phone calls, email, and/or office visit.
[2] If during the follow-up assessment the patient states that he/she has undergone any repeat intervention, diagnostic testing/imaging, or has had any ischemic symptoms, the patient should return to the clinic for a full follow-up office visit.
[3] For women of childbearing potential only.
[4] Within 7 days prior to procedure.
[5] CBC with differential (including eosinophils) only.
[6] Within 72 hours prior to procedure.
[7] Within 6-8, 12-16 hours, and 20-24 hours post-procedure or prior to hospital discharge, whichever comes first.
[8] Within 24 hours post-procedure or at discharge, which ever comes first.
[9] It is expected that clopidogrel will be used, unless the patient develops or sensitive to this medication. For patients becoming unable to take clopidogrel, or at the discretion of the physician, ticlopidine will be used.

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6.5.1.6 Patient Accountability

There were a total of 29 clinical research sites in the United States that enrolled 436 patients from February 19, 2004 to September 18, 2004. There were three sites that received approval but did not enroll any patients. There were not more than 30 active investigational sites at any time. In cases where a site was active and did not enroll any patients, the site may have been deactivated and a new site was activated.

All 436 enrolled study patients were scheduled to undergo an angiogram and IVUS at eight months.

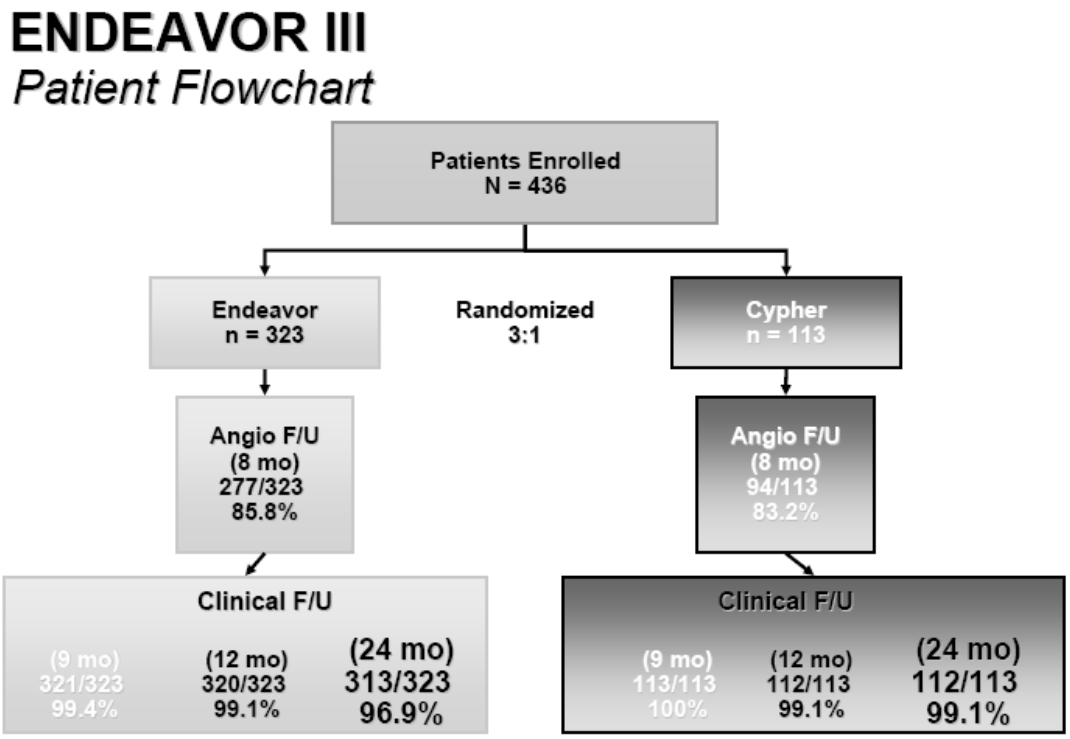

Figure 6.5-1: Patient flowchart for ENDEAVOR III at 24 months

6.5.2 Statistical Methodology

6.5.2.1 Clinical trial objectives and hypotheses

The ENDEAVOR III clinical trial was a prospective, multi-center, single-blinded, parallel, two-arm, randomized, controlled trial designed to assess the equivalency of the Endeavor stent compared to the Cypher stent.

The trial is being conducted at 29 sites in the United States and enrolled 436 patients, randomized in a 3:1 (Endeavor: Cypher) ratio. Patients were blinded to the randomized treatment arm.

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Analysis Samples

The primary analysis sample was based on the principle of intention-to-treat (ITT). For this study, all patients who met the study entry criteria, signed the written informed consent, were randomized to a treatment arm, and were counted in the primary analysis. Missing data for the primary and secondary endpoints was imputed via the multiple imputation technique if applicable.

Analysis was also performed on the per-treatment population, defined as patients with a successful procedure and follow-up information.

Primary Endpoint

The primary endpoint evaluated in this study was in-segment late lumen loss at 8-months as measured by quantitative coronary angiography (QCA).

This randomized study measured equivalency of eight-month in-segment late lumen loss between the two arms, using an equivalency definition (delta) late lumen loss of 0.2 mm. Therefore, the null hypothesis for this study was that the Endeavor stent will have a primary endpoint (in-segment late lumen loss) mean equal to or exceeding that of the control Cypher stent by 0.2 mm or more.

The alternative hypothesis is that the Endeavor has a mean in-segment late lumen loss less than the control Cypher stent mean plus 0.2 mm. Specifically:

H_o: $\mu_A \geq \mu_C + 0.20$
H_1: $\mu_A < \mu_C + 0.20$

Where μ_A is the mean late lumen loss for Endeavor and μ_C is the mean late lumen loss for control.

Rejection of the null hypothesis signifies that the Endeavor stent is not inferior to the control Cypher stent with regard to eight-month in-segment late lumen loss.

The estimated sample size for this study was based on a two sample t-test at an α=0.05 (1-sided) significance level with 90% statistical power to reject the null hypothesis of non-equivalence in favor of the alternative hypothesis that the means of late loss of the two groups were equivalent. Assuming a true equivalence of the means between the two groups, with a common standard deviation of 0.55 mm, an 80% angiographic follow-up rate (i.e., a 20% non-evaluable rate) and 3:1 randomization, a total sample size of 436 patients (348 evaluable) was required. This represents 327 patients (261 evaluable) in the Endeavor group and 109 patients (87 evaluable) in the Cypher group.

Secondary Endpoints

Treatment groups will be compared on the dichotomous secondary endpoints of device success, lesion success, procedure success, major adverse cardiac events (MACE) rate (at each time point), target vessel failure (TVF) rate, 8-month restenosis rate, and 9-month target site revascularization (TSR) rate, and target vessel revascularization (TVR) rate at a 0.05 level of significance using the chi-square test or Fisher's Exact test, depending on the event rate. The time-sensitive nature of MACE, TVF, TSR and TVR will also be displayed using Kaplan-Meier plots, with differences between groups tested by the log rank test.

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The secondary endpoints of in-stent late lumen loss, in-stent and in-lesion minimum luminal diameter (MLD) and neointimal hyperplastic volume will be carried out using the two-sample t-test (or nonparametric techniques, as appropriate) at the 0.05 level of significance.

Analysis on Baseline Characteristics
All clinically relevant baseline variables were tabulated and compared between patients assigned the Endeavor stent and control arm of the study. Categorical variables will be tested using appropriate contingency table analyses (exact or chi-square approximations), and continuous variables will be tested using unpaired Student's t-test or Wilcoxon rank-sum test, depending on variable distribution.

6.5.3 Results

The effectiveness and safety results for Endeavor and Cypher are presented in the table below. Baseline angiographic results were obtained for 436 enrolled patients on whom treatment was attempted. Follow up angiographic results were obtained for 371 patients with qualified angiographic films at the eight-month follow-up period. Safety measures were obtained for patients with follow-up information before the lower window of the follow-up period or with an incidence of the corresponding safety measure prior to the time of interest.

The mean and standard deviation for the primary endpoint of In-Segment Late Lumen Loss at eight months for the Endeavor arm was 0.36 ±0.46 (mm) and for the Cypher arm it was 0.13 ±0.33 (mm). The mean and standard deviation for the secondary endpoint of In-Stent Late Lumen Loss at eight months for the Endeavor group was 0.62±0.49 (mm) and for the Cypher group it was 0.15± 0.34 (mm). The rate of In-Stent Binary Restenosis at eight months for the Endeavor arm was 9.7% (27/277); for the Cypher arm it was 2.1% (2/94).

Table 6.5-3: Primary Endpoint from ENDEAVOR III

Study	Primary Endpoint	Test/ Control	Parameter Mean ± SD	Difference [90% CI]	p-value
ENDEAVOR III	In-segment Late Lumen Loss at 8 months post-procedure (mm)	Endeavor	0.36 ± 0.46	0.24 [0.15,0.32]	0.791*
		Cypher	0.13 ± 0.33		

* P-value is for the test of Non-Inferiority.

Effectiveness measures were reported for 436 patients with available baseline angiographic data. The lesion success rate was 100.0% (323/323) for patients in the Endeavor arm and 99.1% (112/113) for patients in the Cypher arm. The device success rate was 98.8% (319/323) for patients in Endeavor arm and 94.7% (107/113) for patients in the Cypher group. The procedure success rate was 99.4% (321/323) for patients in the Endeavor arm and 95.6% (108/113) for patients in the Cypher arm. The Device-Specific Procedure Success, defined as device success and no in-hospital MACE, rate for Endeavor arm patients was 98.1% (317/323) and 91.2% (103/113) for Cypher patients.

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Additionally, in-hospital incidence of MACE was 0.6% (2/323) for patients in the Endeavor arm and 3.5% (4/113) for patients in the Cypher arm. Incidence of MACE at 720 days was 9.3% (29/313) for patients in the Endeavor group and 11.6% (13/112) for patients in the Cypher group.

The cumulative incidence of TLR at 720 days post-index procedure for Endeavor was 7.0% (22/313); for Cypher it was 4.5% (5/112). The cumulative incidence of TVR at 720 days post-index procedure for Endeavor was 13.7% (43/313); for Cypher it was 9.8% (11/112). The cumulative incidence of TVF at 720 days post-index procedure for Endeavor was 14.4% (45/313); for Cypher it was 13.4% (15/112).

The Kaplan-Meier estimate of freedom from MACE at 720 days for the Endeavor arm was 90.9%; for the Cypher arm it was 88.5%.

6.5.3.1 Hypothesis Test

The primary endpoint evaluated in this study was in-segment late lumen loss at 8 months as measured by quantitative coronary angiography (QCA).

This randomized study assessed non-inferiority of Endeavor to Cypher with respect to 8-month in-segment late lumen loss, using a non-inferiority definition (delta) of late lumen loss of 0.2 mm. Specifically, the null hypothesis for this study was that the Endeavor Zotarolimus-Eluting Coronary Stent System had a primary endpoint (in-segment late lumen loss) mean exceeding that of the control Cypher stent by 0.2 mm or more. The alternative hypothesis was that the Endeavor Zotarolimus-Eluting Coronary Stent System had a mean in-segment late lumen loss less than the control Cypher stent mean plus 0.2 mm. Specifically, the null and alternative hypotheses are:

$$H_o: \mu_A \geq \mu_C + 0.20$$
$$H_1: \mu_A < \mu_C + 0.20$$

where μA is the mean late lumen loss for Endeavor and μC is the mean late lumen loss for the control arm. The mean late lumen loss was 0.36 mm ±0.46 mm (n=277) in the Endeavor arm and was 0.13 mm ±0.33 mm (n=94) for the Cypher arm, yielding a difference (Endeavor minus Cypher) of 0.24 mm. The upper bound of the one-sided 95% confidence interval is 0.32 mm, which is greater than 0.20 mm, therefore signifying at a one-sided 0.05 significance level that the criterion for non-inferiority of Endeavor to Cypher has not been met for the Endeavor Zotarolimus-Eluting Coronary Stent System with regard to 8-month in-segment late lumen loss.

A two-way analysis of variance adjusting for study site was used to assess the consistency of treatment effect across study sites; specifically, a treatment-by-study site interaction effect was assessed at the 0.10 level of significance. A non-significant interaction with a p-value of 0.2193 supported the acceptability of pooling sites for the primary analysis.

The table below summarizes the principal effectiveness and safety results of the ENDEAVOR III trial through 24 months.

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Table 6.5-4: Principal Effectiveness and Safety Results through 720 Days for ENDEAVOR III

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]*	P-value*
Lesion Success	100.0% (323/323)	99.1% (112/113)	--	--
Device Success	98.8% (319/323)	94.7% (107/113)	--	--
Procedure Success	99.4% (321/323)	95.6% (108/113)	--	--
Device-Specific Procedure Success	98.1% (317/323)	91.2% (103/113)	--	--
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.67±0.42 (323)	2.67±0.40 (112)	--	--
In-Segment	2.27±0.45 (323)	2.28±0.47 (113)	--	--
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	4.33±9.77 (323)	5.92±9.07 (112)	--	--
In-Segment	19.38±9.25 (323)	20.17±11.74 (113)	--	--
Eight-Month Follow-Up MLD (mm)				
In-Stent	2.06±0.57 (277)	2.52±0.56 (94)	--	--
In-Segment	1.91±0.53 (277)	2.16±0.50 (94)	--	--
Eight-Month Follow-up %DS				
In-Stent	24.90±17.45 (277)	11.01±15.91 (94)	--	--
In-Segment	30.42±15.57 (277)	23.86±13.87 (94)	--	--
Eight-Month Follow-up Late Loss (mm)				
In-Stent	0.62±0.49 (277)	0.15±0.34 (94)	--	--
In-Segment	0.36±0.46 (277)	0.13±0.33 (94)	0.24 [0.13,0.34]	<0.001
Eight-Month Follow-up Binary Restenosis			--	--
In-Stent	9.7% (27/277)	2.1% (2/94)	--	--
In-Segment	12.3% (34/277)	4.3% (4/94)	--	--
Eight-Month Volume Obstruction (%)	15.94±10.94 (187)	2.66±3.11 (61)	--	--
Eight-Month Minimal Lumen Area (mm^2)	4.89±1.96 (209)	5.77±1.97 (66)	--	--
Eight-Month NIH Volume (mm^3)	24.09±21.16 (209)	3.74±5.20 (67)	--	--
In-Hospital MACE	0.6% (2/323)	3.5% (4/113)	--	--
MACE to 30 Days	0.6% (2/323)	3.5% (4/113)	--	--
MACE to 270 Days	7.5% (24/321)	7.1% (8/113)	--	--
MACE to 360 Days	7.8% (25/320)	8.0% (9/112)	--	--

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Table 6.5-4: Principal Effectiveness and Safety Results through 720 Days for ENDEAVOR III

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]*	P-value*
MACE to 720 Days	9.3% (29/313)	11.6% (13/112)	--	--
Death to 720 Days	1.6% (5/313)	4.5% (5/112)	--	--
Vascular Complications to 720 Days	1.9% (6/313)	5.4% (6/112)	--	--
Major Bleeding to 720 Days	2.2% (7/313)	6.3% (7/112)	--	--
Early Stent Thrombosis to 30 Days	0.0% (0/323)	0.0% (0/113)	--	--
Late Stent Thrombosis to 270 days	0.0% (0/321)	0.0% (0/113)	--	--
Late Stent Thrombosis to 360 days	0.0% (0/320)	0.0% (0/112)	--	--
Late Stent Thrombosis to 720 days	0.0% (0/313)	0.0% (0/112)	--	--
Cerebrovascular Accident (CVA) to 720 Days	0.6% (2/313)	0.9% (1/112)	--	--
Perforation to 720 Days	0.0% (0/313)	0.9% (1/112)	--	--
Target Vessel Revascularization to 30 days	0.0% (0/323)	0.9% (1/113)	--	--
Target Vessel Revascularization to 270 days	11.2% (36/321)	8.0% (9/113)	--	--
Target Vessel Revascularization to 360 days	12.2% (39/320)	8.0% (9/112)	--	--
Target Vessel Revascularization to 720 days	13.7% (43/313)	9.8% (11/112)	--	--
Target Vessel Failure to 30 days	0.6% (2/323)	4.4% (5/113)	--	--
Target Vessel Failure to 270 days	11.8% (38/321)	11.5% (13/113)	--	--
Target Vessel Failure to 360 days	12.8% (41/320)	11.6% (13/112)	--	--
Target Vessel Failure to 720 days	14.4% (45/313)	13.4% (15/112)	--	--
Target Lesion Revascularization to 30 days	0.0% (0/323)	0.0% (0/113)	--	--
Target Lesion Revascularization to 270 days	6.2% (20/321)	3.5% (4/113)	--	--
Target Lesion Revascularization to 360 days	6.6% (21/320)	3.6% (4/112)	--	--
Target Lesion Revascularization to 720 days	7.0% (22/313)	4.5% (5/112)	--	--

*Confidence Intervals and p-values are provided only for powered endpoints.

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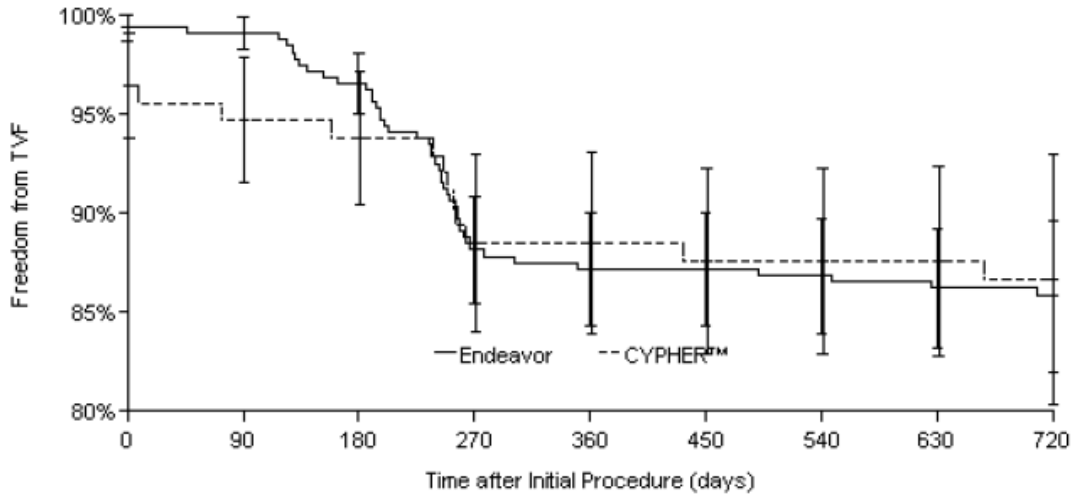
Kaplan-Meier Estimate	ENDEAVOR III (N= 323 Patients)	CYPHER™ (N= 113 Patients)
MACE-Free at 720 days	90.9%	88.5%
TLR-Free at 720 days	93.0%	95.5%
TVR-Free at 720 days	86.4%	90.2%
TVF-Free at 720 days	85.8%	86.7%



TVF	0	90	180	270	360	450	540	630	720
Endeavor									
# Entered	323	321	318	310	281	274	268	264	262
# Censored	0	2	0	2	4	6	3	0	102
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	2	1	8	27	3	0	1	2	1
% Survived	99.4%	99.1%	96.6%	88.1%	87.2%	87.2%	86.9%	86.2%	85.8%
SE	0.4%	0.5%	1.0%	1.8%	1.9%	1.9%	1.9%	2.0%	2.6%
CYPHER™									
# Entered	113	109	107	106	100	98	97	97	95
# Censored	0	0	0	0	2	0	0	2	38
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	4	2	1	6	0	1	0	0	1
% Survived	96.5%	94.7%	93.8%	88.5%	88.5%	87.6%	87.6%	87.6%	86.7%
SE	1.7%	2.1%	2.3%	3.0%	3.0%	3.1%	3.1%	3.2%	4.2%

Figure 6.5-2: Survival Free from Target Vessel Failure at 720 days (ITT)

6.5.3.2 Other Analysis

Analysis of Homogeneity Between Single-Blind and Single-Blind Plus Groups

The ENDEAVOR III study was a prospective, multi-center, randomized, two-arm, single-blind trial. In an effort to minimize bias (selection, observation, etc.) in the trial, Medtronic introduced additional blinding procedures. To ensure that introducing additional blinding measures during the course of the study had no effect on outcomes, the patient population was divided into two cohorts: (1) a cohort of patients accrued prior to introducing the additional measures; and (2) a cohort of patients accrued post-

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introduction of the additional measures. Two logistic regression models were applied, with qualified angiographic follow-up available (Y/N) as the dependent variable. The first logistic regression model simply assessed the relationship between cohort and follow-up, and yielded a p-value of 0.4298 indicating no relationship between cohort and patient availability for follow-up. The second model included two main effect variables, treatment and patient cohort, and the interaction between treatment and patient cohort. A non-significant interaction term (p-value of 0.3380) provided evidence that the rate of follow-up between treatments did not differ between the two cohorts of patients.

Homogeneity between the two cohorts of patients on baseline characteristics was also assessed. For each baseline characteristic, simple comparisons were performed to compare baseline demographics between cohorts for both treatments combined (see Homogeneity Table below). As is seen in the table, the only significant difference between cohorts is for the prevalence of IIb/IIIa Inhibitor use. This is not expected to have markedly affected treatment comparisons on primary and secondary endpoints, since, as will be discussed below, the distribution of the prevalence of IIb/IIIa use between treatments did not differ between cohorts.

Table 6.5-5: Homogeneity Table - Baseline Demographics and Clinical Characteristics by Blinding Status - ITT Population

Patient Characteristic	Single-Blind (N= 242 Patients)	Single-Blind Plus* (N= 194 Patients)	All Patients (N= 436 Patients)
Age (yrs)			
Mean±SD (n)	61.60±10.75 (242)	61.39±10.97 (194)	61.50±10.84 (436)
Range (min,max)	(34.00,85.00)	(37.00,86.00)	(34.00,86.00)
Number of Men	66.9% (162/242)	72.7% (141/194)	69.5% (303/436)
History of Smoking	69.7% (168/241)	67.5% (129/191)	68.8% (297/432)
Diabetes Mellitus	29.3% (71/242)	29.4% (57/194)	29.4% (128/436)
Revascularization for Angina or MI	84.3% (204/242)	86.1% (167/194)	85.1% (371/436)
Angina Status			
Stable	46.1% (94/204)	37.7% (63/167)	42.3% (157/371)
Unstable	48.0% (98/204)	57.5% (96/167)	52.3% (194/371)
MI	5.9% (12/204)	4.8% (8/167)	5.4% (20/371)
Race			
White	92.1% (223/242)	91.2% (177/194)	91.7% (400/436)
Black	2.9% (7/242)	4.6% (9/194)	3.7% (16/436)
Asian	1.2% (3/242)	0.5% (1/194)	0.9% (4/436)
Native Hawaiian or Other Pacific Islander	0.4% (1/242)	0.0% (0/194)	0.2% (1/436)
American Indian or Alaska Native	2.1% (5/242)	1.0% (2/194)	1.6% (7/436)
Other	1.2% (3/242)	2.6% (5/194)	1.8% (8/436)
In-Segment Post-Procedure MLD			
Mean±SD (n)	2.28±0.44 (242)	2.25±0.48 (194)	2.27±0.46 (436)
Stent/Lesion Length			
Mean±SD (n)	1.69±0.62 (240)	1.65±0.63 (193)	1.67±0.62 (433)

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Table 6.5-5: Homogeneity Table - Baseline Demographics and Clinical Characteristics by Blinding Status - ITT Population

Patient Characteristic	Single-Blind (N= 242 Patients)	Single-Blind Plus* (N= 194 Patients)	All Patients (N= 436 Patients)
IIb/IIIa Use	38.2% (92/241)	51.5% (100/194)	44.1% (192/435)

N = the maximum number of eligible patients, n = number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter.
* Medtronic is committed to maximizing the quality and integrity of data from ENDEAVOR III and has worked to implement additional blinding procedures to minimize bias (selection, observation, etc.) in this trial.

In addition, a logistic regression model and analysis of variance were applied for binary and continuous baseline characteristics, respectively. In each model, the baseline characteristic was the dependent variable. The independent variables included two main effects, treatment and patient cohort, and an interaction term between treatment and patient cohort. No interaction term was significant at the 0.10 level of significance, implying that the distribution of the baseline characteristic between treatments did not differ between the two cohorts of patients.

The following baseline characteristics were assessed:

Characteristic	P-value for Interaction
Age	0.7748
Gender	0.2529
Race: White vs Non-White	0.1479
In-Segment Post Procedure MLD	0.7077
Stent/Lesion Length	0.2874
Diabetes	0.3032
Revascularization for Angina or MI	0.7332
Smoking status	0.1880
IIb/IIIa Use	0.5231

Outcome poolability between cohorts was assessed on the primary endpoint of in-segment late lumen loss at 8 months and on the secondary endpoints of 30-day MACE and 9-month TVF. Analysis of variance was applied for in-segment late lumen loss at 8 months. In addition to using baseline characteristics and treatment indicators as independent variables, an indicator variable for cohort, and the interaction between treatment and cohort were added as independent variables into the model. A non-significant treatment-by-cohort interaction term (p-value= 0.5410) indicated that the treatment effect was consistent between the two cohorts of ENDEAVOR III patients with respect to the primary endpoint.

A logistic regression model was applied for 30-day MACE using the same independent variables as were used for in-segment late loss above. (Note, due to the small number of events, the model may not be valid.) The lack of significant treatment-by-cohort interaction term indicated treatment effect was consistent between the two cohorts of ENDEAVOR III patients with respect to the secondary endpoint of 30-day MACE. Finally, a logistic regression model was applied for 9-month TVF. A non-significant

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treatment-by-cohort interaction term indicated treatment effect was consistent between the two cohorts of ENDEAVOR III patients with respect to the secondary endpoint of 9-month TVF.

The above analysis supports pooling the data between the two cohorts prior to carrying out analysis on the primary and secondary endpoints.

6.5.4 Conclusions

Comparison of the Endeavor Zotarolimus-Eluting CSS to the Cypher stent in ENDEAVOR III provided the first Endeavor clinical data in a US population. Acute success (discussed above) and 30-day MACE rates favored the Endeavor Zotarolimus-Eluting CSS over the Cypher stent, with a six-fold lower frequency of in-hospital MACE in the Endeavor Zotarolimus-Eluting CSS cohort. At later time points, the two groups demonstrated similar efficacy, with no statistically significant differences for rates of MACE-free, target lesion or vessel revascularization, or target vessel failure during nine month or 12 month follow-up evaluations. The designated primary endpoint of in segment late lumen loss at eight months was significantly higher among patients treated with Endeavor Zotarolimus-Eluting CSS versus the Cypher stent (0.36±0.46 mm vs. 0.13±0.33mm, P=0.791 for non-inferiority), corresponding to a higher frequency of in-segment binary restenosis (12.3% vs. 4.3%). It is noteworthy that the in-segment late loss value of the Cypher stent was lower than the observed values in other recent Cypher stent clinical trials.[1,2,3]A significant objective in designing the ENDEAVOR III clinical trial was to determine if the angiographic and clinical results seen with the Endeavor Zotarolimus-Eluting CSS in this US clinical trial were harmonious with those from previous international clinical trials assessing Endeavor Zotarolimus-Eluting CSS. Late lumen loss values for Endeavor Zotarolimus-Eluting CSS in the ENDEAVOR III trial were virtually identical to those observed in the ENDEAVOR II and ENDEAVOR II-CA trials, indicating that the performance of Endeavor Zotarolimus-Eluting CSS was consistent throughout the clinical development program, and in particular between trials conducted abroad (ENDEAVOR II and II-CA) and in the US (ENDEAVOR III).

[1] Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
[2]Morice, M-C., Serruys, P.W., Sousa, J.E., Fajadet, J., Hayashi, E.B., Perin, M., Colombo, A., *et al.* "A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization." *New England Journal of Medicine* 346(23):1773-1781 (2002).
[3] Morice, M-C., Colombo, A., Meier, B., Serruys, P., Tamburino, C., Guagliumi, G., Sousa, E., Stoll, H-P. "Sirolimus – vs Paclitaxel-Eluting Stents in De Novo Coronary Artery Lesions." *Journal of the American Medical Association* 295(8):895-904 (2006).

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6.6 ENDEAVOR IV Clinical Study Summary

6.6.1 Clinical Study Description

Endeavor IV study was A Randomized, Controlled Trial of the Medtronic Endeavor Zotarolimus-Eluting Coronary Stent System versus the Taxus Paclitaxel-Eluting Coronary Stent System in *De Novo* Native Coronary Artery Lesions.

6.6.1.1 Study Design

The study was designed as a prospective, multi-center, randomized, two-arm, single-blind trial.

6.6.1.2 Study Objectives

To assess the equivalence in safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Taxus Paclitaxel-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.5-3.5 mm.

6.6.1.3 Primary Endpoints

Target vessel failure (TVF) rate at 9 months post-procedure.

6.6.1.4 Secondary Endpoints

- Acute success (device, lesion, and procedure)
- Major adverse cardiac event (MACE) rate at 30 days, 6, 9, and 12 months post-procedure
- Target site revascularization (TSR) rate and clinically-driven TSR rate at 9 months post-procedure
- Target vessel revascularization (TVR) rate and clinically-driven TVR rate at 9 months post-procedure
- Angiographic parameters (in-stent and in-segment) in a subset of patients at 8 months post-procedure including:
  - Percent diameter stenosis (%DS)
  - Late lumen loss (in-segment late lumen loss is a powered secondary endpoint)
  - Late loss index
  - Angiographic binary restenosis (ABR) rate
  - Minimum luminal diameter (MLD)
- Neointimal hyperplastic volume and percent volume obstruction (%VO) at 8 months post-procedure as measured by intravascular ultrasound (IVUS) in a subset of patients

6.6.1.5 Patient/Study Population

The study population will consist of patients with symptomatic ischemic heart disease due to stenotic lesions of *de novo* native coronary arteries with reference vessel diameters between 2.5 mm and 3.5 mm and a lesion length ≤ 27 mm that are amenable to percutaneous treatment with stenting.

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General Inclusion Criteria

Candidates were considered for inclusion if the following conditions were met:

1. The patient is ≥ 18 years of age.
2. The patient has clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, or a positive functional study.
3. The patient is an acceptable candidate for PTCA, stenting, and emergent CABG surgery.
4. Female patients of childbearing potential must have a negative pregnancy test within 7 days before the procedure.
5. The patient or patient's legal representative has been informed of the nature of the study and agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board/Ethics Committee (IRB/EC) of the respective clinical site.
6. The patient agrees to return to the same research facility for all required post-procedure follow-up visits.

Angiographic Inclusion Criteria

The target lesion / vessel met the following criteria:

1. The target lesion must be a single *de novo* lesion in a native coronary artery.
2. The target lesion must be ≤ 27 mm in length.
3. The target lesion must have a stenosis of ≥ 50% and < 100%.
4. The target vessel has a thrombolysis in myocardial infarction (TIMI) flow 2 or greater.
5. The target vessel reference diameter must be ≥ 2.5 mm and ≤ 3.5 mm.

   Note: Measurements may be made by careful visual estimate, on-line QCA, or IVUS.

General Exclusion Criteria

1. A known hypersensitivity or contraindication to aspirin, heparin or bivalirudin, ticlopidine or clopidogrel, cobalt, nickel, chromium, molybdenum, polymer coatings (e.g., Phosphorylcholine or Translute), or a sensitivity to contrast media, which cannot be adequately pre-medicated.
2. History of an allergic reaction or significant sensitivity to drugs such as Zotarolimus, rapamycin, tacrolimus, everolimus, or any other analogue or derivative.
3. History of an allergic reaction or significant sensitivity to paclitaxel or drugs in similar class.
4. A platelet count < 100,000 cells/mm³ or > 700,000 cells/mm³, or a white blood cell (WBC) count < 3,000 cells/mm³.
5. A serum creatinine level > 2.0 mg/dl within seven days prior to index procedure.
6. Evidence of an acute MI within 72 hours of the intended index procedure (defined as: QWMI or non-Q wave myocardial infarction (NQWMI) having CK enzymes ≥

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2X the upper laboratory normal with the presence of a CK-MB elevated above the Institution's upper limit of normal).

Note: Patients with evidence or suspicion of an acute MI must have CK and CK-MB labs drawn and the results reviewed prior to randomization.

7. Previous PCI of the target vessel within 9 months pre-procedure.

   Note: Refer to table 3 of the report (Appendix 5) for staging criteria of the target vessel and criteria for previous PCI of other (non-target) vessels.

8. Planned PCI of any vessel within 30 days post-procedure.
9. During the index procedure, the target lesion requires treatment with a device other than PTCA prior to stent placement (including but not limited to, cutting balloon, any atherectomy, any laser, thrombectomy, etc.).
10. History of a stroke or transient ischemic attack (TIA) within the prior 6 months.
11. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months.
12. History of bleeding diathesis or coagulopathy or will refuse blood transfusions.
13. Concurrent medical condition with a life expectancy of less than 12 months.
14. Any previous or planned treatment of the target vessel with anti-restenotic therapies including, but not limited to brachytherapy.
15. Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints; or requires coronary angiography, IVUS or other coronary artery imaging procedures. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.]
16. Documented left ventricular ejection fraction (LVEF) < 30% at most recent evaluation.

Angiographic Exclusion Criteria

1. Target lesion is located in a native vessel distal to anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass with more than 40% diameter stenosis anywhere within the graft.
2. Previous stenting (drug-eluting or bare metal) in the target vessel unless the following conditions are met:
   a) It has been at least 9 months since the previous stenting, and
   b) The target lesion is at least 15 mm away from the previously placed stent.
3. Target vessel has other lesions with greater than 40% diameter stenosis based on visual estimate or on-line QCA.
4. The target vessel has evidence of thrombus.
5. The target vessel is excessively tortuous.
6. The target lesion has any of the following characteristics:
   a) Lesion location is aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA)

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b) Involves a side branch > 2.0 mm in diameter
c) Is at or distal to a > 45º bend in the vessel
d) Is severely calcified
e) Involves a bifurcation

7. Unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery).

Key Baseline Characteristics

The key baseline characteristics are summarized below.

Table 6.5-1: Key Baseline Characteristics

Baseline Variables	Endeavor		Taxus	
	N	%	N	%
Age (years)	773		775	
Mean (SD*)	63.5±11.1		63.6±11.0	
Range	27-92		31-89	
Gender				
Male	517	66.9%	531	68.5%
Race	769		771	
White/Caucasian	695	90.4%	684	88.7%
Clinical Characteristics				
History of diabetes mellitus	241/773	31.2%	236/775	30.5%
History of hypertension	614/773	79.4%	640/775	82.6%
Lesion Characteristics				
Reference Vessel Diameter	772	2.73±0.47	774	2.70±0.46
Lesion length	771	13.41±5.67	773	13.80±6.09
Discreet (< 10mm)	241/771	31.3%	233/773	30.1%
Tubular (10-19.9 mm)	439/771	56.9%	422/773	54.6%
Diffuse (≥20mm)	91/771	11.8%	118/773	15.3%
ACC/AHA lesion class				
A	52/772	6.7%	51/774	6.6%
B1	183/772	23.7%	174/774	22.5%
B2	338/772	43.8%	332/774	42.9%
C	199/772	25.8%	217/774	28.0%

*Standard Deviation

Enrollment/ Randomization

Study Period (enrollment): 11 April 2005 to 27 June 2006

Patients were stratified by diabetic status and subsequently randomized in a 1:1 ratio to receive either the Endeavor or Taxus stent.

Randomized patients who are not treated with the assigned study stent were followed-up for safety purposes to be included in the ITT population. Patients included in the ITT population were to be followed throughout the primary endpoint period and undergo the follow-up assessments through the 9 month follow-up. Patients who participated in the ENDEAVOR IV clinical trial remained blinded to their treatment assignments through the 12-month follow-up visit.

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Randomization was achieved using an Interactive Voice Response System (IVRS). A randomization block size of eight was used at each site. At each site, the system generated eight randomization numbers starting with the first patient enrolled and then every ninth patient.

Antiplatelet Medications

All patients in ENDEAVOR IV received aspirin (a minimum of 75 mg daily, starting within 24 hours prior to the procedure) and clopidogrel (≥ 300 mg loading dose prior to or immediately post-procedure (typically within 30 minutes after removal of the last catheter), if the patient is not currently taking clopidogrel). If the patient has taken at least 3 doses (75 mg/dose) of clopidogrel within 72 hours prior to the procedure, no loading dose is required.

During the procedure, heparin or bivalirudin was administered. Activated clotting time (ACT) was monitored and adjusted to keep the patient's ACT at a therapeutic level (ACT ≥ 250 seconds, or 200-250 seconds if a glycoprotein (GP) IIb/IIIa receptor blocker was administered) prior to advancing the stent delivery system through the guide catheter. A GP IIb/IIIa receptor blocker may have been administered at physician's discretion.

The use of low molecular weight heparin (e.g., Enoxaparin) was not allowed in this study. If a patient was transferred from another facility other than the research facility, where low molecular weight heparin was used, the patient was considered for enrollment if low molecular weight heparin was discontinued and heparin or bivalirudin was administered prior to obtaining the appropriate ACT.

Following the procedure, patients received a minimum of 75 mg of aspirin daily indefinitely and 75 mg of clopidogrel daily for a minimum of 6 months. Clopidogrel was prescribed to the patient unless the patient developed a sensitivity to this medication. If a patient developed a sensitivity or intolerance to clopidogrel subsequent to enrollment, the patient may have been given ticlopidine (250 mg BID).

Patient Follow-up

Clinical follow-up was performed post-procedure and during an office visit for all patients at 30 days and 9 months post-procedure and included assessment for angina status (Canadian Cardiovascular Society Classification of angina), all adverse events and concomitant medications, any interventional treatment that occurred since the previous contact (e.g. repeat revascularization), laboratory tests (30 days) and angiography/IVUS (8 months) in a subset of the first 328 subjects enrolled who have received single or multiple stents.

Clinical assessments by telephone, email and/or office visits consisting of the collection of angina status, all adverse events, all concomitant medications, and any interventional treatment that occurred since the previous contact (e.g., repeat revascularization) for all patients, are performed at 6 and 12 months and annually thereafter out to 5 years post-procedure. Adverse events are reported up to 9 months. Subsequently, SAEs (including MACE) and device-related adverse events are reported to 5 years. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. A Clinical Events Committee (CEC) adjudicated all clinical endpoint events. A Data Safety Monitoring Board (DSMB)

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reviewed the study on a regular basis. The primary analysis subset is the Intent-to-treat (ITT) population for the primary endpoint of TVF at 9 months post-procedure.

Schedule of Treatments and Assessments

A summary of treatments and assessments is provided below.

Table 6.5-2: Schedule of Treatments and Assessments

Event	Index Hospitalization					Follow-up				
	Screening/Pre-procedure			Procedure	Post-procedure[1]	30 Day	6 Month	8 Month	9 Month	1-5 Years Annually
	Prior to procedure	Prior to procedure within: 7 days	Prior to procedure within: 72 hours			Clinic Visit	Patient Contact [2]	Clinic Visit [3]	Clinic Visit	Patient Contact
Informed Consent signed	X									
Medical and cardiac history	X									
Angina status	X					X	X	X	X	X
Pregnancy test [4]		X								
Chemistry panel		X								
CBC with differential (including eosinophils)		X				X				
Lipid panel		X								
Liver function test		X								
12 lead ECG		X			X Within 24 hours					
CK and CK-MB			X		X 6-8 hours 12-16 hours 20-24 hours[5]					
ACT measurements				X						
Clinically-driven revascularization verification								X [6]		
QCA	X			X				X		
IVUS				X[3]				X		

[1] Post-procedure is defined as removal of the last catheter.
[2] Patient contact includes phone calls, email, and/or office visit.
[3] For Angiographic/IVUS and Multi-stent subsets only.
[4] For women of childbearing potential only.
[5] If a patient is discharged prior to 20 hours, the 20-24 hour blood draw may be omitted.
[6] Functional study/stress test, FFR, or IVUS should be conducted prior to diagnostic imaging for Angiographic/IVUS and Multi-stent subsets.

Table 6.5-2: Schedule of Treatments and Assessments

Event	Index Hospitalization					Follow-up				
	Screening/Pre-procedure			Procedure	Post-procedure[1]	30 Day	6 Month	8 Month	9 Month	1-5 Years Annually
	Prior to procedure	Prior to procedure within: 7 days	Prior to procedure within: 72 hours			Clinic Visit	Patient Contact [2]	Clinic Visit [3]	Clinic Visit	Patient Contact
AE monitoring				X	X	X	X	X	X	X SAEs only
Medication regimen [1]	X Within 24 hours			X	X	X	X	X	X	X [2]

[1] Refer to the Concomitant Medication section in the study report (Appendix 5).
[2] Antiplatelet/anticoagulation medications only.

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6.6.1.6 Patient Accountability

There were a total of 80 sites in the United States that enrolled 1,548 patients from April 11, 2005 to June 27, 2006. There were two sites that received approval to begin enrollment but did not enroll any patients.

Angiography and IVUS evaluations immediately post-procedure and at eight months post-procedure were scheduled for a subset of the first 328 consecutively enrolled patients at all sites (164 per treatment arm).

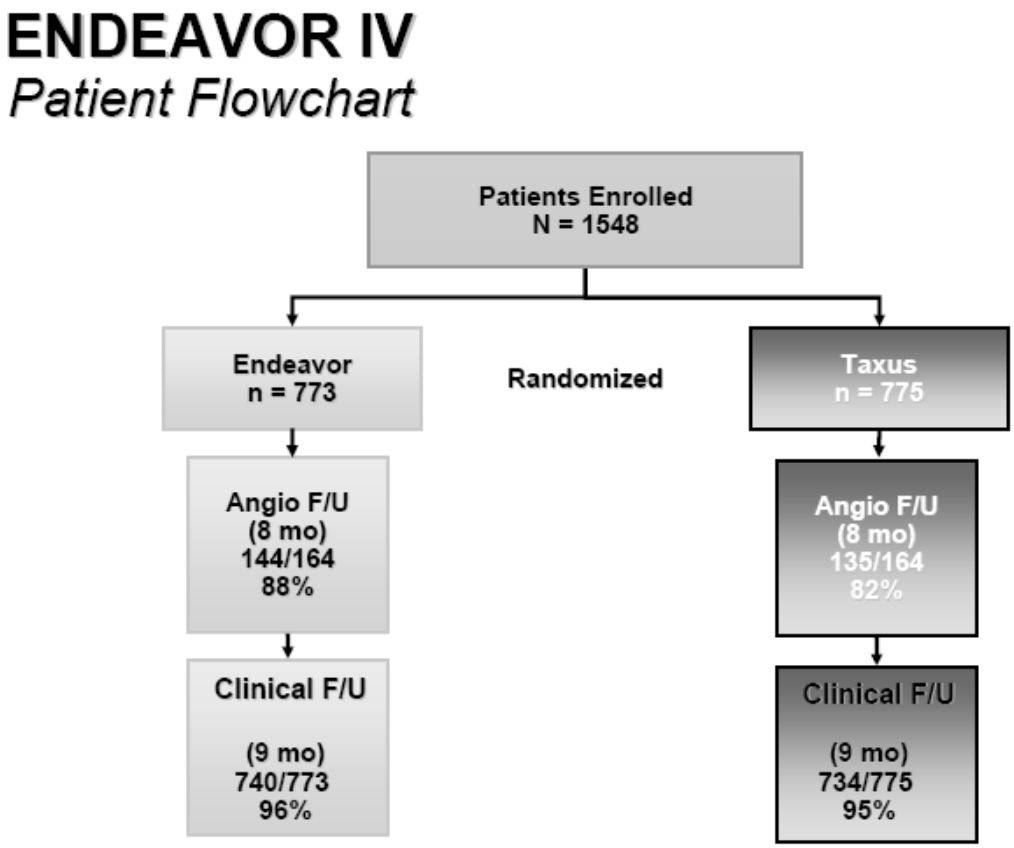

Figure 6.5-1: 1 Patient Flowchart for ENDEAVOR IV at 9 Months

6.6.2 Statistical Methodology

6.6.2.1 Clinical Trial Objectives and Hypotheses

This is a prospective, multi-center, single-blind, parallel, two-arm, randomized, controlled trial designed to assess the non-inferiority of the Endeavor stent compared to the Taxus stent. To test the non-inferiority of the primary clinical endpoint (9 month

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TVF), the Blackwelder (1982)[1] approach was used. A statistical significance level of 0.05 was used.

The final statistical analysis plan (version 6.0 dated January 24, 2007) was the source document for the analyses completed in this report.

The trial was conducted at 80 active sites in the US and enrolled 1,548 patients randomized to the Endeavor and Taxus stent in a 1:1 ratio. The number of patients in each group was 773 and 775 for Endeavor and Taxus, respectively.

All statistical analyses were performed using Statistical Analysis System (SAS) for Windows (Version 8.02 or higher).

Analysis Samples

The primary analysis sample was based on the principle of ITT. For this study, all patients who met the study entry criteria, signed the written informed consent, and are randomized were counted in the primary analysis.

Analyses were also performed on the per-treatment evaluable population, defined as patients with a successful procedure and complete follow-up information.

Primary Endpoint

The primary clinical endpoint evaluated in this non-inferiority study is TVF rate defined as the composite of cardiac death, recurrent MI, or clinically-driven TVR rate of the treated vessel at 9 months post-procedure. The null hypothesis for this study is that the Endeavor stent arm will 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 will have a 9 month TVF rate that is no more than that of the control stent, or exceeds that of the control stent but by less than δ. Rejection of the null hypothesis will signify that the Endeavor stent is non-inferior to the control stent with regard to 9 month TVF.

Specifically, the null (H_o) and alternative (H_a) hypotheses are:

$$H_o: \pi_A \geq \pi_C + \delta$$
$$H_a: \pi_A < \pi_C + \delta$$

Where π_A is the true TVF rate for the Endeavor stent and π_C is the true TVF rate for the control stent (Taxus stent). The sample size estimation is based on a non-inferiority test at an $\alpha = 0.05$ (1-sided) significance level with 84% statistical power to reject the null hypothesis of inferiority in favor of the alternative hypothesis of non-inferiority of the proportion of patients with TVF of the Endeavor arm compared to the Taxus arm. Assuming that the expected TVF rates of the Endeavor and Taxus arms are both equal to 7.6%, a non-inferiority margin of 3.8%, 90% clinical follow-up rate (i.e., a 10 percent non-evaluable rate) and 1:1 randomization, a total sample size of 1,548 patients (1,394 evaluable) is required. This represents 774 (697 evaluable) patients in the Endeavor arm

[1] Blackwelder WC. "Proving the null hypothesis" in clinical trials. *Control Clin Trials.* 1982; 3: 345–353.

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and the Taxus arm. Power Analysis and Sample Size (PASS) was used to compute sample size.

Secondary Endpoints

Powered Secondary Endpoint

The powered secondary endpoint evaluated in this study is in-segment late lumen loss at 8 months measured by QCA.

This randomized study measured the non-inferiority of 8 month in-segment late lumen loss of the Endeavor arm compared to the Taxus arm, using a non-inferiority margin (delta) of 0.2 mm. Therefore, the null hypothesis for the secondary endpoint is that the Endeavor stent will have a secondary endpoint (in-segment late lumen loss) mean equal to or exceeding that of the control by 0.2 mm or more.

The alternative hypothesis is that the Endeavor stent will have a mean in-segment late lumen loss less than the control Taxus stent mean plus 0.2 mm. Specifically,

$$H_o: \mu_{Endeavor} \geq \mu_{Taxus} + 0.2$$
$$H_a: \mu_{Endeavor} < \mu_{Taxus} + 0.2$$

Where $\mu_{Endeavor}$ is the mean late lumen loss for Endeavor and μ_{Taxus} is the mean late lumen loss for the control Taxus stent.

Rejection of the null hypothesis will indicate that the Endeavor stent is not inferior to the control Taxus stent with regard to 8 month in-segment late lumen loss.

The estimated sample size for the angiographic subset is based on a two sample t-test at an $\alpha = 0.05$ (1-sided) significance level with 80 percent statistical power to reject the null hypothesis of inferiority in favor of the alternative hypothesis of non-inferiority of means of late lumen loss of the Endeavor arm compared to the Taxus arm. Assuming a true equivalence of the means between the two groups, a non-inferiority margin of 0.2, with a common standard deviation of 0.55 mm, an 80 percent angiographic follow-up rate (i.e., a 20 percent non-evaluable rate) and 1:1 randomization, a total sample size of 328 patients (262 evaluable) is required. This represents 164 (131 evaluable) patients in the Endeavor arm and the Taxus arm. PASS[2] was used to compute sample size.

Analysis on Baseline Characteristics:

All clinically relevant baseline variables were tabulated and compared between subjects assigned the Endeavor stent and control arm of the trial. Categorical variables were tested using appropriate contingency table analyses (exact test), and continuous variables were tested using unpaired Student's t-test.

6.6.3 Results

Randomized subjects had an overall mean age of 63.5 years, 67.7% were men, 30.8% had diabetes, 43.9% had multivessel coronary artery disease, 28.9% had prior PCI, 9.1% had prior CABG, and mean left ventricular ejection fraction was 57.38%. No statistical

[2] Hintze, JL. PASS 2000 User's Guide: Power Analysis and Sample Size for Windows. Version January 2000. Kaysville, UT: Number Cruncher Statistical Systems; 2000.

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difference was observed between groups for any of the baseline characteristics summarized.

No statistically significant differences in baseline subject characteristics were observed between the treatment groups (clinical or lesion). The subjects enrolled in this study are representative of cardiac patients with moderate risk for development of restenosis and 9-month clinical events, based upon their baseline clinical characteristics. Compared with the published SIRIUS[3] and TAXUS IV[4] studies, the proportion of subjects with diabetes in this trial is slightly higher (24% in TAXUS IV and 26% in SIRIUS), and reference diameter (2.76 mm in TAXUS IV and 2.81 mm in SIRIUS) and lesion length are similar (13.4 mm in TAXUS IV and 14.4 mm in SIRIUS).

The effectiveness and safety results for Endeavor and Taxus are presented in the Table 6.5-4 below. Study results show that the two treatment arms were comparable with respect to baseline demographics and clinical characteristics. Clinical data were available on 99.5% (N=1541), 98.5% (N=1525), and 95.2% (N=1474) of subjects at 30, 180, and 270 days, respectively (Table 1a). Baseline quantitative coronary analysis (QCA) was performed in 99.9% (N=1546) of subjects. For the Angiographic/IVUS cohort, 85.1% (279/328) of the subjects had follow-up QCA available at 8-months post-procedure, and 46.0% (151/328) had IVUS data available for the assessment of the two pre-specified IVUS effectiveness endpoints.

6.6.3.1 Primary Clinical Endpoint Hypothesis Test

The primary clinical endpoint evaluated in this non-inferiority study was TVF, defined as the rate of the composite of cardiac death, MI, or clinically-driven TVR at 9 months post-procedure. The inferiority null hypothesis for this study assumed that the Endeavor arm had a 9 month TVF rate that exceeded that of the control (Taxus) arm by the pre-specified margin of δ (delta) or greater. The alternative hypothesis was that the Endeavor arm had a 9 month TVF rate that was less than that of the Taxus arm, or exceeded that of the control but by less than δ.

Rejection of the null hypothesis signified that the Endeavor was non-inferior to Taxus with regard to 9 month TVF. The pre-specified non-inferiority margin for this trial was 3.8%.

Specifically, the null (H_o) and alternative (H_a) hypotheses were:

$$H_o: \pi_A \geq \pi_C + \delta$$
$$H_a: \pi_A < \pi_C + \delta$$

Where π_A was the true TVF rate for Endeavor and π_C was the true TVF rate for Taxus.

[3] Moses, JW; Leon, MB; Popma, JJ; Fitzgerald, PJ; Holmes, DR; O'Shaughnessy, C; Caputo, RP; Kereiakes, DJ; Williams, DO; Teirstein, PS, Jaeger, JL; Kuntz, RE. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. The New England Journal of Medicine 2003; 349:1315-1323.

[4] Stone, GW; Ellis, SG; Cox, DA; Hermiller, J; O'Shaughnessy, C; Mann, JT; Turco, M; Caputo, R; Bergin, P; Greenberg, J; Popma, JJ; Russell, ME. A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease. The New England Journal of Medicine 2004; 350:221-331.

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The results were as follows:

- The 9-month TVF rate for Endeavor was observed to be 6.8% (50/740).
- The 9-month TVF rate for Taxus was observed to be 7.4% (54/734).

The 9-month post-procedure TVF rate in the Endeavor arm was 6.8% compared with 7.4% in the Taxus arm with an observed difference of -0.6% and a 95% Confidence Interval of the difference of [-3.2%, 2.0%]. The upper limit of the one sided 95% Confidence Interval of the difference is 1.6% and is below the protocol specified non-inferiority margin of 3.8%. The p-value of the test of the null hypothesis that the TVF rate in the Endeavor arm is greater than in the Taxus arm was 0.0005. Therefore, the non-inferiority of Endeavor to Taxus with respect to TVF rate was demonstrated in this study.

Table 6.5-3: Primary Endpoint from ENDEAVOR IV

Primary Endpoint	ENDEAVOR (N=773 Patients)	TAXUS (N=775 Patients)	One Sided 95% Upper CI	Delta	P-value*
TVF at 9 month post procedure	6.8% (50/740)	7.4% (54/734)	1.6%	3.8%	0.0005

*P-value is for the test of Non-Inferiority.

This study showed that the safety profiles of the two study devices are comparable; the Endeavor device showed statistically significantly lower in-hospital MACE, 30-day MACE and 30-day TVF. No statistically significant differences were observed for 6- and 9-month MACE and 9-month TLR and TVR.

6.6.3.2 Powered Secondary Endpoint

The study pre-specified to test the hypothesis of non-inferiority of in-segment late loss at 8 months as measured by QCA. The non-inferiority of 8 month in-segment late lumen loss was tested using a non-inferiority margin (delta) of 0.2 mm between the Endeavor arm compared to the Taxus arm. Therefore, the null hypothesis for the secondary endpoint was that the Endeavor stent had a secondary endpoint (in-segment late lumen loss) mean equal to or exceeding that of the control by 0.2 mm or more.

The alternative hypothesis was that the Endeavor stent had a mean in-segment late lumen loss less than the control Taxus stent mean plus 0.2 mm. Specifically,

$$H_o: \mu_{Endeavor} \geq \mu_{Taxus} + 0.2$$
$$H_a: \mu_{Endeavor} < \mu_{Taxus} + 0.2$$

Where $\mu_{Endeavor}$ was the mean late lumen loss for Endeavor and μ_{Taxus} was the mean late lumen loss for the control Taxus stent.

The results were as follows:

- The mean in-segment late lumen loss at 8 months in the Endeavor arm was 0.36 ± 0.47 mm (N=143).
- The mean in-segment late lumen loss at 8 months in the Taxus control arm was 0.23 mm ± 0.45 mm (N=135).

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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 90% Confidence Interval for the difference was 0.22, which exceeded the 0.2 mm pre-specified non-inferiority margin. Therefore, the secondary objective of demonstrating non-inferiority of Endeavor to Taxus with respect to in-segment late loss was not met.

In summary, the 270-day results of ENDEAVOR IV show that the well balanced randomized groups performed fairly equally in most clinical measures and that some angiographic and IVUS measures that are significantly different between treatment groups still show that the Endeavor stent system is within acceptable clinical parameters and consistent with other clinical trial data for the product.

(1) The Endeavor Zotarolimus-Eluting Coronary Stent System demonstrates safety based on the following:
   A. Device success is greater than 97% and compares favorably with Taxus.
   B. The 30-day MACE rate is significantly lower than the rate in the Taxus arm.
   C. The long term MACE rates are consistent with the Taxus arm as well as other contemporary DES results.
   D. There were relatively few instances of early or late stent thrombosis.

(2) The Endeavor Zotarolimus-Eluting Coronary Stent System demonstrates efficacy with
   A. A significant non-inferior result with regard to the primary endpoint of 9 month TVF.
   B. Clinically acceptable angiographic result regarding late loss and %DS.
   C. Acceptably low rates of angiographic binary restenosis (in-stent and in-segment).

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Table 6.5-4: Principal Effectiveness and Safety Results through 270 days for ENDEAVOR IV-ITT Set

Safety and Effectiveness Measures	ENDEAVOR (N=773 Patients)	TAXUS (N=775 Patients)	Difference [95% CI]*	P-Value*
Lesion Success	99.6% (767/770)	99.2% (766/772)	--	--
Device Success	97.3% (751/772)	97.9% (757/773)	--	--
Device Specific Procedure Success	96.5% (745/772)	95.6% (739/773)	--	--
Procedure Success	98.7% (760/770)	96.8% (747/772)	--	--
Post-Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.62±0.43 (763)	2.61±0.44 (763)	--	--
In-Segment	2.22±0.47 (770)	2.19±0.50 (772)	--	--
Post-Procedure Percent Diameter Stenosis (% DS)				
In-Stent	5.50±9.61 (763)	5.01±10.49 (763)	--	--
In-Segment	20.47±9.54 (770)	20.97±11.12 (772)	--	--
8-Month Follow-up Minimal Lumen Diameter (mm)			--	--
In-Stent	1.95±0.61 (143)	2.25±0.61 (135)	--	--
In-Segment	1.80±0.55 (144)	1.98±0.56 (135)	--	--
8-Month Follow-up Percent Diameter Stenosis (%)				
In-Stent	26.41±19.74 (143)	16.09±17.99 (135)	--	--
In-Segment	32.28±17.02 (144)	26.61±15.52 (135)	--	--
8-Month Follow-up Late Loss (mm)				
In-Stent	0.67±0.49 (142)	0.42±0.50 (135)	--	--
In-Segment	0.36±0.47 (143)	0.23±0.45 (135)	0.13 [0.02, 0.23]	0.023
8-Month Binary Restenosis				
In-Stent	13.3% (19/143)	6.7% (9/135)	--	--
In-Segment	15.3% (22/144)	10.4% (14/135)	--	--

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Safety and Effectiveness Measures (to 270 days)	**ENDEAVOR (N=773 Patients)**	**TAXUS (N=775 Patients)**	Difference [95% CI]*	P-Value*
Out-of-Hospital MACE to 270 Days	4.7% (35/740)	3.0% (22/734)	--	--
MACE to 270 Days	5.7% (42/740)	5.7% (42/734)	--	--
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%]	--
Vascular Complications	0.5% (4/740)	0.8% (6/734)	--	--
Stent Thrombosis	0.8% (6/740)	0.1% (1/734)	--	--
Acute Stent Thrombosis	0.0% (0/740)	0.0% (0/734)	--	--
Subacute Stent Thrombosis	0.4% (3/740)	0.1% (1/734)	--	--
Late Stent Thrombosis	0.4% (3/740)	0.0% (0/734)	--	--
Cerebrovascular Accident (CVA)	0.7% (5/740)	0.5% (4/734)	--	--
Perforation	0.1% (1/740)	0.4% (3/734)	--	--
Target Vessel Revascularization	5.5% (41/740)	5.0% (37/734)	0.5% [-1.8%, 2.8%]	--
Target Lesion Revascularization	4.2% (31/740)	2.7% (20/734)	1.5% [-0.4%, 3.3%]	--
Target Vessel Failure	6.8% (50/740)	7.4% (54/734)	-0.6% [-3.2%, 2.0%]	0.685

*Confidence Intervals and p-values are provided only for powered endpoints. Confidence Intervals are provided only for components of powered endpoints.

Kaplan-Meier Estimate	**ENDEAVOR (N=773 Patients)**	**TAXUS (N=775 Patients)**	**P-Value***
TLR-Free at 270 days	95.8%	97.3%	--
TVR-Free at 270 days	94.4%	95.0%	--
TVF-Free at 270 days	93.3%	92.8%	0.626
MACE-Free at 270 days	94.4%	94.5%	--

*P-values provided only for powered endpoints.

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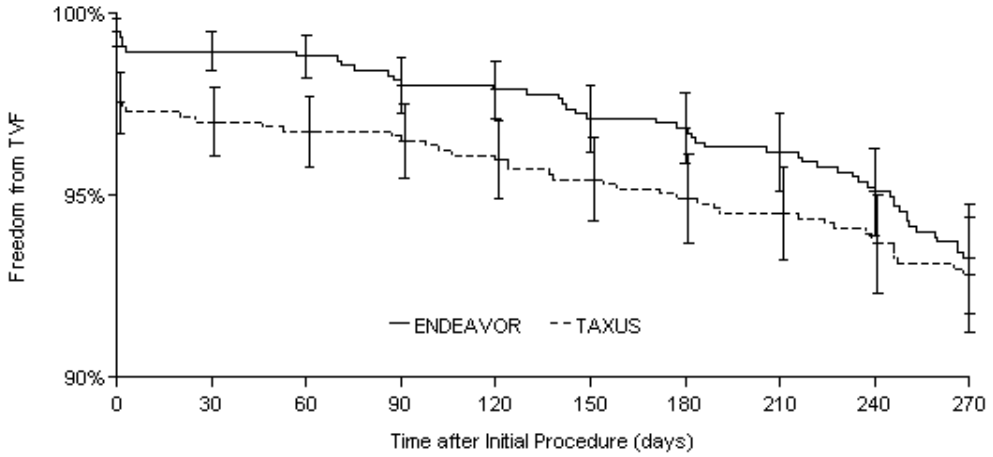

TVF	0	7	14	21	30	60	90	120	150	180	210	240	270
ENDEAVOR													
# Entered	773	769	760	760	760	756	750	744	743	736	728	718	703
# Censored	0	5	0	0	4	5	0	0	1	6	5	7	118
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	4	4	0	0	0	1	6	1	6	2	5	8	13
% Survived	99.5%	99.0%	99.0%	99.0 %	99.0 %	98.8 %	98.0 %	97.9 %	97.1 %	96.9 %	96.2 %	95.1 %	93.3%
SE	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.6%	0.6%	0.7%	0.8%	1.0%
TAXUS													
# Entered	775	755	748	748	747	744	735	732	726	720	710	694	683
# Censored	1	5	0	0	2	7	1	2	2	6	13	5	105
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	19	2	0	1	1	2	2	4	4	4	3	6	6
% Survived	97.5%	97.3%	97.3%	97.2 %	97.0 %	96.8 %	96.5 %	96.0 %	95.4 %	94.9 %	94.5 %	93.7 %	92.8%
SE	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.7%	0.7%	0.8%	0.8%	0.8%	0.9%	1.0%

Figure 6.5-2: Survival Free from Target Vessel Failure at 270 days (ITT)

6.6.3.3 Other Analysis

Acute procedural results and device performance:
Device success was achieved in 97.3% and 97.9% of Endeavor and Taxus subjects respectively.

Procedural success was shown to be 98.7% (760/770) for Endeavor and 96.8% (747/772) for the Taxus arm. In-hospital MACE occurred in 0.9% of subjects in the Endeavor arm and 2.6% of subjects in the Taxus arm.

Thirty-day MACE and early stent thrombosis (defined as occurring <30 days post-procedure):
By 30 days, MACE had occurred in 1.2% of subjects in the Endeavor arm and 3.0% of subjects in the Taxus arm. The observed rates for both arms are consistent with the results of DES devices for other contemporary stent trials. The difference in 30-day non-Q wave MI rate was 0.5% (4/770) for Endeavor vs. 2.2% (17/771) for Taxus. The 30-day

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percentage of TVF was 1.0% (8/770) for Endeavor compared with 3.0% (23/771) for the Taxus group [3.0% (23/771)].

Early stent thrombosis occurred in 0.3% of subjects overall [0.4% (3/770) Endeavor vs. 0.3% (2/771) Taxus]. Early target vessel repeat revascularization was infrequent, occurring in 0.6% of subjects overall [0.4% (3/770) Endeavor vs. 0.9% (7/771) Taxus].

Six-month MACE and late stent thrombosis:
By 180 days post-procedure, subjects experiencing MACE events occurred in 3.0% (23/766) of Endeavor subjects and 4.3% (33/759) of Taxus subjects, a result that did not achieve statistical significance. Between day 30 and 180 days, subjects in the Endeavor arm experienced the following new MACE events: 1 cardiac and 1 non-cardiac death, 4 non-Q wave MIs (NQWMI), and 10 new TLR events. For Taxus subjects, the new events were 4 deaths (2 cardiac and 2 non-cardiac) and 8 additional TLRs. There were no statistically significant differences in the component events of MACE between the two groups at 180 days. Three subjects experienced late stent thrombosis in the Endeavor group, but the difference between groups at 180 days did not achieve statistical significance. The rates for TVF at 180 days were 3.1% (24/766) and 5.1% (39/759), for the Endeavor and Taxus groups, respectively.

Eight-month Follow-up Angiographic and IVUS Results:
IVUS Cohort Analysis
For the 8 Month Angio/IVUS subset, all subjects were required to have the 8 Month IVUS follow-up. Of the 328 subjects, 202 had the follow-up within the protocol specified time window, 5 subjects had their follow-up earlier than the protocol specified window, 50 subjects had their follow-up performed beyond the protocol specified window, and 70 subjects had no follow-up IVUS performed, and one subject died before having follow-up IVUS.

Angiographic and IVUS Results
Of the 328 subjects enrolled in the angiographic/IVUS cohort, 8 Month angiograms were available for 87.2% (286/328) of the subjects, of which 279 subjects had qualifying angiograms. With respect to IVUS, 73.8% (242/328) of the cohort had IVUS performed; only 46% (151/328) of subjects had evaluable data for the 8-months evaluation of the secondary endpoints of interest (neointimal hyperplastic volume and percent volume obstruction). All subjects in this cohort had one lesion treated during the index procedure.

6.6.4 Conclusions

Non-inferiority of the Endeavor Zotarolimus-Eluting Coronary Stent System to the Taxus Paclitaxel-Eluting Coronary Stent System was demonstrated on the primary clinical endpoint of Target Vessel Failure. Based on the totality of acute procedural results, 8-month angiographic and IVUS, and 9-month clinical follow-up the Endeavor Zotarolimus-Eluting Coronary Stent System has demonstrated similar clinical safety and efficacy outcomes and acceptable overall angiographic results compared with the Taxus Paclitaxel-Eluting Coronary Stent System.

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6.7 ENDEAVOR Pharmacokinetic (PK) Clinical Study Summary

6.7.1 Clinical Study Description

Endeavor US PK Registry was a prospective, multi-center, single arm, open-label trial to evaluate Pharmacokinetics and Safety of the Medtronic ENDEAVOR Zotarolimus-Eluting Coronary Stent System in *De Novo* Native Coronary Artery Lesions.

6.7.1.1 Study Design

The study was designed as a prospective, multi-center, single arm, open-label study.

6.7.1.2 Study Objectives

To evaluate the pharmacokinetics and safety associated with Drug Zotarolimus administered using the Medtronic ENDEAVOR Zotarolimus-Eluting Coronary Stent System in the treatment of single *de novo* lesions in native coronary arteries between 2.5 - 3.5 mm in diameter and ≤ 27mm lesion length

6.7.1.3 Primary Endpoints

The primary endpoints evaluated in this study are the pharmacokinetic parameters of the drug Zotarolimus on the Endeavor stent including: maximum observed blood concentration (Cmax), time to maximum concentration (Tmax), area under the blood concentration-time curve (AUC), and the value of total clearance (CL) corresponding to AUC. Additional pharmacokinetic parameters (e.g. half-life, volume of distribution, etc) were also assessed.

6.7.1.4 Secondary Endpoints

The secondary endpoints assessed in this study include

- Acute success (device, lesion, and procedure)
- Major adverse cardiac event (MACE) rate at 30 days, 6, 9 and 12 months post-procedure
- Target site revascularization (TSR), target vessel revascularization (TVR) and target vessel failure (TVF) rate at 9 months post-procedure
- Following additional parameters will be assessed for patients receiving overlapping stents at the target lesion.
- Angiographic parameters (in-stent and in-segment) at 8 months post-procedure, including:
    - Late Lumen Loss
    - Late Loss Index
    - Angiographic Binary Restenosis (ABR) rate
    - Minimum Luminal Diameter (MLD)
    - Percent Diameter Stenosis (%DS)
- Neointimal Hyperplastic Volume at 8 months post-procedure as measured by intravascular ultrasound (IVUS)

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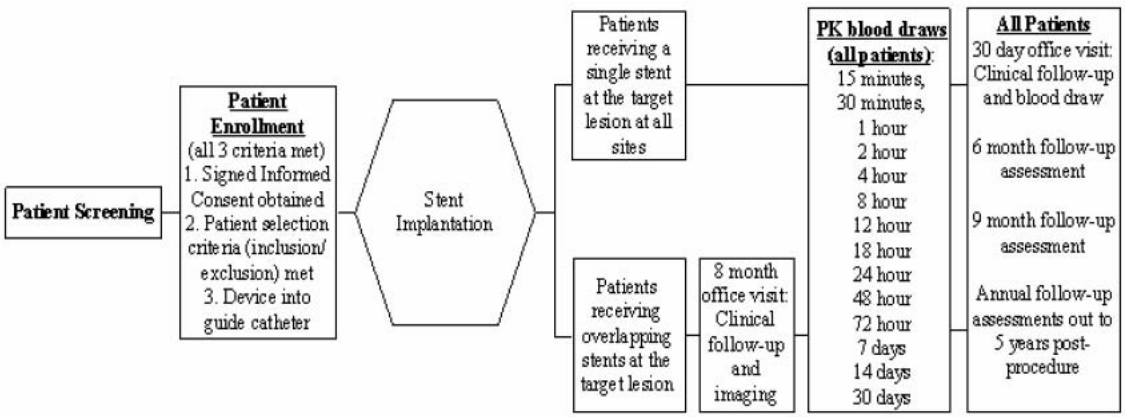
6.7.1.5 Patient/Study Population

General Inclusion Criteria

Candidates were considered for inclusion if the following conditions were met:

1. The patient was ≥18 years of age.
2. The patient had clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, or a positive functional study.
3. The patient was an acceptable candidate for percutaneous transluminal coronary angioplasty (PTCA), stenting, and emergent coronary artery bypass graft (CABG) surgery.
4. Female patients of childbearing potential must have had a negative pregnancy test within seven (7) days before the procedure.
5. The patient or patient's legal representative had been informed of the nature of the study and agreed to its provisions and had provided written informed consent as approved by the Institutional Review Board of the respective clinical site.
6. The patient agreed to return for all required post-procedure follow-up visits.



Angiographic Inclusion Criteria

Candidates met the following angiographic criteria to be considered for inclusion in the study:

The target lesion/vessel must have met the following criteria:

1. The target lesion was a single *de novo* lesion in a native coronary artery.
2. The target lesion was ≤27 mm in length.
3. The target vessel had a stenosis of ≥50% and <100%.
4. The target vessel had a thrombolysis in myocardial infarction (TIMI) flow 2 or greater.
5. The target vessel reference diameter was ≥2.5 mm and ≤3.5 mm.

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Note: Measurements may have been made by careful visual estimate, on-line QCA, or intravascular ultrasound (IVUS).

General Exclusion Criteria

Candidates were excluded from the study if any of the following conditions were present:

1. A known hypersensitivity or contraindication to aspirin, heparin or bivalirudin, ticlopidine or clopidogrel, cobalt, nickel, chromium, molybdenum, polymer coatings (e.g., Phosphorylcholine), or a sensitivity to contrast media, which could not be adequately pre-medicated.
2. History of an allergic reaction or significant sensitivity to drugs such as Zotarolimus, rapamycin, tacrolimus, everolimus, or any other analogue or derivative.
3. A platelet count <100,000 cells/mm³ or >700,000 cells/mm³, or a white blood count (WBC) <3,000 cells/mm³.
4. A serum creatinine level >2.0 mg/dl within seven days prior to index procedure.
5. Evidence of an acute myocardial infarction within 72 hours of the intended index procedure (defined as: Q wave or non-Q wave myocardial infarction having creatine kinase (CK) enzymes >2X the upper laboratory normal with the presence of a creatine kinase myocardial-band isoenzyme (CK-MB) elevated above the Institution's upper limit of normal).

   Note: Patients with evidence or suspicion of an acute MI must have had CK and CK-MB labs drawn and the results reviewed prior to randomization.
6. Previous PCI of the target vessel within 9 months pre-procedure.
7. Planned PCI of any vessel within 30 days post-procedure.
8. During the index procedure, the target lesion required treatment with a device other than PTCA prior to stent placement (such as, but not limited to, cutting balloon, any atherectomy, any laser, thrombectomy, etc.).
9. History of a stroke or transient ischemic attack (TIA) within the prior 6 months.
10. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months.
11. History of bleeding diathesis or coagulopathy or would refuse blood transfusions.
12. Concurrent medical condition with a life expectancy of less than 12 months.
13. Any previous or planned treatment of the target vessel with anti-restenotic therapies including, but not limited to, brachytherapy.
14. Currently participating in an investigational drug or another device study that had not completed the primary endpoint or that clinically interfered with the current study endpoints; or required coronary angiography, intravascular ultrasound (IVUS) or other coronary artery imaging procedures.

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Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, were not considered investigational trials.

15. Documented left ventricular ejection fraction <30% at most recent evaluation.

Angiographic Exclusion Criteria

Candidates were excluded from the study if any of the following conditions were met:

1. Target lesion was located in a native vessel distal to anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass with more than 40% diameter stenosis anywhere within the graft.
2. Previous stenting (drug-eluting or bare metal) in the target vessel unless the following conditions were met:
   a) It had been at least 9 months since the previous stenting, and
   b) The target lesion was at least 15 mm away from the previously placed stent.
3. Target vessel had other lesions with greater than 40% diameter stenosis based on visual estimate or on-line QCA.
4. The target vessel had evidence of thrombus.
5. The target vessel was excessively tortuous.
6. The target lesion had any of the following characteristics:
   a) Lesion location was aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA)
   b) Involved a side branch >2.0 mm in diameter
   c) Was at or distal to a >45º bend in the vessel
   d) Was severely calcified
   e) Involved a bifurcation.
7. Unprotected left main coronary artery disease (an obstruction greater than 50% in the left main coronary artery).

Key Baseline Characteristics

The key baseline characteristics are summarized below.

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Table 6.7-1: Key Baseline Characteristics

Key Baseline Variables	Endeavor System	
	N	%
Age (years)	43	
Mean (SD*)	64.74 ± 11.06	
Range	42-81	
Gender	43	
Male	34	(79.1%)
Female	9	(20.9%)
Race	43	
White/Caucasian	41	(95.3%)
Clinical Characteristics	N	%
History of diabetes mellitus	18/43	(41.9%)
History of hypertension	39/43	(90.7%)
Lesion Characteristics	N	Mean (SD*)
Reference Vessel Diameter (mm)	43	2.54 ± 0.45
Lesion length (mm)	43	15.02 ± 5.62
	N	%
Discreet (< 10mm)	8/43	18.6%
Tubular (10-19.9 mm)	26/43	60.5%
Diffuse (≥20mm)	9/43	20.9%
ACC/AHA lesion class	N	%
A	1/43	2.3%
B1	13/43	30.2%
B2	17/43	39.5%
C	12/43	27.9%

* SD = Standard Deviation.

Enrollment/ Randomization

Study Period (enrollment): 24 January 2006 to 14 April 2006

ENDEAVOR US PK Registry was non-randomized study and all patients were planned to be treated with the Endeavor stent.

Antiplatelet Medications

All patients were to have received a minimum of 75 mg of aspirin daily indefinitely, and 75 mg daily of clopidogrel for at least 3 months. If a patient develops a sensitivity or intolerance to clopidogrel subsequent to enrollment, the patient may be given ticlopidine (250 mg BID). Patients with a known hypersensitivity or contraindication to aspirin, clopidogrel, or ticlopidine were to be excluded from the study.

Patient Follow-up

Blood samples (5 mL) for zotarolimus assay were collected by venipuncture within 15 minutes prior to the start of the Percutaneous Transluminal Coronary (balloon) Angioplasty (PTCA) procedure (0 hour) and at 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 48 and 72 hours and at 7, 14 and 30 days post-procedure.

Clinical follow-up was performed for all patients during an office visit at 30 days. Angiography, IVUS and a clinical follow-up was conducted at 8 months for patients receiving overlapping stents at the target lesion. Follow-up assessments for all patients were performed at 6- and 9-months, and then will be conducted at 12 month and annually thereafter out to 5 years post-procedure. Follow-up assessments may be conducted by telephone, email, and/or office visits, unless stated otherwise. Adverse events up to 9

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months are to be reported. Subsequently, SAEs (including MACE) and device-related adverse events are to be reported to 5 years. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. A Clinical Events Committee (CEC) adjudicates all clinical endpoint events. A Data Safety Monitoring Board (DSMB) reviews the study on a regular basis.

Schedule of Treatments and Assessments

A summary of treatments and assessments is provided below.

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Table 6.7-2: Schedule of Treatments and Assessments

Index Hospitalization										
Event	Screening/ Pre-procedure			Proce -dure	Post-proce-dure[1]	30 Day	6 Month	8 Month	9 Month	1-5 Years Annually
	Prior to proce-dure	Prior to procedure within: 7 day	Prior to procedure within: 72 hour			Clinic Visit	Patient Contact[2]	Clinic Visit[3]	Patient Contact[2]	Patient Contact[2]
Informed Consent signed	X									
Medical and cardiac history	X									
Angina status	X					X	X	X	X	X
Pregnancy test[4]		X								
Chemistry panel		X								
CBC with differential (including eosinophils)		X				X				
Lipid panel		X								
Liver function test		X								
12 lead ECG		X			X Within 24 hours					
CK and CK-MB			X		X 6-8 hours 12-16 hours 20-24 hours					
ACT measurements				X						
QCA	X			X				X[3]		
IVUS				X[3]				X[3]		
Zotarolimus[5] Blood Collection			X[5]	X[5]	X[5]	X[5]				
AE monitoring				X	X	X	X	X	X	X SAEs only
Medication regimen[6]	X Within 24 hours			X	X	X	X	X	X	X[7]

[1] Post-procedure is defined as post deployment balloon inflation/stent implantation.
[2] Patient contact includes phone calls, email, and/or office visit.
[3] Angiography/IVUS assessment for patients receiving overlapping stents.
[4] For women of childbearing potential only.
[5] At baseline (Within 60 minutes prior to stent implantation) and post-implant (time 0 is defined as delivery balloon inflation) at: 15 min, 30 min, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 18 hours, 24 hours, 48 hours, 72 hours, 7 days, 14 days, and 30 days.
[6] Refer to the Concomitant Medication section in the study report (Appendix 6).
[7] Antiplatelet/anticoagulation medications only.

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6.7.1.6 Patient Accountability

There were a total of six sites in the United States that enrolled a total of 43 patients from January 24, 2006 through April 14, 2006. Three other sites were activated to begin enrollment but did not enroll any patients.

ENDEAVOR PK
Patient Flowchart

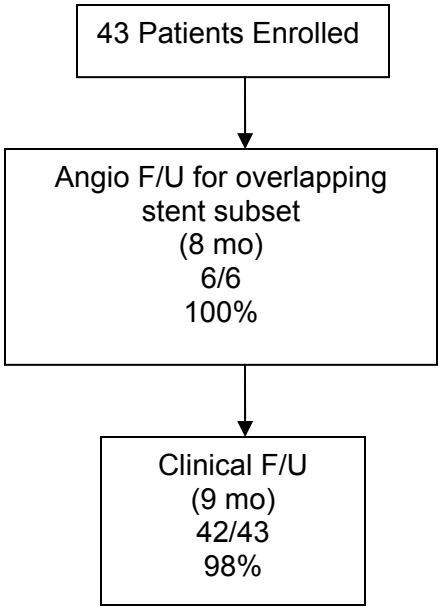

Figure 6.7-1: 1 Patient Flowchart for ENDEAVOR PK at 9 Months

6.7.2 Statistical Methodology

6.7.2.1 Clinical Trial Objectives and Hypotheses

ENDEAVOR US PK Registry was a prospective, multi-center, single-arm, open-label trial designed to evaluate the pharmacokinetics (PK) and safety of the Endeavor Zotarolimus-Eluting Coronary Stent System in *de novo* native coronary artery lesions.

This trial included six (6) study sites in the United States, forty-three (43) patients were enrolled in the study.

Computations for all results were performed using SAS Version 8.2 or higher computer software package.

Descriptive statistics are provided. The statistics for continuous variables included numbers of known values, the mean, median, standard deviation, 1st and 3rd quartiles, and minimum and maximum values. Categorical variables were described with counts and percentages. Percentages were rounded to one decimal place.

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Analysis Samples

Per Protocol (PP): For this study, all patients who signed the written informed consent, met the study entry criteria and received the study stent were counted in the primary analysis.

Safety Set: All patients who signed the written informed consent, met the study entry criteria but did not receive the study stent because the procedure was stopped prior to the study device being delivered beyond the guide catheter; these patients were followed-up for 30 days post-procedure for safety measures. There were no patients who fell into this group.

Overlapping Stent Subset: Included at least 6 patients with overlapping stents in the target lesion. These patients will undergo follow-up angiography and IVUS at 8-months post-index procedure and will be analyzed in future reports.

Primary Endpoint

ENDEAVOR US PK was a prospective, single-arm, open-label, multicenter safety and pharmacokinetic trial. Pharmacokinetic evaluation was conducted on all patients participating in the ENDEAVOR US PK trial.

Forty-three (43) patients received the zotarolimus eluting Endeavor stent. The length of stent was dependent on patient's vessel lesion length. The following table summarizes the stent length assignment in the study. The dose of zotarolimus was calculated as total implanted stent length (mm) multiplied by 10, since the amount of zotarolimus coated on a stent was 10 μg/mm.

Table 6.7-3: Zotarolimus Dose

Dose Group	Number of Patients	Stent length[$] (mm)	Total Zotarolimus Dose (μg)
I	1	9	90
II	1	8 + 8*	168
III[‡]	24	18 or 9 +9[#]	180
IV[a]	6	24	240
V	2	18 + 9	270
VI[a]	7	30	300
VII	1	18 + 9 + 9	360
VIII	1	24 + 18	420

$ Length of first stent + second stent + third stent.

* Subject 663405 (Group II; 168 μg of zotarolimus) the first stent (18 mm) was unable to cross was removed and then two 8.4 mm stents were implanted.

\# Subject 663402 (Group III; 180 μg of zotarolimus) had the first stent (18 mm) was unable to cross, was removed and then two 9 mm stents were implanted.

‡ Primary dose groups (≥ 3 patients).

The primary endpoints evaluated in this study are the pharmacokinetic parameters of the drug zotarolimus on the Endeavor stent including: maximum observed blood concentration (Cmax), time to maximum concentration (Tmax), area under the blood concentration-time curve (AUC), and the value of total clearance (CL) corresponding to AUC. Additional pharmacokinetic parameters may be assessed if deemed appropriate (e.g., half life, volume of distribution, etc.)

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For each pharmacokinetic variable and for the zotarolimus blood concentration at each scheduled time of sampling, descriptive statistics were provided for each Endeavor stent length utilized in patients. The $AUC0_{-24}$ and $AUC0_{-72}$ values were also calculated and summarized for each dose level for corresponding AUCτ values in the ENDEAVOR II PK subset and in the 300 µg group from Study M01-336[1]

For investigating dose proportionality across dose ranges, an analysis of covariance (ANCOVA) was performed on β and the logarithms of dose-normalized Cmax and AUCs. The explanatory variables included in the ANCOVA model were dose level and the variable or variables selected by the above linear regression variable selection procedure. Within the ANCOVA, three tests that had good power for testing for dose proportionality were performed on the effect of dose levels. The primary test investigated dose proportionality across 180, 240, and 300 µg. In the secondary test, the ANCOVA was performed across a) 180, 240, 270, and 300 µg, and β) across the entire dose range from 90 µg to 420 µg. The point estimate and 95% confidence interval were also provided for β, Cmax, and AUCs for each dose level. Linear regression was performed on the terminal phase elimination rate constant (β), logarithms of dose-normalized Cmax and dose-normalized AUC to explore for explanatory variables. The explanatory variables of interest were dose, age, body weight, gender, Creatinine clearance (CL_{CR}), and blood urea nitrogen (BUN). A linear model was used initially including the above explanatory variables. The dummy variables for dose were forced to be included in the final model and other explanatory variables were eliminated from the model in a stepwise fashion using a significance level of 0.15 as the criterion, that is, the variable was eliminated if the p-value of the variable was not smaller than 0.15. The statistical significance of the covariate on the pharmacokinetic parameter was evaluated at a p-value of 0.05.

Analysis on Baseline Characteristics:
All clinically relevant baseline variables are tabulated. Categorical variables are reported using contingency tables, and continuous variables are reported by giving the number of known values, the mean and standard deviation.

6.7.3 Results

The pharmacokinetics of zotarolimus delivered from the Endeavor Zotarolimus-Eluting Coronary Stent System has been determined in patients with coronary artery disease after implantation in the ENDEAVOR US Pharmacokinetic trial. The dose of zotarolimus was calculated from the total implanted stent length; the parameters determined from these patients are provided in Table 6.7-4.

[1] Palaparthy R. An escalating, intravenous-dose study of the safety and pharmacokinetics of ABT-578 in healthy patients (Protocol M01-336) [internal scientific report R&D/02/339], Abbott Park, Illinois: Abbott Laboratories, 2002.

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Table 6.7-4: Zotarolimus Pharmacokinetics in Patients after Implantation of Endeavor-Zotarolimus Eluting Coronary Stents

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	1.584	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
$AUC_{0\text{-last}}$	(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
$AUC_{0\text{-inf}}$	(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
B	(1/h)	0.010	0.013	0.012 ± 0.003	0.012 ± 0.002	0.010	0.012 ± 0.003	0.010	0.012
t½‡	(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
Cmax Maximum blood concentration
Tmax Time to Cmax
$AUC_{0\text{-last}}$ Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration
$AUC_{0\text{-inf}}$ AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).
t½ Harmonic mean half-life
CL/F Mean apparent clearance

a. Primary dose groups
‡ Harmonic mean ± pseudo-standard deviation
† No SD was reported when N ≤ 2
§ Mean only
# N = 6

The results in Table 6.7-4 show that pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 2), 180, 240 and 300 µg, following the implantation of Endeavor zotarolimus-eluting stents as illustrated by dose proportional increases in Cmax, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$. Mean apparent clearance and harmonic mean half-life for the primary dose groups ranged from 2.8 to 3.5 L/h and 57.5 to 59.7 h, respectively. The mean time to reach peak systemic concentration (T_{max}) ranged from 1.2 to 1.5 h after stent implantation.

The 30-, 180- and 270-day safety results are presented in Table 1. The effectiveness results showed that the lesion success rate was 100.0% (43/43). The device success rate was 97.7% (42/43), the procedure success rate was 95.3% (41/43) and the device-specific procedure success was also 95.3% (41/43). Major Adverse Cardiac Event (MACE) rate to 30 days post-procedure was 4.7% (2/43), to 180 days was 7.0% (3/43), and to 270 days was 7.1% (3/42). Target site (or lesion) revascularization at 9 months post-procedure was 2.4% (1/42); target vessel revascularization at 9 months post-procedure was 7.1% (3/42), and target vessel failure at 9 months post-procedure was 11.9% (5/42).

Angiographic parameters (in-stent) for the 6 patients who received overlapping stents at 8 months post-procedure showed that the percent diameter stenosis (%DS) was 33.56 ± 23.59, late lumen loss was 0.73 ± 0.65 (mm), late loss index was 0.46 ± 0.33 (mm),

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angiographic binary restenosis (ABR) rate was 16.7% (1/6), and the minimum lumen diameter was 1.69 ± 0.57 (mm). Angiographic parameters (in-segment) for the 6 patients who received overlapping stents at 8 months post-procedure showed that the percent diameter stenosis (%DS) was 36.34 ± 20.85, late lumen loss was 0.70 ± 0.72 (mm), late loss index was 0.41 ± 0.31 (mm), angiographic binary restenosis (ABR) rate was 16.7% (1/6), and the minimum lumen diameter was 1.62 ± 0.51.

Though only two measures were available for analysis, the neointimal hyperplastic volume (mm^3) at 8 months post-procedure as measured by intravascular ultrasound for patients who received overlapping stents was 52.41 ± 5.62 and the volume obstruction (%) was 21.41 ± 0.43.

Table 6.7- 5: Principal Effectiveness and Safety Results – Per Protocol Set

Safety and Effectiveness Measure	ENDEAVOR PK Registry (N= 43 Patients)
Lesion Success	100.0% (43/43)
Device Success	97.7% (42/43)
Procedure Success	95.3% (41/43)
Device-Specific Procedure Success	95.3% (41/43)
Post-Procedure Minimal Lumen Diameter (MLD, in mm)	
In-Stent	2.44±0.40 (43)
In-Segment	2.15±0.47 (43)
Post-Procedure Percent Diameter Stenosis (% DS)	
In-Stent	5.38±8.55 (43)
In-Segment	17.56±6.88 (43)

Safety Measure to 30 Days	ENDEAVOR PK Registry (N= 43 Patients)
In-Hospital MACE	4.7% (2/43)
Out-of-Hospital MACE to 30 days	0.0% (0/43)
MACE to 30 days	4.7% (2/43)
Death	2.3% (1/43)
Vascular Complications	9.3% (4/43)
Acute Stent Thrombosis	0.0% (0/43)
Subacute Stent Thrombosis	0.0% (0/43)
Cerebrovascular Accident (CVA)	0.0% (0/43)
Perforation	0.0% (0/43)
Target Vessel Revascularization	0.0% (0/43)
Target Lesion Revascularization	0.0% (0/43)
Target Vessel Failure	4.7% (2/43)

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Safety Measure to 180 Days	ENDEAVOR PK Registry (N= 43 Patients)
Out-of-Hospital MACE to 180 days	2.3% (1/43)
MACE to 180 days	7.0% (3/43)
Death	4.7% (2/43)
Vascular Complications	11.6% (5/43)
Acute Stent Thrombosis	0.0% (0/43)
Subacute Stent Thrombosis	0.0% (0/43)
Cerebrovascular Accident (CVA)	0.0% (0/43)
Perforation	0.0% (0/43)
Target Vessel Revascularization	2.3% (1/43)
Target Lesion Revascularization	0.0% (0/43)
Target Vessel Failure	9.3% (4/43)

Safety Measure to 270 Days	ENDEAVOR PK Registry (N= 43 Patients)
Out-of-Hospital MACE to 270 days	4.8% (2/42)
MACE to 270 days	7.1% (3/42)
Death	4.8% (2/42)
Vascular Complications	11.9% (5/42)
Acute Stent Thrombosis	0.0% (0/42)
Subacute Stent Thrombosis	0.0% (0/42)
Cerebrovascular Accident (CVA)	0.0% (0/42)
Perforation	0.0% (0/42)
Target Vessel Revascularization	7.1% (3/42)
Target Lesion Revascularization	2.4% (1/42)
Target Vessel Failure	11.9% (5/42)

Kaplan-Meier Estimate	ENDEAVOR PK Registry (N= 43 Patients)
MACE-Free at 270 days	93.0%
TLR-Free at 270 days	97.3%
TVR-Free at 270 days	92.5%
TVF-Free at 270 days	88.3%

6.7.3.1 Other Analysis

Comparison of the Pharmacokinetics of Zotarolimus from Endeavor-II PK and Endeavor US PK

ENDEAVOR-II (PK subset) was the first study to examine the pharmacokinetic profile of zotarolimus from a drug eluting stent following implantation in patients with native coronary artery lesions. The blood sampling for pharmacokinetics in this study was conducted up to 144 hrs after implantation. In most patients, over the stent dose range studied, the blood concentrations of zotarolimus were below the LLOQ (0.2 ng/mL) beyond 24 hours following stent implantation. Due to the shorter sampling time schedule and less sensitive assay method, the estimates of CL/F and $t_{½}$were not considered accurate. Therefore, the comparison of these estimates from Endeavor-II PK and

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Endeavor US PK could not be determined. However, C_{max}, T_{max} and AUC_{0-24} were the only pharmacokinetic parameters that could be compared as shown in the following table.

Table 6.7-6: Comparison of Zotarolimus Pharmacokinetics between Endeavor US PK and Endeavor-II PK Studies

	Endeavor US PK Study			Endeavor-II PK Study		
PK Parameters (units)	**180 µg (N = 24)**	**240 µg (N = 6)**	**300 µg (N = 7)**	**180 µg (N = 10)**	**240 µg (N = 22)**	**300 µg (N = 15)**
C_{max} (ng/mL)	1.513 ± 0.616	1.830 ± 0.210	2.658 ± 0.998	1.64 ± 0.57	1.84 ± 0.41	2.45 ± 0.40
T_{max} (h)	1.2 ± 0.6	1.4 ± 1.3	1.48 ± 1.29	1.18 ± 0.48	1.03 ± 0.54	0.90 ± 0.52
AUC_{0-24} (ng•h/mL)	20.02 ± 6.45	23.68 ± 3.57	31.45 ± 9.17	25.1 ± 7.4	24.6 ± 6.8	31.7 ± 6.0

6.7.4 Conclusions

The pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 2), 180, 240 and 300 µg, following the implantation of zotarolimus-eluting Endeavor stents as illustrated by dose proportional increases in C_{max}, AUC_{0-last} and AUC_{0-inf}. Mean apparent clearance and harmonic mean half-life for the primary dose groups ranged from 2.8 to 3.5 L/hr and 57.5 to 59.7 hr, respectively. The mean T_{max} ranged from 1.2 to 1.5 h after stent implantation. The pharmacokinetics of zotarolimus from this study are similar to those observed from the Endeavor-II study. Additionally, this study shows that the Endeavor stent releases zotarolimus gradually into the systemic circulation without any evidence of dose dumping.

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6.8 ENDEAVOR JAPAN Clinical Study Summary

6.8.1 Clinical Study Description

ENDEAVOR Japan is a prospective, multi-center (Japan) single-arm open-label, study for Clinical Evaluation of MDT-4104 Zotarolimus-Eluting Coronary Stent[1] in *De Novo* Native Coronary Artery Lesions.

6.8.1.1 Study Design

The study was designed as a prospective, multi-center, single-arm, open-label study.

6.8.1.2 Study Objectives

To evaluate the safety and efficacy of the MDT-4104 Stent for the treatment of single *de novo* lesions in native coronary arteries.

6.8.1.3 Primary Endpoints

Target Vessel Failure (TVF) rate at 9 months post-procedure - Target vessel revascularization, recurrent Q- or NQMI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel.

6.8.1.4 Secondary Endpoints

- Device Success
- Lesion Success
- Procedure Success
- Major adverse cardiac events (MACE) – 30 days, 6 and 9 months post-procedure
- Clinically-driven target lesion revascularization (TLR) – 9 months post-procedure
- Clinically-driven target vessel revascularization (TVR) – 9 months post-procedure
- In stent and in segment late loss – 8 months post-procedure (measured by Quantitative Coronary Angiography [QCA])
- In stent and in segment binary angiographic restenosis (50% diameter or more stenosis) – 8 months post-procedure (measured by QCA)
- In stent and in segment minimal lumen diameter (MLD) – 8 months post-procedure (measured by QCA)

[1] Endeavor Zotarolimus-Eluting Coronary Stent System was previously known as MDT-4104 Drug Eluting Coronary Stent

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6.8.1.5 Patient/Study Population

General Inclusion Criteria

Candidates were considered for inclusion if the following conditions were met:

1. Patient ≥ 20 years of age
2. Patient had clinical evidence of ischemic heart disease, stable or unstable angina (according to the Canadian Cardiovascular Society [CCS] classification), silent ischemia, or a positive cardiac function study.
3. Patient was an acceptable candidate for percutaneous transluminal coronary angioplasty (PTCA), stenting, and emergent coronary artery bypass grafting (CABG).
4. Patient had tolerated at least 14 days of 200 mg b.i.d. ticlopidine (i.e., a total of 200 mg per day divided into two daily doses of 100 mg each) and was expected to be able to tolerate ticlopidine for at least 3 months following the coronary intervention.
5. Patient or his/her legal representative was informed of the nature of the study, agreed to its provisions, and provided written consent as approved by the Institutional Review Board of the respective clinical site.
6. Patient agreed to return for all required post-procedure follow-up visits.

Angiographic Inclusion Criteria

The target lesion / vessel met the following criteria:

1. Target lesion must be a single de novo lesion that had not been previously treated with any interventional procedure.
2. Target vessel must be a native coronary artery with an inner diameter stenosis of 50% and < 100%.
3. Target vessel had a TIMI flow of 2 or greater.
4. Target lesion must be 14 mm and ≤ 27 mm in length.
5. Target vessel reference diameter must be 2.25 mm and ≤ 3.5 mm.

Measurements were made by careful visual estimate or on-line QCA.

General Exclusion Criteria

1. Premenopausal female patients
2. Patients with allergies to materials used in the study device, including cobalt, nickel-chromium, and molybdenum, or hypersensitivity to aspirin, heparin, ticlopidine or contrast media, who could not be adequately medicated prior to the procedure because of contraindications to these substances
3. Patients with a history of an allergic reaction or hypersensitivity to drugs similar to Zotarolimus (sirolimus or sirolimus analog).
4. Platelet count of < 100,000 cells/mm^3 or > 700,000 cells/mm^3, or a white blood cell count (WBC) of < 3,000 cells/mm^3
5. Creatinine level of > 2.0 mg/dl
6. History of hepatitis (active or chronic, viral, ischemic or chemically induced)

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7. History of hepatic cirrhosis or present hepatic dysfunction with aspirate amino transferase (AST) greater than 2.5 times the Institution's upper limit of normal
8. Documented left ventricular ejection fraction of < 30% prior to the procedure, unless two subsequent consecutive assessments demonstrated an ejection fraction of > 30%. Left ventriculography at the time of the procedure was acceptable to serve as the second assessment.
9. Evidence of an acute MI within 72 hours prior to the procedure (defined as: Qwave or NQMI with a CK two times the Institution's upper limit of normal and a CK-MB elevated above the Institution's upper limit of normal)
10. Previous or planned placement of a drug-eluting stent in any vessel
11. Previous or planned treatment of any vessel with percutaneous coronary intervention within 30 days pre- or post-study procedure
12. Stenting in the target vessel
13. Planned direct stenting of the target lesion
14. During the study procedure, a target lesion that required treatment with a device other than PTCA prior to stent placement (such as cutting balloon, directional coronary atherectomy (DCA), rotablator or thrombectomy)
15. History of a stroke or transient ischemic attack within 6 months prior to the procedure
16. History of active peptic ulcer or upper gastrointestinal bleeding within 6 months prior to the procedure
17. Bleeding diathesis or history of coagulopathy or the patient was expected to refuse blood transfusions
18. Concurrent medical condition with a life expectancy of less than 12 months
19. Any previous or planned treatment of the target lesion with anti-restenotic therapies
20. Was currently participating or had previously participated (within the last 30 days) in another investigational drug or investigational device study that had not completed the primary endpoint or that interfered with the current study endpoints or assessment of the current study, or required coronary angiography, intravascular ultrasound (IVUS) or other coronary artery imaging procedures. [Note: Trials requiring extended follow-up for products that had been investigational, but were commercially available by the time of study enrollment, were not considered investigational studies.]

<u>Angiographic Exclusion Criteria</u>

1) Target lesion was located in a native coronary vessel distal to anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass graft.
2) Target vessel had other lesions in addition to the target lesion, with greater than 40% inner diameter stenosis (based on visual estimate or on-line QCA)
3) Target vessel had evidence of thrombus
4) Target vessel was severely tortuous
5) Target lesion had any of the following characteristics:

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a) Lesion was a coronary ostial left main coronary lesion unprotected by coronary bypass, or located within 5 mm of the origin of the left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA)
b) Lesion involved a side branch > 2.0 mm in vessel diameter
c) Target lesion was at or proximal to a > 45º bend
d) Lesion was severely calcified

6) Left main coronary artery disease unprotected by coronary bypass (> 50% stenosis in left main coronary trunk
7) Target lesion involved a bifurcation

Key Baseline Characteristics

The key baseline characteristics are provided below.

Table 6.8-1: Key Baseline Variables

Baseline Variables	Endeavor Japan
	N
Age (years)	99
Mean (SD*)	67.7 ± 10.3
	%
Gender	
Male	67.7%
Clinical Characteristics	%
Prior MI	24.2%
Prior PCI	31.3%
History of diabetes mellitus Insulin-dependent	38.4% 10.1%
Unstable angina	4.0%
Hyperlipidemia	76.8%
Current smoker (within 30 days)	27.3%
Lesion Characteristics (mm)	Mean (SD*)
Reference Vessel Diameter	2.78 ± 0.52
Lesion length	13.90 ± 6.05
Pre-procedure MLD	0.84 ± 0.38
ACC/AHA lesion class and type	%
B2	55.6%
C	33.3%
LAD	39.4%

*SD = Standard Deviation.

Enrollment/ Randomization

Study Period (enrollment): 6 July 2005 to 19 February 2007

Eligible patients were enrolled prospectively in this study. Ninety-nine subjects were enrolled with a subset of 20 subjects who had pharmacokinetic analysis performed

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Antiplatelet medications

- Ticlopidine: 200mg b.i.d.[1] – Started 2 weeks prior to enrollment (if tolerability was unknown) and continued for a minimum of 12 weeks post-procedure.
- Aspirin: 200 mg b.i.d.[2] – Started at least 24 hours prior to the procedure and continued for a minimum of 12 weeks post-procedure.
- Aspirin 100 mg daily – Administered indefinitely after 12 weeks minimum of aspirin 200 mg b.i.d.[2], but suspended or discontinued in consideration of the safety of the patient.

[1] "b.i.d." should be interpreted according to Japanese clinical use: Ticlopidine dosage was the usual and approved dose in Japan, a total of 200 mg per day divided into two daily doses of 100 mg each.

[2] "b.i.d." should be interpreted according to Japanese clinical use: For at least 24 hours prior to, and a minimum 12 weeks after the procedure, aspirin was dosed as a total of 200 mg per day divided into two daily doses of 100 mg each.

The investigational protocol required that patients continue antiplatelet/anticoagulation therapy with ticlopidine and aspirin for at least 12 weeks post-procedure and continue aspirin indefinitely if possible. All study patients (100%; 99/99) were taking both ticlopidine and aspirin at discharge.

Patient Follow-up

Clinical follow-up was performed during an office visit for all patients at 30 days and 9 months and included assessment for angina status (Canadian Cardiovascular Society Classification of angina), all adverse events and concomitant medications, any interventional treatment that occurred since the previous contact (e.g. repeat revascularization), laboratory tests (30 days) and angiography (8 months).

Subject contact was by telephone, email and/or office visit for clinical assessment, consisting of the collection of angina status, all adverse events, all concomitant medications, and any interventional treatment that occurred since the previous contact (e.g., repeat revascularization) for all subjects, is performed at 6 and 12 months and annually thereafter out to 5 years post-procedure. All adverse events up to 9 months whether associated with the investigational product or not are to be reported. Serious adverse events also include unanticipated adverse device effects (UADE), MACE, major hemorrhagic or vascular complications and device-related adverse events and are to be reported. An independent Angiographic Core Laboratory will analyze all baseline and follow-up angiograms. A Clinical Events Committee (CEC) adjudicates all clinical events. A Data Safety Monitoring Board (DSMB) reviews the study on a regular basis.

Schedule of Treatments and Assessments

A summary of treatments and assessments is provided below.

Table 6.8-2: Schedule of Treatments and Assessments

Event	Index Hospitalization				Follow-up				
	Screen-ing	Induction Phase	Intra-Procedure	Post-Procedure	30 Day +/- 5 Days Clinic Visit	6 Month +/- 14 Days Patient Contact[1]	8 Month +/- 14 Days Angio	9 Month +/- 14 Days Clinic Visit	Annually for 5 Years Post-Procedure Patient Contact
Inclusion/Exclusion Criteria	X								
Medical and Cardiac History	X								
Previous Ticlopidine administration	X[2]								
Angina Status [3]	X[3]				X[3]	X[3]		X[3]	
Written patient consent obtained (9_month study and long-term follow-up study)	X								
Administration of Ticlopidine for 14 days (if applicable)		X[4]							
CBC/chemistry panel (including serum urea, creatinine, electrolytes)		X[5]		X[6]	X			X	
CK and CK-MB		X[5]		X[7]					
12-Lead ECG		X[5]		X[6]					
ACT Measurements (per Institution protocol)			X						
Medication regimen		X	X	X	X	X	X	X	

[1] Post-procedure CK and CK-MB were measured in the following time windows after the removal of the final catheter: 6 to 8 hours; 12 to 16 hours; 20 to 24 hours
[2] Patients for whom prior experience with Ticlopidine was confirmed via interview and who were considered able to tolerate the drug by the Sub/Investigator could be considered for exemption from the required 2 week pre-treatment.
[3] According to CCS Classification of Angina.
[4] Any patient considered intolerant of ticlopidine during the 14 day administration period or who exhibited decrease in CBC parameters to below the reference range was to be excluded from the study.
[5] Examinations performed before procedure included cardiac enzymes (CK and CK-MB), 12-lead ECG, CBC with differential (including serum urea, creatinine, electrolytes), chemistry panel. While these are in the protocol (v03.03 pg 28) as within 72 hours pre-procedure, CK/CK-MB was the only timed Inclusion/Exclusion criterion.
[6] Examinations performed within 24 hours post-procedure or at discharge, whichever came first, included CBC parameters, Chemistry panel, 12-lead ECG

Table 6.8-2: Schedule of Treatments and Assessments

Index Hospitalization					Follow-up				
Event	Screen-ing	Induction Phase	Intra-Procedure	Post-Procedure	30 Day +/- 5 Days Clinic Visit	6 Month +/- 14 Days Patient Contact[1]	8 Month +/- 14 Days Angio	9 Month +/- 14 Days Clinic Visit	Annually for 5 Years Post-Procedure Patient Contact
Adverse event monitoring			X	X	X	X	X	X	X
Angiography (QCA)		X[1]	X				X[2]		
PK Assessment [3]			X	X	X				

[1] When appropriate, coronary angiographic data taken before consent to the trial could be used for eligibility assessment for the trial
[2] All enrolled patients, underwent angiographic study at 8 months post-procedure, except for 1 patient
[3] PK analysis was obtained from 20 of the 99 study patients.

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6.8.1.6 Patient Accountability

There were a total of 11 clinical research sites in Japan that enrolled 99 patients from July 6, 2005 to February 19, 2007 for this study. There were 12 sites that received approval but one site did not enroll any patients.

All enrolled study patients (except one) underwent angiographic follow-up at eight months post-procedure.

ENDEAVOR Japan
Patient Flowchart

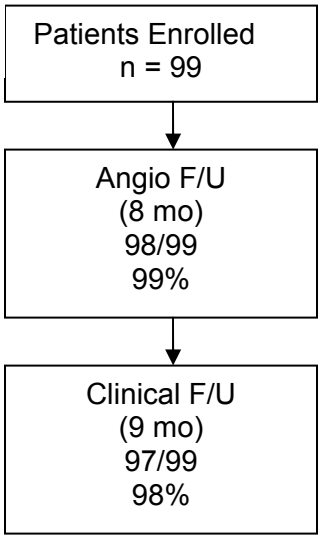

Figure 6.8-1: Patient Flowchart for Endeavor Japan at 9 Months

6.8.2 Statistical Methodology

6.8.2.1 Clinical Trial Objectives and Hypotheses

ENDEAVOR Japan was a prospective, multicenter (Japan) single-arm open-label, study for Clinical Evaluation of MDT-4104 Drug Eluting Coronary Stent in De Novo Native Coronary Artery Lesion. Eleven clinical research sites in Japan enrolled 99 patients.

All analyses were based upon “intention to treat” (ITT). For clinical follow-up events, such as MACE within the 30-day, 6-month, and 9 month periods, the denominator of the percentage was the number of “ITT” patients having an event (death, MI, TLR, TVR, stent thrombosis, major bleeding, CVA/stroke, or vascular complication) by the time of interest, or having follow up information beyond the lower window of the follow up.

Statistical comparisons were performed using two-sided significance tests unless otherwise specified. Where appropriate, 0.05 level was used to test statistical significance.

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For continuous variables, the number of patients, mean, standard deviation, minimum, and maximum were given. For categorical variables, a simple count and percentage was given. Where necessary or appropriate, other descriptive statistics and plots of descriptive statistics are provided.

All statistical analyses were performed using SAS (version 8.2). All data presented in this report were generated and validated under the guidance of the DCRI Statistical SOPs, which were reviewed and approved by the Sponsor's clinical team, data management, and biostatistics group.

Analysis Samples

The primary analysis subset is the Intent-to-Treat (ITT) population for TVF at 9 months. Pharmacokinetic evaluations were to be performed in 20 subjects.

All clinically relevant baseline and follow up variables were tabulated through 9 months follow up. Mean, standard deviation, number of evaluable patients, and range were reported for continuous variables, and count and percentage were listed for categorical variables.

All angiographic endpoints were determined from the QCA data. Although final percent stenosis was captured on the case report form (CRF), the final percent stenosis reported and used in calculation of the endpoints was derived from the QCA data.

Secondary endpoints were presented and analyzed using the same techniques as described for the baseline variables.

All analyses used CEC adjudicated results for endpoints containing any of these events unless otherwise specified.

Clinical endpoints were reported for in hospital, out-of-hospital to 30 days, out-of-hospital to 180 days, out-of-hospital to 270 days, combined (both in- and out-of-hospital) to 30 days, combined to 180 days, and combined to 270 days.

Primary Endpoint

The primary endpoint evaluated in this study was Target Vessel Failure (TVF). TVF was a composite endpoint, defined as any target vessel revascularization procedure, QMI or NQMI, or cardiac death that could not be clearly attributed to a non-target vessel. TVF included any revascularization or adverse endpoint due to restenosis of any portion of the target vessel. The study definition of TVF assumed that the entire vessel was vulnerable to late treatment failures because of guiding catheter or guide wire trauma or progression of disease remote from the treatment site.

Secondary Endpoints:

- Device Success
- Lesion Success
- Procedure Success
- Major adverse cardiac events (MACE) – 30 days, 6 and 9 months post-procedure
- Clinically-driven target lesion revascularization (TLR) – 9 months post-procedure

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- Clinically-driven target vessel revascularization (TVR) – 9 months post-procedure
- In stent and in segment late loss – 8 months post-procedure (measured by Quantitative Coronary Angiography [QCA])
- In stent and in segment binary angiographic restenosis (50% diameter or more stenosis) – 8 months post-procedure (measured by QCA)
- In stent and in segment minimal lumen diameter (MLD) – 8 months post-procedure (measured by QCA)

Analysis on Baseline Characteristics:
All clinically relevant baseline and follow up variables were tabulated. Mean, standard deviation, number of evaluable patients, and range were reported for continuous variables, and count and percentage were listed for categorical variables.

6.8.3 Results

The following table summarizes the principal efficacy and safety results.

Table 6.8-3: Principal Effectiveness and Safety Result (ITT) N = 99

Safety and Effectiveness Measures	EJ - All Patients
Lesion Success	100.0% (99/99)
Device Success	97.0% (96/99)
Procedure Success	98.0% (97/99)
Device-Specific Procedure Success	94.9% (94/99)
Post-procedure Minimal Luminal Diameter (MLD, mm)	
In-stent	2.68 ± 0.46 (99)
In-segment	2.23 ± 0.51 (99)
Post-procedure Percent Diameter Stenosis (% DS)	
In-stent	3.05 ± 11.37 (99)
In-segment	20.15 ± 9.37 (99)
Eight-month Follow-up MLD (mm)	
In-stent	2.15 ± 0.63 (98)
In-segment	2.00 ± 0.57 (98)
Eight-month Follow-up Percent Diameter Stenosis (% DS)	
In-stent	23.67 ± 17.93 (98)
In-segment	29.19 ± 15.27 (98)
Eight-month Follow-up Late Loss (mm)	
In-stent	0.53 ± 0.43 (98)
In-segment	0.23 ± 0.42 (98)
Eight-month Binary Restenosis	
In-stent	8.2% (8/98)
In-segment	8.2% (8/98)
Safety Measures (30 days)	**EJ - All Patients**
In hospital MACE	2.0% (2/99)
Out of hospital MACE to 30 days	0.0% (0/99)
MACE to 30 days	2.0% (2/99)
Death	0.0% (0/99)
Vascular Complications	0.0% (0/99)
Acute Stent Thrombosis	0.0% (0/99)
Subacute Stent Thrombosis	0.0% (0/99)
Cerebrovascular Accident (CVA)	0.0% (0/99)
Target Vessel Revascularization	0.0% (0/99)
Target Lesion Revascularization	0.0% (0/99)
Target Vessel Failure	2.0% (2/99)
Safety Measures (180 days)	**EJ - All Patients**
Out of hospital MACE to 180 days	0.0% (0/99)
MACE to 180 days	2.0% (2/99)

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Table 6.8-3: Principal Effectiveness and Safety Result (ITT) N = 99

Safety and Effectiveness Measures	EJ - All Patients
Death	0.0% (0/99)
Vascular Complications	0.0% (0/99)
Early Stent Thrombosis	0.0% (0/99)
Late Definite Stent Thrombosis	0.0% (0/99)
Cerebrovascular Accident (CVA)	0.0% (0/99)
Target Vessel Revascularization	0.0% (0/99)
Target Lesion Revascularization	0.0% (0/99)
Target Vessel Failure	2.0% (2/99)
Safety Measures (270 days)	**EJ - All Patients**
Out of hospital MACE to 270 days	3.1% (3/97)
MACE to 270 days	5.2% (5/97)
Death	0.0% (0/97)
Vascular Complications	0.0% (0/97)
Early Stent Thrombosis	0.0% (0/97)
Late Definite Stent Thrombosis	0.0% (0/97)
Cerebrovascular Accident (CVA)	0.0% (0/97)
Target Vessel Revascularization	3.1% (3/97)
Target Lesion Revascularization	3.1% (3/97)
Target Vessel Failure	5.2% (5/97)
Kaplan-Meier Estimate (270 days)	**EJ - All Patients**
MACE-free at 270 days	94.9% (90.6%, 99.3%)
TLR-Free at 270 days	97.0% (93.6%, 100.0%)
TVR-Free at 270 days	97.0% (93.6%, 100.0%)
TVF-free at 270 days	94.9% (90.6%, 99.3%)

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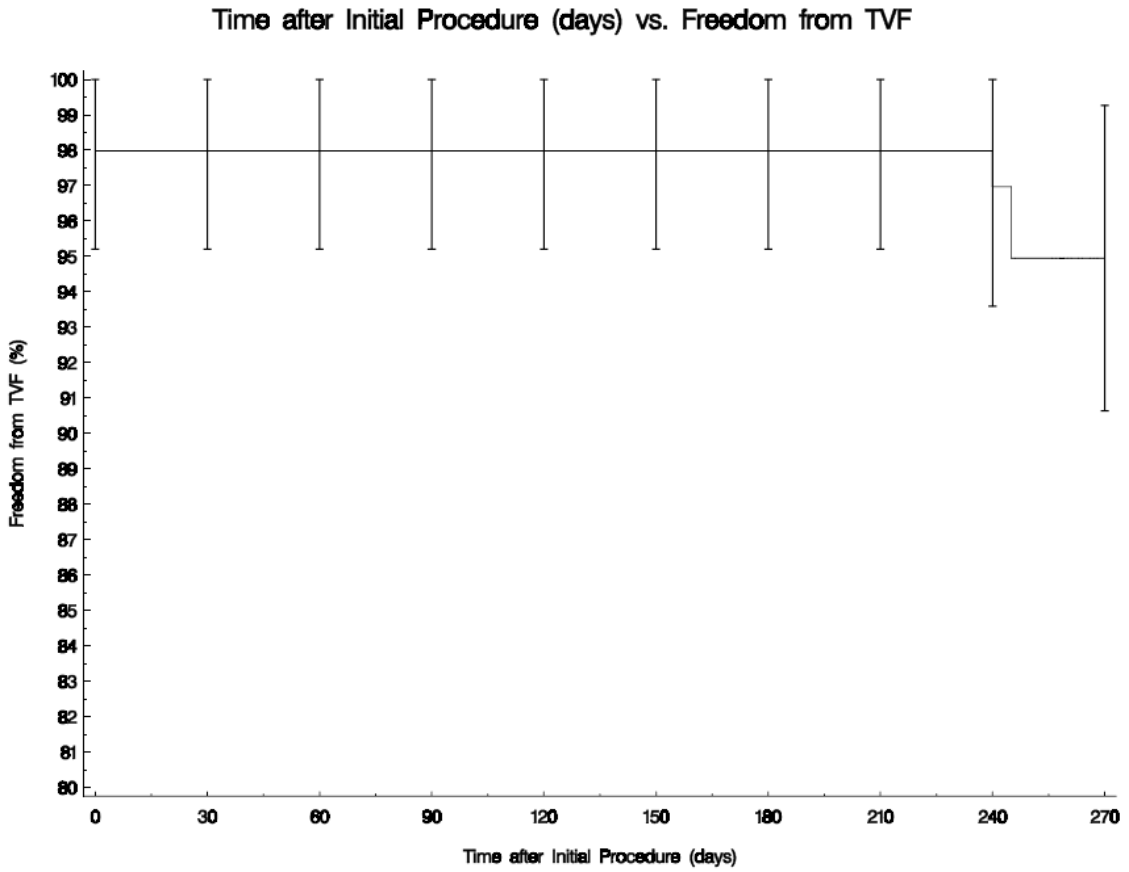

TVF	0	7	14	21	30	60	90	120	150	180	210	240	270
# Entered	99	97	97	97	97	97	97	97	97	97	97	97	96
# Censored	0	0	0	0	0	0	0	0	0	0	0	0	40
# Events	2	0	0	0	0	0	0	0	0	0	0	1	2
% Survived	98.0%	98.0%	98.0%	98.0%	98.0%	98.0%	98.0%	98.0%	98.0%	98.0%	98.0%	97.0%	94.9%
SE	1.4%	1.4%	1.4%	1.4%	1.4%	1.4%	1.4%	1.4%	1.4%	1.4%	1.4%	1.7%	2.2%

Figure 6.8-2: Freedom from TVF at 270 days

The primary endpoint was target vessel failure (TVF) at 9 months (270 days) post-procedure. TVF-defining events included target vessel revascularization, recurrent Q wave or Non-Q wave MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel. They are tabulated in Table 6.8-4 below. Two (2) patients experienced non-fatal non-Q wave MI while still in–hospital. Three (3/97; 3.1%) underwent target vessel revascularization. As of 9 months there had been no other events of TVF.

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Table 6.8-4: Patients with Target Vessel Failure at 9 months (ITT)

Target Vessel Failure-Defining Event	Intention-to-Treat Population N = 97
Total TVF at 270 days	5.2% (5/97)
Cardiac death	0.0% (0/97)
Myocardial infarction*	2.1% (2/97)
Target vessel revascularization	3.1% (3/97)

* 2 patients experienced non-fatal non-Q wave MI in hospital.

6.8.3.1 Other Analysis

The safety outcomes for the ENDEAVOR Japan clinical study are outlined in Section 7.0 Safety, of the report (Appendix 7). The adverse events for the ENDEAVOR Japan clinical study are comparable and consistent with the ENDEAVOR II clinical study. There were no cases of early or late stent thrombosis reported in the 9 month follow-up period of the ENDEAVOR Japan clinical study.

A 20 patient pharmacokinetic (PK) study was also conducted as part of the ENDEAVOR Japan study. The results were analyzed and compared with the PK cohorts for the ENDEAVOR II and ENDEAVOR US PK clinical studies. The bioanalytic analysis was performed and the report was written by Abbott Laboratories. The report was reviewed and approved by Medtronic and Abbott Laboratories. The maximum observed blood concentration (Cmax), time to maximum concentration (Tmax), area under the blood concentration-time curve (AUC) and value of total clearance (CL) corresponding to AUC were comparable and consistent between the studies and show that there are no differences based on ethnicity. Any perceived difference is offset by the adjustment for body surface area.

The pharmacokinetics of zotarolimus were essentially linear following the implantation of Endeavor System stents in Japanese patients as illustrated by dose proportional increase in the pharmacokinetic parameters over the studied dose range. The mean apparent clearances and harmonic mean half-lives ranged from 1.6 to 2.8 L/h and 54.0 to 91.9 h, respectively, in these patients. The mean T_{max} ranged from 1.0 to 2.0 hr after stent implantation. Additionally, the pharmacokinetics of zotarolimus are essentially similar among ENDEAVOR-II, ENDEAVOR-US PK and ENDEAVOR-Japan PK studies.

6.8.4 Conclusions

Combined MACE per CEC were recorded for 5.2% (5/97) patients. Incidence of MACE included two (2) patients with myocardial infarction (MI), which were both categorized as NQMI (2.1%; 2/97); and three (3) patients with target lesion revascularization (TLR), (3.1%; 3/97). No deaths occurred over the study duration, through end of follow-up at 270 days.

The results showed that the stent was safe and efficacious with a total target vessel failure rate of 5.2%. The acute success rate was high, with 100% (99/99) lesion success, 97.0% (96/99) device success, 98.0% (97/99) procedure success and 94.9% (94/99) device-specific procedure success. At 8-month angiography, mean in stent late loss was 0.53 mm and in segment late loss was 0.23 mm. Binary restenosis at 8 months was 8.2% (8/98),

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both in segment and in stent. These angiographic secondary endpoints meet or exceed expectations compared to ENDEAVOR II and most certainly in view of the older patients and high percentage of B2C lesions.

The pharmacokinetics of zotarolimus were essentially linear following the implantation of Endeavor System stents in Japanese patients as illustrated by dose proportional increase in the pharmacokinetic parameters over the studied dose range. The mean apparent clearances and harmonic mean half-lives ranged from 1.6 to 2.8 L/hr and 54.0 to 91.9 hr, respectively, in these patients. The mean T_{max} ranged from 1.0 to 2.0 hr after stent implantation. Additionally, the pharmacokinetics of zotarolimus are essentially similar among ENDEAVOR-II, ENDEAVOR-US PK and ENDEAVOR-Japan PK studies.

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6.9 ENDEAVOR FIVE Clinical Study Summary

6.9.1 Clinical Study Description

The E-Five Registry is a Post Market Release Registry to Evaluate the Clinical Performance of the Medtronic Endeavor™ Zotarolimus-Eluting Coronary Stent System, a Prospective, Multi-center Registry.

6.9.1.1 Study Design

The E-Five Registry is a prospective, multicenter registry to evaluate the 'real world' clinical performance of the Medtronic Endeavor stent system. By design, the E-Five Registry is a Post Market Release Registry, meaning that patients are only enrolled in countries where the Endeavor Stent System has obtained national regulatory approval and is commercially available. Patients included in the E-Five registry are receiving the same treatment as any other patients would under normal hospital routine.

6.9.1.2 Study Objectives

To document the safety and overall clinical performance of the Endeavor™ Zotarolimus-Eluting CSS (Coronary Stent System) in a "real world" patient population requiring stent implantation.

To assess the event rate in patient subgroups with specific clinical indications and /or vessel- or lesion characteristics. This objective is not covered in this interim report.

6.9.1.3 Primary Endpoints

Major Adverse Cardiac Events (MACE) rate at 12 months post-procedure, defined as death, myocardial infarction (Q-wave and non-Q wave), emergent cardiac bypass surgery or clinically driven target lesion revascularization (repeat PTCA or CABG).

6.9.1.4 Secondary Endpoints

- MACE rate at 30 days and at 6 months
- Stent thrombosis rate (acute <24h; subacute 2-30 days; late >30 days)
- Procedural success rate
- Device success rate
- Lesion success rate

6.9.1.5 Patient/Study Population

General Inclusion Criteria

The following inclusion criteria identify patients suitable for receiving an Endeavor stent and therefore eligible for enrollment to the registry.

Note: Subjects could only be included in the study once.

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1. Patient is ≥ 18 years of age (or minimum age as required by local regulations).
2. The patient has consented to participate by signing the "Patient Informed Consent Form" and/or has authorized the collection and release of his medical information by signing the "Patient Data Release Consent Form".
3. Patient is suitable for implantation of one or more Endeavor™ Zotarolimus-Eluting Coronary Stent System in one or more native artery target lesions.
4. Lesion length and vessel diameter of the target lesion(s) are according to the 'Indications for Use' as mentioned in the 'Instructions for Use' that comes with every Endeavor ™ Zotarolimus-Eluting Coronary Stent System.
5. The patient is willing and able to cooperate with registry procedures and required follow up visits.

Exclusion Criteria:

The following exclusion criteria indicate patients who are not supposed to be suitable for receiving an Endeavor stent and/or not an eligible candidate for enrollment to the E-Five registry.

1. Women with known pregnancy or who are lactating.
2. Patients with hypersensitivity or allergies to aspirin, heparin, clopidogrel, ticlopidine, drugs such as Zotarolimus, rapamycin, tacrolimus, sirolimus or similar drugs, or any other analogue or derivative, cobalt, chromium, nickel, molybdenum or contrast media.
3. Patients in whom anti-platelet and/or anticoagulation therapy is contraindicated.
4. Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.
5. Current medical condition with a life expectancy of less than 12 months.
6. The subject is participating in another device or drug study. Subject must have completed the follow-up phase of any previous study at least 30 days prior to enrollment in this trial. The subject may only be enrolled in this E-five registry once.
7. Patients with medical conditions that preclude the follow-up as defined in the protocol or that otherwise limits participation in this registry.

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Key Baseline Characteristics

The key baseline characteristics are summarized below for E-FIVE at 30 days.

Table 6.9-1: Key Baseline Variables

Key Baseline Variables	Endeavor	
	N	%
Age (years)	2015	
Mean (SD*)	63.05 ± 11.45	
Range	23-93	
Gender		
Male	1543 / 2015	(76.6%)
Female	472 / 2015	(23.4%)
Clinical Characteristics	N	%
History of diabetes mellitus	710 / 2015	(35.2%)
History of hypertension	1397 / 2015	(69.3%)
Lesion Characteristics	N	Mean (SD*)
Reference Vessel Diameter (mm)	2458**	2.92±0.45
Lesion length (mm)	2458**	18.28±9.91
ACC/AHA lesion class	N	%
A	204 / 2458**	8.3%
B1	781 / 2458**	31.8%
B2	922 / 2458**	37.5%
C	551 / 2458**	22.4%

*SD = Standard Deviation.
** Number of target lesions.

Enrollment/ Randomization

Study Period (enrollment): 26 September 2005 to 15 November 2006

All patients with an indication for coronary stent implantation according to the 'Instructions for Use' of the Endeavor Stent System could be enrolled into the E-Five registry. The registry expects to include all consecutive patients who receive one or more Endeavor stents in one or more target lesions. However, lesions should meet the specific vessel and lesion characteristics as described in the 'Instructions for Use' to be selected for implantation with the Endeavor Stent. Choice of stents for lesions not meeting these characteristics was left at physician's discretion.

A total of 8260 patients were enrolled in this registry.

Subjects are considered enrolled into the registry when the following two conditions have been met:

1. A signed consent form is obtained
2. The study device is introduced into the guide catheter.

The site research staff enters the recruited subject on the electronic Case Report Form to enroll the patient.

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Antiplatelet Medications

It is recommended that all subjects receive the medication regimen listed below. Anti-platelet and anti-coagulant medications administered are recorded on the electronic Case Report Form.

Prior to Procedure: Clopidogrel 75 mg per day for 3 days pre-procedure; or a pre-procedural loading dose of a minimum of 300 mg Clopidogrel should be administered for patients not taking Clopidogrel.

Post-procedure: Clopidogrel 75 mg for at least 12 weeks. Aspirin at least 75 mg QD indefinitely.

Specification of pre-procedure medications and at 30-day follow-up can be found in Table 5 of the report (Appendix 8).

All other co-medication use is at the discretion of the investigator and according to hospital routine practice.

Patient Follow-up

Clinical follow-up assessments are performed at 30 days ± 5 days, at 180 ± 14 days (6 months), and at 365 days (12 months; visit window: -14 / +30 days) after the index procedure. Each follow-up can be done by a routine outpatient clinic visit or by telephone and focuses on the onset of new symptoms and/or new events (especially MACE and stent thrombosis events). Clinical follow-up is to be extended to 2 years in a limited number of centers for specific patient subsets (for approximately 3000 patients) and will include the same date collection procedure as for the 1-year follow-up. Centers to be included will be selected after patient recruitment has been completed.

At each follow-up the following information is recorded:

- Date of follow-up
- Type of follow-up visit (telephone or routine clinic visit)
- Current cardiac status (asymptomatic, silent ischemia, stable angina or unstable angina)
- Any new MACE or stent thrombosis events since discharge or previous visit
- Anti-platelet medication

There are no mandatory angiographic or IVUS follow-up requirements for this registry. Angiographic documentation is requested for adjudication purposes in case certain events occurred, like but not limited to revascularization events.

Schedule of Treatments and Assessments

This registry does not require any specific test or procedure that falls outside a standard stenting procedure as routinely done in the hospital. The table below summarizes the data being collected prospectively within this registry.

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Table 6.9-2: Summary of Registry Procedures

	Baseline	Procedure	Discharge	Follow-up[1]
Eligibility criteria	X	-	-	-
Demographics	X	-	-	-
Cardiac Risk Factors	X	-	-	-
Current Cardiac Status	X	-	-	X
Lesion Characteristics	X	-	-	-
Pre-procedure angiography (visual)	X	-	-	-
Procedure data (number of lesions treated; devices used; implantation technique etc.)	-	X	-	-
Angiographic outcome (visual)	-	X	-	-
Anti-Platelet medication	-	X	X	X
MACE	-	X	X	X
Cardiac enzymes	-	X	-	-
ECG	-	X	-	-
Event related:				
- Peak CK and CK-MB values [2]	-	-	X	X
- ECG [3]	-	-	X	X
- Angiogram [4]	-	-	X	X

[1] Follow-up is planned after 30 days, 6 months, and 12 months. For specific patients subsets and for a limited number of centers, patient's follow-up will be extended to 24 months.
[2] If a Myocardial Infarction has occurred after procedure, peak CK and CK-MB values will be collected on the Myocardial Infarction Form.
[3] Printouts of ECG will be collected for specific ischemic - or MACE event that occurs after the index procedure for adjudication.
[4] There is no mandatory angiographic follow-up in the protocol. If the patient had an angiography performed with a clinical indication, then the angiogram might be needed for adjudication of the event by the Clinical Event Committee. Only those angiograms will be collected that are possibly related to a study endpoint, like but not limited to a target lesion revascularization.

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6.9.1.6 Patient Accountability

Approximately 186 centers located in Europe, Asia, Australia, New Zealand and South America recruited patients into this registry. This interim report includes results from 73 centers.

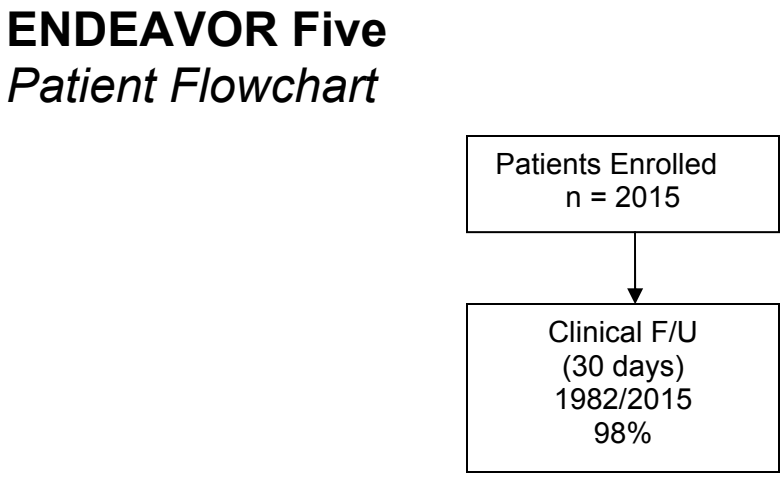

Figure 6.9-1: Patient Flowchart for ENDEAVOR Five at 30 Days

6.9.2 Statistical Methodology

6.9.2.1 Clinical Trial Objectives and Hypotheses

This is a prospective, multi-center registry designed to evaluate the safety, effectiveness and overall clinical performance of the Endeavor™ Zotarolimus-Eluting Coronary Stent System in a "real world" patient population requiring stent implantation.

A total of 8260 patients were enrolled into this registry. The interim report includes 30 days results from first 2015 patients at 73 centers. Twelve month clinical follow-up data from 1016 patients is summarized in Section 6.9.3.1.

All patients with an indication for coronary stent implantation according to the 'Instructions for Use' of the Endeavor Stent System could be enrolled into the E-Five registry. The registry includes all consecutive patients who received one or more Endeavor stents in one or more target lesions. However, lesions were to meet the specific vessel and lesion characteristics as described in the 'Instructions for Use' to be selected for implantation with the Endeavor Stent. Choice of stents for lesions not meeting these characteristics was left to the physician's discretion.

In order to ensure data quality, a pre-defined percentage of the clinical sites will be visited for source data verification. The aim is to monitor 10% (approximately 800 patients) of all patients with focus on study endpoints and to ensure accurate safety data reporting. For the patient subset studied in this interim report, 24 monitoring visits have been conducted at 23 different hospitals. In total 243 patients included in this interim analysis have been monitored, which results in 12.1% of the analyzed patients.

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An independent Clinical Event Committee adjudicates all major adverse cardiac events (MACE) and stent thrombosis events, and an independent Data Safety Monitoring Board monitors the trial.

Analysis Samples

In total 8260 patients were enrolled into this registry. The primary data set for analysis includes all patients who signed the written informed consent and for whom the Endeavor device was introduced through the guide catheter. The lesion-related parameters are also analyzed for all the target lesions, defined as lesions on which the Endeavor device was introduced.

Interim analysis is performed at the request of the FDA to support the Endeavor PMA and provides interim results for the first 2015 patients with 30-day clinical follow-up. To determine the patients to be included in the subset for the interim analysis the date of procedure was used. The procedure date of March 16, 2006, yielded 2130 enrolled patients. Out of the 2130 patients, a total of 114 from two centers were excluded from the analysis because of European privacy laws. Both centers used their standard patient informed consent for registries which did not specifically mention the transfer of data to the United States of America where the European Directive on Data Protection does not apply. Because a corrective action regarding the informed consent and data transfer was still in progress at the time of the analysis, the data of these patients had been excluded. One patient was enrolled into the trial but no Endeavor stent was attempted to be used, hence data from this patient was not presented in this report.

As a result, this report presents data from 2015 patients in the 73 centers with data transfer allowance.

Primary Endpoint

The primary endpoint is the Major Adverse Cardiac Events (MACE) rate at 12 months post-procedure. MACE is defined as the composite endpoint of: death, myocardial infarction (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (repeat PTCA or CABG).

This interim report does not yet have information available on the complete study cohort for the primary endpoint (12 months MACE rate).

Secondary Endpoints

The secondary endpoints of this study include:

- Major Adverse Cardiac Events rate (MACE) at 30 days and at 6 months
- Stent thrombosis rate (acute <24 h; subacute 2-30 days; late >30 days)
- Procedural success rate
- Device success rate
- Lesion success rate

All secondary endpoints are tabulated with contingency tables. Counts and event rates are provided.

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Analysis on Baseline Characteristics
All clinically relevant baseline variables are tabulated. Categorical variables are reported using contingency tables, and continuous variables are reported by giving the number of known values, the mean, standard deviation, minimum and maximum values.

Demographics and clinical characteristics show a mean age of 63.05±11.45 years and 76.6% male enrollment. Patient history revealed a previous percutaneous coronary intervention (PCI) in 24.0%, previous coronary artery bypass graft (CABG) in 6.7%, diabetes mellitus in 35.2% with insulin dependent diabetes in 8.8% of the patients. Current cardiac status at baseline was unstable angina in 31.5% and recent myocardial infarction in 21.8% of the patients.

The 2015 patients had 2458 lesions in which Endeavor stents were implanted or attempted, which were included in the analysis. 67.9% of the patients had one lesion being treated, most frequent vessel location was the LAD in 48.6% of the cases. In total, 15.7% of the lesions involved a bifurcation. The ACC/AHA lesion classification was reported by sites as type B2 or C for 59.9% of the lesions.

6.9.3 Results

A total of 2015 patients were included into the analysis from 73 study sites located in Europe, Asia and South America. The effectiveness and safety results for the Endeavor Drug Eluting Coronary Stent System are summarized in the table below.

Angiographic measurements were done by the sites by visual estimate and are shown in Mean lesion length was 18.28±9.91mm and the mean reference vessel diameter was 2.92±0.45mm; the mean minimum lumen diameter was 0.54±0.43mm and the mean pre-procedure diameter stenosis reported was 81.53±14.22%. The post-procedure angiographic results showed a mean diameter stenosis of 2.13±6.84%.

In 86.7% of the lesions, one Endeavor stent was implanted. The mean of total stent length implanted was 23.35±11.98mm. The minimum diameter of the Endeavor stents used was ≤ 2.75mm in 43.6% of the target lesions. The Endeavor stent was successfully delivered in 99.4% (2444/2458). The reason for unsuccessful delivery was mostly failure to reach the target lesion (9/14). Implantation of an Endeavor stent in combination with other drug-eluting stents occurred in 3.3% of the target lesions, with bare metal stents in 2.2% of the target lesions.

Table 6.9-3: Principal Effectiveness and Safety Results for First 2015 patients at 30 days

	Endeavor Five Registry (Number of Patients =2015
	Number of Lesions =2458*)
Effectiveness Measures	
Lesion Success % (#/n)	99.6%(2449/2458)
Device Success % (#/n)	94.2%(2316/2458)
Procedure Success % (#/n)	98.5%(1985/2458)
Device-Specific Procedure Success% (#/n)	92.5%(1864/2458)
Post-index Procedure Minimal Lumen Diameter (MLD, in mm)	
Mean±SD (n)	0.54±0.43(2458)
Range (min, max)	(0.00,3.30)
Pre-index Procedure Percent Diameter Stenosis (%DS)	

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Table 6.9-3: Principal Effectiveness and Safety Results for First 2015 patients at 30 days

	Endeavor Five Registry (Number of Patients =2015
	Number of Lesions =2458*)
Mean±SD (n)	81.53±14.22(2458)
Range (min, max)	(0.00,100.00)
Post-index Procedure Percent Diameter Stenosis (%DS)	
Mean±SD (n)	2.13±6.84(2458)
Range (min, max)	(0.00,100.00)
Safety Measures (to 30 days) % (#/n)	
In-Hospital complications	
MACE (Death, Q wave or non-Q wave MI, Em CABG, TLR)	1.0%(21/2015)
Death	0.5%(10/2015)
MI (Q Wave or Non-Q wave)	0.5%(11/2015)
Q Wave MI	0.2%(4/2015)
Non-Q Wave MI	0.3%(7/2015)
Emergent CABG	0% (0/2015)
Target Lesion Revascularization	0% (0/2015)
TL-CABG	0% (0/2015)
TL-PTCA	0% (0/2015)
Target Vessel Revascularization not involving Target Lesion	0% (0/2015)
TV/non-TL-CABG	0% (0/2015)
TV/non-TL-PTCA	0% (0/2015)
Target Vessel Revascularization	0% (0/2015)
Target Vessel Failure	1.0%(20/2015)
Stent Thrombosis	0.3%(6/2015)
Acute	0.0%(1/2015)
Subacute	0.2%(5/2015)
Out-of-Hospital complications to 30 days	
MACE (Death, Q wave or non-Q wave MI, Em CABG, TLR)	0.7%(13/1982)
Death	0.4%(7/1982)
MI (Q Wave or Non-Q wave)	0.3%(6/1982)
Q Wave MI	0.1%(2/1982)
Non-Q Wave MI	0.2%(4/1982)
Emergent CABG	0% (0/1982)
Target Lesion Revascularization	0.4%(8/1982)
TL-CABG	0% (0/1982)
TL-PTCA	0.4%(8/1982)
Target Vessel Revascularization not involving Target Lesion	0.1%(2/1982)
TV/non-TL-CABG	0% (0/1982)
TV/non-TL-PTCA	0.1%(2/1982)
Target Vessel Revascularization	0.5%(9/1982)
Target Vessel Failure	0.7%(14/1982)
Stent Thrombosis	0.6%(12/1982)
Acute	0.1%(1/1982)
Subacute	0.6%(11/1982)
Combined In- and Out-of-Hospital complications to 30 days	
MACE (Death, Q wave or non-Q wave MI, Em CABG, TLR)	1.7%(34/1982)
Death	0.9%(17/1982)
MI (Q Wave or Non-Q wave)	0.9%(17/1982)
Q Wave MI	0.3%(6/1982)
Non-Q Wave MI	0.6%(11/1982)
Emergent CABG	0% (0/1982)
Target Lesion Revascularization	0.4%(8/1982)

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Table 6.9-3: Principal Effectiveness and Safety Results for First 2015 patients at 30 days

	Endeavor Five Registry (Number of Patients =2015
	Number of Lesions =2458*)
TL-CABG	0% (0/1982)
TL-PTCA	0.4%(8/1982)
Target Vessel Revascularization not involving Target Lesion	0.1%(2/1982)
TV/non-TL-CABG	0% (0/1982)
TV/non-TL-PTCA	0.1%(2/1982)
Target Vessel Revascularization	0.5%(9/1982)
Target Vessel Failure	1.7%(34/1982)
Stent Thrombosis	0.9%(18/1982)
Acute	0.1%(2/1982)
Subacute	0.8%(16/1982)
Hierarchical Complications (to 30 days)	
Any MACE (Death, Q wave or non-Q wave MI, Em CABG, TLR)	1.7%(34/1982)
Death	0.9%(17/1982)
Non-fatal Q Wave MI	0.3%(6/1982)
Non-fatal Non-Q Wave MI	0.5%(9/1982)
Emergent CABG without Death or MI	0% (0/1982)
TL-CABG without Death or MI	0% (0/1982)
TL-PTCA without Death, MI, or TL-CABG	0.1%(2/1982)
Non-Hierarchical Complications (to 30 days)	
Any MACE (Death, Q wave or non-Q wave MI, Em CABG, TLR)	1.7%(34/1982)
Death	0.9%(17/1982)
MI (Q Wave or Non-Q wave)	0.9%(17/1982)
Q Wave MI	0.3%(6/1982)
Non-Q Wave MI	0.6%(11/1982)
Emergent CABG	0% (0/1982)
Target Lesion Revascularization	0.4%(8/1982)
TL-CABG	0% (0/1982)
TL-PTCA	0.4%(8/1982)
Target Vessel Revascularization not involving Target Lesion	0.1%(2/1982)
TV/non-TL-CABG	0% (0/1982)
TV/non-TL-PTCA	0.1%(2/1982)
Target Vessel Revascularization	0.5%(9/1982)
Target Vessel Failure	1.7%(34/1982)
Stent Thrombosis	0.9%(18/1982)
Acute	0.1%(2/1982)
SubAcute	0.8%(16/1982)

* Target lesion is defined as: at least one Endeavor stent was implanted or attempted.

Note: Definitions are as in the study report.

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6.9.3.1 Other Analyses

An analysis of 12 month follow-up data for the first 1016 patients enrolled in the registry was performed for all patients as well as for the diabetic subgroup. The results are summarized in the following tables.

Table 6.9-4: Baseline Characteristics First 1016 Patients at 12 months– All Patients

Subject Characteristics	E-Five (# of Patients=1016 # of Lesions =1228)
Sex % (#/n)	
Male	77% (782/1016)
Female	23% (234/1016)
Age (year)	
Mean±SD (n)	62.72± 11.46(1016)
Range (min, max)	27- 93
Previous Q MI % (#/n)	25.5% (259/1016)
Previous Non-Q MI % (#/n)	10.3% (105/1016)
Previous PTCA % (#/n)	24.3% (247/1016)
Previous CABG % (#/n)	7.1% (72/1016)
Diabetes Mellitus % (#/n)	33% (335/1016)
Insulin Dependent	8.1% (82/1016)
Non Insulin Dependent	24.9% (253/1016)
Unstable Angina % (#/n)	31.3% (318/1016)
Recent MI % (#/n)	18.6% (189/1016)
Hypertension % (#/n)	66.8% (679/1016)
Hypercholesterolemia % (#/n)	61.2% (622/1016)
Current Smoker % (#/n)	20.8% (211/1016)
Vessel Location % (#/n)	
LAD	48.5% (596/1228)
LCX	19.8% (243/1228)
RCA	27.9% (343/1228)
Left main	1.9% (23/1228)
SVG	1.9% (23/1228)
Lesion Class % (#/n)	
A	7.6% (93/1228)
B1	32.6% (400/1228)
B2	36.4% (447/1228)
C	23.5% (288/1228)
Lesion Length % (#/n)	
< 11mm	21.6% (265/1228)
11 – 15 mm	28.9% (355/1228)
> 15 mm	49.5% (608/1228)
Reference Vessel Diameter % (#/n)	
< 2.5 mm	8.6% (105/1228)
2.5 – 3.0 mm	64.2% (788/1228)
> 3.0 mm	27.3% (335/1228)
Total Stent length (mm)	
Mean±SD (n)	23.26± 12.01(1228)
Range (min, max)	8- 96
Ratio stent/lesion length	
Mean±SD (n)	1.34± 0.47(1228)
Range (min, max)	0.5- 9
Overlapping Stents if multiple stents implanted % (#/n)	10.2% (125/1228)

n = Number of patients or lesions with evaluable data

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Table 6.9-5: Safety Measurements First 1016 Patients at 12 months– All Patients

Endpoints (at 12 months) % (#/n)	E-Five (N=1016)
Major Adverse Cardiac Events (MACE)	6.3% (61/970)
Target Lesion Revascularization (TLR)	3.3% (32/970)
Target Vessel Revascularization (TVR)	3.7% (36/970)
Target Vessel Failure (TVF)	5.8% (56/970)

n = Number of patients with evaluable data

Table 6.9-6: Major Adverse Cardiac Events (MACE) First 1016 Patients at 12 months– All Patients

	E-Five (N=1016)
MACE % (#/n)	
30 days	1.7% (17/1011)
6 months	4.2% (42/1008)
12 months	6.3% (61/970)
Death % (#/n)	
30 days	0.9% (9/1011)
6 months	1.9% (19/1008)
12 months	2.5% (24/970)
Cardiac Death % (#/n)	
30 days	0.8% (8/1011)
6 months	1.5% (15/1008)
12 months	1.6% (16/970)
Non-cardiac Death % (#/n)	
30 days	0.1% (1/1011)
6 months	0.4% (4/1008)
12 months	0.8% (8/970)
Q Wave MI % (#/n)	
30 days	0.1% (1/1011)
6 months	0.3% (3/1008)
12 months	0.4% (4/970)
Non Q Wave MI % (#/n)	
30 days	0.7% (7/1011)
6 months	1.1% (11/1008)
12 months	1.1% (11/970)
Emergent CABG % (#/n)	
30 days	0% (0/1011)
6 months	0% (0/1008)
12 months	0% (0/970)
TLR % (#/n)	
30 days	0.5% (5/1011)
6 months	1.8% (18/1008)
12 months	3.3% (32/970)
Stent Thrombosis #	
Early Stent Thrombosis	
0 – 1 days	0.1% (1/1011)
2 – 30 days	0.7% (7/1011)
Late Stent Thrombosis	
31 – 180 days	0.1% (1/1008)
181 – 365 days	0% (0/970)

n = Number of patients with evaluable data

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Table 6.9-7: Baseline Characteristics First 1016 Patients at 12 months–Diabetic Patients

Subject Characteristics	E-Five (# of Patients=335 # of Lesions =409)
Sex % (#/n)	
Male	68.7% (230/335)
Female	31.3% (105/335)
Age (year)	
Mean±SD (n)	64.19± 10.70(335)
Range (min, max)	27- 93
Previous Q MI % (#/n)	24.8% (83/335)
Previous Non-Q MI % (#/n)	9.6% (32/335)
Previous PTCA % (#/n)	21.2% (71/335)
Previous CABG % (#/n)	7.8% (26/335)
Diabetes Mellitus % (#/n)	100% (335/335)
Insulin Dependent	24.5% (82/335)
Non Insulin Dependent	75.5% (253/335)
Unstable Angina % (#/n)	33.7% (113/335)
Recent MI % (#/n)	14.9% (50/335)
Hypertension % (#/n)	79.1% (265/335)
Hypercholesterolemia % (#/n)	70.1% (235/335)
Current Smoker % (#/n)	13.7% (46/335)
Vessel Location % (#/n)	
LAD	45.7% (187/409)
LCX	20.8% (85/409)
RCA	28.9% (118/409)
Left main	1.5% (6/409)
SVG	3.2% (13/409)
Lesion Class % (#/n)	
A	10.3% (42/409)
B1	30.6% (125/409)
B2	34.7% (142/409)
C	24.4% (100/409)
Lesion Length % (#/n)	
< 11mm	19.6% (80/409)
11 – 15 mm	30.1% (123/409)
> 15 mm	50.4% (206/409)
Reference Vessel Diameter % (#/n)	
< 2.5 mm	10% (41/409)
2.5 – 3.0 mm	62.3% (255/409)
> 3.0 mm	27.6% (113/409)
Total Stent length (mm)	
Mean±SD (n)	24.14± 13.38(409)
Range (min, max)	8- 96
Ratio stent/lesion length	
Mean±SD (n)	1.32± 0.39(409)
Range (min, max)	0.61- 4.56
Overlapping Stents if multiple stents implanted % (#/n)	11.7% (48/409)

n = Number of patients or lesions with evaluable data

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Table 6.9-8: Safety Measurements First 1016 Patients at 12 months– Diabetic Patients

Endpoints (at 12 months) % (#/n)	E-Five (N=335)
Major Adverse Cardiac Events (MACE)	9.4% (30/318)
Target Lesion Revascularization (TLR)	4.4% (14/318)
Target Vessel Revascularization (TVR)	5.3% (17/318)
Target Vessel Failure (TVF)	8.5% (27/318)

n = Number of patients with evaluable data

Table 6.9-9: Major Adverse Cardiac Events (MACE) First 1016 Patients at 12 months– Diabetic Patients

	E-Five (N=335)
MACE % (#/n)	
30 days	2.7% (9/333)
6 months	6.3% (21/333)
12 months	9.4% (30/318)
Death % (#/n)	
30 days	2.1% (7/333)
6 months	3.6% (12/333)
12 months	5% (16/318)
Cardiac Death % (#/n)	
30 days	1.8% (6/333)
6 months	3% (10/333)
12 months	3.5% (11/318)
Non-cardiac Death % (#/n)	
30 days	0.3% (1/333)
6 months	0.6% (2/333)
12 months	1.6% (5/318)
Q Wave MI % (#/n)	
30 days	0.3% (1/333)
6 months	0.3% (1/333)
12 months	0.6% (2/318)
Non Q Wave MI % (#/n)	
30 days	0.9% (3/333)
6 months	1.5% (5/333)
12 months	1.6% (5/318)
Emergent CABG % (#/n)	
30 days	0% (0/333)
6 months	0% (0/333)
12 months	0% (0/318)
TLR % (#/n)	
30 days	0.9% (3/333)
6 months	2.7% (9/333)
12 months	4.4% (14/318)
Stent Thrombosis #	
Early Stent Thrombosis	
0 – 1 days	0.3% (1/333)
2 – 30 days	1.2% (4/333)
Late Stent Thrombosis	
31 – 180 days	0% (0/333)
181 – 365 days	0% (0/318)

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6.9.4 Conclusions

This interim analysis is performed at request of the FDA to provide supplementary experience on 2015 patients. Results available to date confirm the postmarket safety and performance of the Endeavor stent.

Interim MACE and early stent thrombosis rates at 30-days:

The interim safety results at 30 day follow-up of 2015 "real world" patients included in the E-Five registry is presented in the safety and effectiveness table above. The incidence of MACE was 1.7% (34/1982) at 30 days. The individual safety components are presented in Table 10 of the report (Appendix 8). Review of the individual safety components shows that death occurred in 0.9% (17/1982) and early stent thrombosis in 0.9% (18/1982) of the patients.

Interim MACE and Death rates at 12 months:
The interim safety results at 12 months follow-up of the first 1016 "real world" patients included in the E-Five registry are presented in the safety and effectiveness tables above in Section 6.9.3.1. An analysis of the end points was performed on the first 1016 patients enrolled in this registry. A subgroup analysis on diabetic patients (335) among these 1016 was also performed. The incidence of MACE was 6.3% (61/970) for all 1016 patients vs. 9.4% (30/318) for the 335 diabetic subset patients at 12 months. Review of the individual safety components shows that death occurred in 2.5% (24/970) for all 1016 patients vs. 5% (16/318) for the 335 diabetic subset patients at 12 months.

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7.0 Endeavor Post-Approval Study Proposal

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7.0 Endeavor U.S. Post-Approval Study Proposal

7.1 Background

In the original PMA for the Endeavor Zotarolimus-Eluting Coronary Stent System, Medtronic Vascular committed to conducting a post-approval study in the United States, with the details to be discussed with FDA during the PMA review process. On January 23, 2007, Medtronic and FDA met to discuss Medtronic's proposal for the Endeavor U.S. Post-approval Study Plan. At that meeting, the FDA agreed that it would be reasonable to allow for pooling of the Endeavor patients from Medtronic's PROTECT study with U.S. registry patients for the purposes of the Endeavor U.S. Post-approval Plan.

The PMA deficiency letter from FDA dated February 16, 2007 included questions and requests regarding the post-approval plan. In subsequent email correspondence during FDA's interactive review of the PMA, Medtronic Vascular submitted a draft U.S. post-approval study overview to FDA on August 14, 2007 and a draft formal study plan on August 23, 2007. FDA and Medtronic Vascular held a conference call on August 31, 2007 to discuss FDA's additional feedback regarding the Endeavor U.S. Post-approval Study Plan.

The proposed Endeavor U.S. Post-approval Study Plan is included in this section. Endpoints and sample size assumptions agreed between Medtronic and FDA are outlined in Section 7.2 below, followed by summaries of the proposed study design and primary analyses in Sections 7.3 and 7.4, respectively.

7.2 Sample Size Assumptions

As a result of feedback received from FDA during the interactive review of the Endeavor PMA, Medtronic Vascular agreed to the following with respect to the enclosed plan:

- The total enrollment will be approximately 5,300 (3,300 OUS PROTECT with core sizes and 2,000 US Post Marketing Registry) patients, in order to yield a total of 1941 on-label, evaluable patients as required based on FDA's feedback regarding the statistical assumptions outlined below.
- Pooling patients from the Endeavor arm of Medtronic's PROTECT study as agreed between FDA and Medtronic is expected to yield a total of 1200 on-label, evaluable patients for the Endeavor U.S. Post-approval Study Plan.
- The rate of on-label use in the post-approval study is assumed to be 40% based on the FDA clinical overview discussion document for the FDA Circulatory System Devices panel meeting regarding DES thrombosis of December 2006.
- The rate of patients lost to follow-up is assumed to be approximately 10 percent.
- Rates for the U.S. registry patients will be reported to FDA annually; however, the formal hypothesis for the stent thrombosis primary endpoint will be tested officially after the third year since the PROTECT study is designed to remain blinded until three years.
- An assumed thrombosis rate of 0.5% post one year of follow-up. Please note this rate is significantly greater than the post-one-year thrombosis rate observed to date in the Endeavor clinical trial program.

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- A co-primary endpoint to compare the rates of cardiac death and MI in on-label patients from the Endeavor post-approval program with the Driver arm of the ENDEAVOR II study was added to the plan.

7.3 Study Design

This study is designed as a prospective, multicenter, non-randomized, single-arm, open-label trial.

The selected primary endpoint is stent thrombosis defined as definite and probable stent thrombosis according to the ARC definition, and the selected co-primary endpoint is to compare the rates of cardiac death and MI from the Endeavor post-approval program on-label patients with the comparator group from the pre-approval trial population. The main secondary endpoint is the composite of death, large and all non-fatal myocardial infarction, which are the typical clinical manifestations of stent thrombosis. These events will be adjudicated by a clinical events committee.

Study enrollment will consist of consecutive patients who in the opinion of the investigator are candidates for treatment with the Endeavor CSS, provide consent to participate in the study, and who receive an Endeavor CSS.

The anti-platelet regimen (Clopidogrel) should be continued minimally for 3 months (as per manufacturer's Instruction For Use) and up to 12 months (as per ACC/AHA/SCAI guidelines), or longer as per physician's decision.

The number of patients treated for a bifurcation lesion or treated by primary PCI for acute myocardial infarction will each be maximally 25% of the total patient population, in order to avoid overrepresentation of each of these specific patient populations.

7.4 Statistical Analysis Plan– Primary Analyses

This study is a prospective, multicenter, non-randomized, single-arm, open-label trial aimed to evaluate the primary endpoint of stent thrombosis years after enrollment using ARC definitions of definite and probable. The evaluation of stent thrombosis will be conducted yearly over 5 years, with the primary interest at 3 years post-procedure. The co-primary endpoint will evaluate the incidence of death/MI over 5 years, with the primary interest at 1-year post-procedure.

7.4.1 Definite/Probable Stent Thrombosis (ARC Definition)

The primary analysis on stent thrombosis is to assess whether the true (population) Endeavor® stent thrombosis rate is <1% at various time intervals. Specifically, a major objective of this study is to have a sufficient number of patients to yield an upper bound of the 95% confidence interval of the Endeavor® observed stent thrombosis rate <1% for the period from 12 to 24 months, 24 to 36 months, 36 to 48 months, and 48 to 60 months post-procedure for the on-label population.

For each post one-year time interval (12-24 months, 24-36 months, 36-48 months, and 48-60 months post-procedure), the following are the hypotheses to be tested:

H_0: π=0.01 or 1%

H_1: π<0.01 or 1%

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where π is the true Endeavor® Definite/Probable Stent Thrombosis rate per ARC definition during the year in question. H_0 can be rejected if the one-sided upper 95% confidence interval (CI) calculated from the observed estimate of π is below 0.01 (or 1%). The primary assessment of the above null-hypothesis will be carried out on the on-label Endeavor® patients.

The following table summarizes the *evaluable on-label* sample size with the assumption of π=0.5%, using a one-sided 0.05 level of significance and at 80% power. The sample sizes were calculated under the further assumption of an exact binomial confidence interval approach to testing the above H_0. The patients will be obtained from the US post-marketing and PROTECT OUS studies.

Table 7-1 On-label Patients

True Event Rate (%)	Total Number of On-Label Evaluable Patients
0.50%	1941

The above table displays *evaluable on-label* Endeavor® arm sample sizes required from US post-marketing and OUS PROTECT studies combined for each follow-up period, or i.e., the number of on-label US post-marketing and OUS PROTECT Endeavor® patients who (a) enter the time period of question without a previous thrombosis; and (b) who are available through the end of the one-year follow-up period.

It is expected 1320 *on-label* Endeavor® patients will be enrolled in the OUS PROTECT trial, as outlined in the table below. However, the number of OUS PROTECT Endeavor® arm patients without stent thrombosis evaluable for the 12-24 month, 24-36 month, etc., analysis is expected to be lower than 1320 due to lost-to-follow-up and due to the fact that only patients entering the yearly time period without stent thrombosis are eligible for the analysis during that year.

Table 7-2 OUS PROTECT On-label Patients

O.U.S PROTECT	8800 pts
Endeavor® arm enrollment	4400 pts
Endeavor® Pts enrolled with 2.5, 3.0 and 3.5 mm sizes	75% of 4400, i.e., 3300*
Out of 3300, 40% On-label patients**	1320 on-label Endeavor® patients in OUS PROTECT

*The following analyses from Endeavor Five were utilized to calculate the approximate sample size of subjects that will be available: Approximately 25.7 % of patients received a 2.25, 2.75 or a 4.0 mm stent, leaving ~75% of patients with 2.5, 3.0 and 3.5 mm stent diameter.
** The anticipated on-label rate of 40% is based on the FDA clinical overview discussion document for the DES thrombosis panel meeting of December, 2006.

Given the OUS PROTECT sample size, the following table displays examples of *evaluable on-label* Endeavor® sample sizes required from each of the US post-marketing and OUS PROTECT studies to ensure, when the on-label Endeavor® patients from the studies are combined, 80% power to reject the above null hypothesis during a given year, under various assumptions of the true event rate:

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Table 7-3 Evaluable On-label Endeavor sample size required

True Event Rate During a 12-Month Period (%)	Total Number of On-Label Endeavor® Evaluable Patients		
	(US and OUS Combined)	OUS Protect	US Post-marketing study
0.50%	1941	1300	641
	1941	1200	741
	1941	1100	841
	1941	1000	941

If the true Endeavor® thrombosis rate is as large as 0.5% and 1200 *on-label evaluable* Endeavor patients are available from PROTECT, approximately 800 *on-label evaluable* Endeavor® patients will be required from the US post-marketing study to ensure adequate power for rejecting the above null hypothesis when US post-marketing study and PROTECT study patients are combined. Assuming a 40% on-label rate, then 2000 patients would be required to be enrolled in US post-marketing study to yield 800 US post-marketing study on-label evaluable Endeavor® patients.

Based on previous experience with Endeavor®, it is anticipated the true post one-year thrombosis rate is no larger than 0.5%. Thus 2000 patients will be enrolled in US post-marketing study.

7.4.2 Cardiac Death/MI Composite

The primary analysis on the composite endpoint of cardiac death/MI will be the assessment of non-inferiority of Endeavor® Zotarolimus Eluting Coronary Stent System cardiac death/MI incidence to the Driver® cardiac death/MI incidence on the Endeavor® on-label patients. This non-inferiority analysis will be performed yearly through 3 years (with descriptive treatment comparisons following through 5 years of follow-up), with the primary interest of showing non-inferiority of Endeavor® to Driver® at 1 year. The Endeavor® patients will be obtained from the US post-marketing and OUS PROTECT studies; the Driver® patients will be obtained from the Endeavor II clinical study (589, 586, and 579 Driver® patients are evaluable at 1, 2 and 3-years post-procedure).

The null hypothesis (H_0) for this endpoint is that the incidence in patients treated with the Endeavor® Zotarolimus Eluting Coronary Stent System ($\pi_{ENDEAVOR}$) will exceed the endpoint incidence by 50% or more for patients treated with Driver® (π_{DRIVER}). The non-inferiority alternative hypothesis (H_1) is that $\pi_{ENDEAVOR}$ will be less than π_{DRIVER} plus a non-inferiority margin approximately 50% of π_{DRIVER}. Thus,

$$H_0: \pi_{ENDEAVOR} \geq \pi_{DRIVER} + \delta$$

$$H_1: \pi_{ENDEAVOR} < \pi_{DRIVER} + \delta.$$

Based on Endeavor II, π_{DRIVER} is estimated to be 4.6%, 5.8%, and 6.7% at 1, 2 and 3-years post-procedure, respectively (these are the point estimates of π_{DRIVER} from Endeavor II). The test of non-inferiority will be carried out using the Farrington-Manning test on the treatment difference.

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The Driver® patients will be obtained from the Endeavor II study; the Endeavor® patients will be obtained from the combined US post-marketing and PROTECT OUS studies.

The table below presents power at a one-sided α of 0.05 for expected evaluable sample sizes and the 1-, 2-, and 3-year post-procedure anticipated results. Power is presented for all patients and for the on-label patients (assuming there are at least 1,900 evaluable on-label Endeavor® patients from the US post-marketing and OUS PROTECT studies combined at each time point; such a sample size is expected with 2000 patients enrolled in US post-marketing study) as analyses will be conducted for all patients and on the subgroup of on-label patients.

Table 7-4 Expected Evaluable Sample Sizes

Time	$\pi_{ENDEAVOR}$	π_{DRIVER}	δ	All Patients (6,000 Endeavor®, ~600 Driver®)	On-Label Patients (At least 1900 Endeavor®, ~600 Driver®)
				Power (1-β)	Power (1-β)
1-year	4.6%	4.6%	2.30%	89%	80%
2-year	5.8%	5.8%	2.90%	94%	87%
3-year	6.7%	6.7%	3.35%	96%	91%

Please refer to the Endeavor U.S. Post-approval Study Plan attached for further detail regarding the proposal.

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ATTACHMENT 7A Endeavor U.S. Post-approval Study Plan

Endeavor U.S. Postmarketing Registry

Prospective, Multi-center, Non-Randomized, Single-arm, Open-label Trial

CLINICAL INVESTIGATION PLAN

DRAFT VERSION 2.0
5 September 2007

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1. SYNOPSIS

Title	Endeavor U.S. Postmarketing Registry
Acronym	TBD
Sponsor	Medtronic Vascular 3576 Unocal Place Santa Rosa, Ca, USA
Patients	Consecutive patients with an indication for coronary stent implantation according to the 'Instructions for Use' of the Endeavor® Zotarolimus Eluting Coronary Stent System. All consecutive patients eligible for drug eluting stent implantation with the Endeavor® stent in one or more target lesions are candidates to be enrolled. Excluded, among others, are patients with implantation of a bare metal stent in the year before enrollment or a drug eluting stent any time before enrollment.
Study Design	Prospective, multi-center, non-randomized, single-arm, open-label trial
Study Stents	Medtronic Endeavor® Zotarolimus Eluting Coronary Stent System or next generation model.
Number of Centers and Patients	Up to 2000 patients will be enrolled at upto 100 centers in the United States. Centers are allowed to enroll a maximum of 200 patients* per center or until study enrollment has been completed, whichever comes first. * The center's clinical investigational plan compliance will be assessed on an ongoing basis. In case of serious non-compliance, the Steering Committee or the sponsor may decide to stop patient enrollment in a center based on it`s assessment.
Primary Objective	To evaluate the overall stent thrombosis rate of the Endeavor® Zotarolimus Eluting Coronary Stent System over the course of five years in a patient population requiring stent implantation and to compare the rates of cardiac death and MI from the Endeavor post-approval program on-label patients with the comparator group from the pre-approval trial population.
Secondary Objective	To evaluate the composite endpoint of total death or cardiac death combined with the number of patients with all non-fatal myocardial infarctions as well as the number of patients with large non-fatal myocardial infarctions for Endeavor® Zotarolimus Eluting Coronary Stent System in a patient population requiring stent implantation. To assess the safety and efficacy in patient subgroups with specific demographics, clinical indications and/or vessel- or lesion characteristics.

Primary Endpoint	To evaluate the overall stent thrombosis rate defined as definite and probable stent thrombosis, according to the Academic Research Consortium (ARC) definition in on-label patients from the Endeavor post-approval program over the course of 5 years.
Co-primary Endpoint	To compare the rates of cardiac death and MI in on-label patients from the Endeavor post-approval program with the Driver arm of the ENDEAVOR II study.
Main secondary Endpoints	Composite endpoint of total death and number of patients with all non-fatal myocardial infarction over the course of 5 years Composite endpoint of cardiac death and number of patients with all non-fatal myocardial infarction over the course of 5 years Composite endpoint of total death and number of patients with large non-fatal myocardial infarction over the course of 5 years Composite endpoint of cardiac death and number of patients with large non-fatal myocardial infarction over the course of 5 years
Additional Secondary Endpoints	Total Death and subcategories of Death Large and all Myocardial Infarctions (MI) Stent thrombosis defined as definite, probable and possible Composite score of clinical outcomes (death, myocardial infarction, stroke and revascularization) Major Adverse Cardiac and Cerebral Events (MACCE) Stroke (hemorrhagic in nature while on clopidogrel) Bleeding complications in general Target lesion revascularization (TLR) Target vessel revascularization (TVR) Non target vessel revascularization (non TVR) Procedural success Device success Lesion success
Primary Analysis Population	All enrolled patients upon intention-to-treat (ITT) basis
Secondary Analysis Population	Patients who received -one or more- of the study stents. Patient subgroups with specific demographics, clinical indications and/or lesion or vessel characteristics.
Delivery Failure	The aim should be to treat all lesions with the study stent. Any drug eluting stent or a bare metal stent (except the Cypher® stent) can be implanted in case of a delivery failure or non-availability of study stent.

Antiplatelet therapy	Aspirin: 75 mg daily for 3 days prior to the procedure, or a peri-procedural loading dose between 250-500 mg. Aspirin (at least 75 mg daily) should be continued indefinitely. Clopidogrel: 75 mg daily for 3 days prior to the procedure, or a pre-procedural loading dose between 300-600 mg. Clopidogrel should be prescribed minimally for 3 months (as per manufacturer's Instructions for Use) and up to 12 months (as per ACC/AHA/SCAI guidelines), or longer as per physician's decision. If a patient develops a sensitivity or intolerance to clopidogrel subsequent to enrollment, the patient may be given ticlopidine (250 mg BID).
Follow-up assessments	Day 0 30 ± 5 days 6 mo ± 14 days 1 yr ± 30 days 1½ yrs ± 30 days 2 yrs ± 30 days 2½ yrs ± 30 days 3 yrs ± 30 days 4 yrs ± 30 days 5 yrs ± 30 days These clinical follow-ups can be done by phone or preferably by outpatient clinic visit. Investigators are urged to avoid patients being Lost-To-Follow-Up.
Treatment Advice	Investigators are advised to perform angiograms only on a clinically driven basis, i.e. systematic control angiograms should be avoided. Investigators are advised to perform (re-)interventions only when it is clinically indicated, i.e. in case of symptoms or demonstrable ischemia. For all additional stent implantation during the follow-up period until the pooling comparison after the 3 year follow-up, investigators are urged to use the same model as the initial study stent in order to prevent any potential interaction between different stents.
Compliance	All requested data need to be reported in the e-CRF in the requested time frame.
Data Collection	Electronic Case Record Form (e-CRF)
Monitoring	100% Patient Informed Consent check and Source Data Verification of approximately 30% of patients
Clinical Event Committee	Adjudication of all deaths and reports of (suspected) myocardial infarctions and stent thrombosis by Clinical Event Committee
clinicaltrials.gov database	The Endeavor U.S. Postmarketing study registry will be registered in the clinicaltrials.gov database.

2. GENERAL INFORMATION

2.1 Introduction

Percutaneous coronary intervention (PCI) has become the most frequently used method for myocardial revascularization [1]. The advent of coronary stenting led to a significant decrease in complications after PCI, resulting in improved patient outcome [2,3]. Yet, restenosis has remained the main and most frequent concern after successful PCI using bare metal stents with an overall incidence close to 30%. Several studies have shown drug eluting stents (Cypher® Cordis, Johnson and Johnson, Taxus® Boston Scientific Corporation, Endeavor® Medtronic) dispatching an anti-proliferative compound (sirolimus, paclitaxel, zotarolimus, respectively) via a non-bioerodable polymer diminish by up to 75% the incidence of in-stent restenosis [4-13]. Since the publication of the first randomized trial comparing drug eluting stents and bare metal stents in highly selected patients and lesions in 2002 and which showed a 0% binary restenosis rate in the DES-arm [4], the use of drug eluting stents in clinical practice has expanded to the majority of coronary lesion subsets (e.g. de novo complex lesions, long lesions, small vessels) as well as to high-risk patients (multi-vessel angioplasty, patients with diabetes) [5, 10-14].

While the problem of restenosis with the introduction of drug eluting stents seems to be addressed, or at least reduced significantly compared to bare metal stents, a debate around stent thrombosis and in particular late stent thrombosis (> 30 days after index procedure) has started in medical scientific journals as well as in laymen's press [15-18]. The reported incidence of late stent thrombosis varies from 0.2 to 0.7% in "real world' patients followed "only" from 9 months up to a mean of 19 months [17, 19-22]. Although the incidence might seem low, the high mortality and morbidity associated with stent thrombosis, and the soaring number of stents implanted annually, make it a significant medical problem.

Premature antiplatelet therapy interruption has been identified as the main risk factor for stent thrombosis after DES implantation [15, 17, 19]. The reasons for premature anti-platelet therapy interruption are patient non-compliance or discontinuation for medical reasons like surgical procedures including dental work. A recently presented study showed a higher incidence of death and myocardial infarction after implantation of a drug eluting stents compared to patients who received a bare metal stent (4.9% vs 1.3%, p=0.01) in the year following discontinuation of clopidogrel treatment [23]. It was believed that less angiographic restenosis implies a better clinical outcome. This hypothesis seems not to be valid anymore as less restenosis may reflect delayed healing and incomplete stent re-endothelialization and therefore the potential occurrence of stent thrombosis and related clinical events, such as death and myocardial infraction [24].

The anti-proliferative characteristics of drug eluting stents should be balanced between reduction of the amount of neointimal formation within the stent in order to prevent restenosis, while avoiding incomplete or delayed endothelialization [25]. In an autopsy study, 23 cases with a drug eluting stent implanted for more than 30 days were compared with 25 matched autopsies of BMS implantation [24]. Fourteen of 23 patients with a drug eluting stent had evidence of late stent thrombosis. The drug eluting stents showed more delayed healing characterized by persistent fibrin deposition and poorer endothelialization compared with a bare metal stent. Also, hypersensitivity reactions possibly related to the degradation of the polymer, the carrier of the drug, have been reported to be associated with late stent thrombosis [15].

Randomized drug eluting stent studies have used either angiographic primary endpoints or composite clinical endpoints including angiographic driven revascularization [1-9]. The clinical safety, including death and myocardial infarction, may have been diluted by the coronary angiogram driven revascularization [26]. In addition, the majority of the early drug eluting stent studies are mostly limited to rather stable patients (i.e. highly selected patient groups) with simple lesions [1-9]. Today, the interventional cardiologist is interested in the safety and efficacy of drug eluting stents in the 'everyday' patient population setting, which in most cases will be patients

with a much higher risk (e.g. patients with acute myocardial Infarction, multi-vessel disease, small vessel disease, and complex lesions) than those investigated so far in the DES studies.

The general consensus in the literature today is that well designed, adequately powered clinical trials are necessary to evaluate and establish the safety, efficacy and long-term clinical outcomes of drug eluting stents in the more high risk patient population, which reflects more closely clinical practice today. The purpose of this multi-center trial is to investigate the long-term clinical safety and efficacy of Endeavor drug eluting stent in both unstable and stable patients with single or multi-vessel disease and complex lesions.

A recent consortium has been developing new clinical endpoints for Drug Eluting Device trials with new categories of definitions that are designed to capture any potential stent thrombotic event. New categories include the traditional very specific definite identification of a thrombus with angiography or autopsy evidence. Additional category of probable stent thrombosis allows for myocardial infarction without an angiogram but with evidence that identifies a large myocardial infarction with the geography of an implanted stent. The new possible stent thrombosis definition now seems too broad for trial endpoints by most authorities. .

2.1.1 Device description Medtronic Endeavor Stent

Medtronic Endeavor® Zotarolimus Eluting Coronary Stent System or next generation model.
Device description details of the Endeavor® Zotarolimus Eluting Coronary Stent System can be found in the Instructions for Use, which are provided with the product.

2.2 Intended Use of the Device, Indication and Contraindications

For more detailed information on intended use of the device, clinical and pre-clinical testing, indications and contraindications, as well as a complete list of warning, precautions and potential adverse events, please refer to the Instructions for Use of device, which is provided with the product.

3. STUDY PLAN

3.1 Study Objectives

The primary objective of this study is to evaluate the stent thrombosis rate of the Endeavor® Zotarolimus Eluting Coronary Stent System in a patient population requiring stent implantation and to compare the rates of cardiac death and MI from the post-approval programs on-label patients with the comparator group from the pre-approval trial.

The secondary objective is to evaluate the composite endpoint of total death or cardiac death combined with the number of patients with all non-fatal myocardial infarctions as well as the number of patients with large non-fatal myocardial infarctions for Endeavor® Zotarolimus Eluting Coronary Stent System in a patient population requiring stent implantation.

Additionally, the safety and efficacy in patient subgroups with specific demographics, clinical indications and/or vessel- or lesion characteristics will be assessed (see statistical section).

3.2 Clinical Endpoints

Primary endpoint:
To evaluate the overall stent thrombosis rate defined as definite and probable stent thrombosis (according to the ARC definition) in on-label patients from the Endeavor post-approval program over the course of 5 years.

Co-primary endpoint:
To compare the rates of cardiac death and MI in the on-label patients from the Endeavor post-approval programs with the Driver arm of ENDEAVOR II study.

Main secondary endpoints:

- Composite endpoint of total death and number of patients with all non-fatal myocardial infarction over the course of 5 years
- Composite endpoint of cardiac death and number of patients with all non-fatal myocardial infarction over the course of 5 years
- Composite endpoint of total death and number of patients with large non-fatal myocardial infarction over the course of 5 years
- Composite endpoint of cardiac death and number of patients with large non-fatal myocardial infarction over the course of 5 years

Additional secondary endpoints:

- Total Death and subcategories of Death
- Large and all Myocardial Infarction (MI)
- Stent thrombosis defined as definite, probable and possible
- Composite score of clinical outcomes (death, myocardial infarction, stroke and revascularization)*
- Major Adverse Cardiac and Cerebral Events (MACCE)
- Stroke (hemorrhagic in nature while on clopidogrel)
- Bleeding complications in general
- Target lesion revascularization (TLR)
- Target vessel revascularization (TVR)
- Non target vessel revascularization (non TVR)
- Procedural success
- Device success
- Lesion success
- Endpoints will be calculated at the follow-up time points and for the mean follow-up period.

* The composite score of clinical outcomes (death, myocardial infarction, stroke and revascularization) constructed from a patient population according to the Delphi method.

3.3 Patient Population

Up to 2000 patients with lesions in native coronary arteries who meet the eligibility criteria are intended to participate in this study, and to be enrolled at upto 100 centers. Centers are allowed to enroll a maximum of 200 patients* per center or until study enrollment has been completed, whatever comes first. Centers should aim to recruit a minimum number of 20 patients.

* The center's clinical investigational plan compliance will be assessed on an ongoing basis. In case of serious non-compliance, the Steering Committee or the sponsor may decide to stop patient enrollment in a center based on the assessment.

3.4 Study Design

This study is designed as a prospective, multi-center, non-randomized, single-arm, open-label trial.

The selected primary endpoint is stent thrombosis defined as definite and probable stent thrombosis according to the ARC definition and the selected co-primary endpoint is to compare the rates of cardiac death and MI from the Endeavor post-approval program on-label patients with the comparator group from the pre-approval trial population. The main secondary endpoint is the composite of death, large and all non-fatal myocardial infarction, which are the typical clinical manifestations of stent thrombosis. These events will be adjudicated by a clinical events committee.

Study enrollment will consist of consecutive patients who in the opinion of the investigator are candidates for treatment with the Endeavor CSS, provide consent to participate in the study, and who receive an Endeavor CSS.

The anti-platelet regimen (Clopidogrel) should be continued minimally for 3 months (as per manufacturer's Instruction For Use) and up to 12 months (as per ACC/AHA/SCAI guidelines), or longer as per physician's decision.

The number of patients treated for a bifurcation lesion or treated by primary PCI for acute myocardial infarction will each be maximally 25% of the total patient population, in order to avoid overrepresentation of each of these specific patient populations.

3.5 Statistical Considerations and Analysis Plan

This study is a prospective, multi-center, non-randomized, single-arm, open-label trial aimed to evaluate the primary endpoint of stent thrombosis years after enrollment using ARC definitions of definite and probable. The evaluation of stent thrombosis will be conducted yearly over 5 years, with the primary interest at 3 years post-procedure. The co-primary endpoint will evaluate the incidence of death/MI over 5 years, with the primary interest at 1-year post-procedure.

3.5.1 Sample Size Calculation

Definite/Probable Stent Thrombosis (ARC Definition) – Primary Analysis:

The primary analysis on stent thrombosis is to assess whether the true (population) Endeavor® stent thrombosis rate is <1% at various time intervals. Specifically, a major objective of this trial is to have a sufficient number of patients to yield an upper bound of the 95% confidence interval of the Endeavor® observed stent thrombosis rate <1% for the period from 12 to 24 months, 24 to 36 months, 36 to 48 months, and 48 to 60 months post-procedure for the on-label population.

For each post one-year time interval (12-24 months, 24-36 months, 36-48 months, and 48-60 months post-procedure), the following are the hypotheses to be tested:

H_0: π=0.01 or 1%
H_1: π<0.01 or 1%

where π is the true Endeavor® Definite/Probable Stent Thrombosis rate per ARC definition during the year in question. H_0 can be rejected if the one-sided upper 95% confidence interval (CI) calculated from the observed estimate of π is below 0.01 (or 1%). The primary assessment of the above null-hypothesis will be carried out on the on-label Endeavor® patients.

The following table summarizes the *evaluable on-label* sample size with the assumption of π=0.5%, using a one-sided 0.05 level of significance and at 80% power. The sample sizes were calculated under the further assumption of an exact binomial confidence interval approach to testing the above H_0. The patients will be obtained from the US post-marketing and PROTECT OUS studies.

True Event Rate (%)	**Total Number of On-Label Evaluable Patients**
0.50%	1941

The above table displays *evaluable on-label* Endeavor® arm sample sizes required from US post-marketing and OUS PROTECT studies combined for each follow-up period, or i.e., the number of on-label US post-marketing and OUS PROTECT Endeavor® patients who (a) enter the time period of question without a previous thrombosis; and (b) who are available through the end of the one-year follow-up period.

It is expected 1320 *on-label* Endeavor® patients will be enrolled in the OUS PROTECT trial, as outlined in the table below. However, the number of OUS PROTECT Endeavor® arm patients without stent thrombosis evaluable for the 12-24 month, 24-36 month, etc., analysis is expected to be lower than 1320 due to lost-to-follow-up and due to the fact that only patients entering the yearly time period without stent thrombosis are eligible for the analysis during that year.

O.U.S PROTECT	8800 pts
Endeavor® arm enrollment	4400 pts
Endeavor® Pts enrolled with 2.5, 3.0 and 3.5 mm sizes	75% of 4400, i.e., 3300*
Out of 3300, 40% On-label patients**	1320 on-label Endeavor® patients in OUS PROTECT

*The following analyses from Endeavor Five were utilized to calculate the approximate sample size of subjects that will be available: Approximately 25.7 % of patients received a 2.25, 2.75 or a 4.0 mm stent, leaving ~75% of patients with 2.5, 3.0 and 3.5 mm stent diameter.
** The anticipated on-label rate of 40% is based on the FDA clinical overview discussion document for the DES thrombosis panel of Dec 2006.

Given the OUS PROTECT sample size, the following table displays examples of *evaluable on-label* Endeavor® sample sizes required from each of the US post-marketing and OUS PROTECT studies to ensure, when the on-label Endeavor® patients from the

studies are combined, 80% power to reject the above null hypothesis during a given year, under various assumptions of the true event rate:

True Event Rate During a 12-Month Period (%)	Total Number of On-Label Endeavor® Evaluable Patients		
	(US and OUS Combined)	OUS Protect	US Post-marketing study
0.50%	1941	1300	641
	1941	1200	741
	1941	1100	841
	1941	1000	941

If the true Endeavor® thrombosis rate is as large as 0.5% and 1200 *on-label evaluable* Endeavor patients are available from OUS PROTECT, approximately 800 *on-label evaluable* Endeavor® patients will be required from the US post-marketing study to ensure adequate power for rejecting the above null hypothesis when US post-marketing study and OUS PROTECT study patients are combined. Assuming a 40% on-label rate, then 2000 patients would be required to be enrolled in US post-marketing study to yield 800 US post-marketing study on-label evaluable Endeavor® patients.

Based on previous experience with Endeavor®, it is anticipated the true post one-year thrombosis rate is no larger than 0.5%. Thus 2000 patients will be enrolled in US post-marketing study.

Cardiac Death/MI Composite Endpoint:

The primary analysis on the composite endpoint of cardiac death/MI will be the assessment of non-inferiority of Endeavor® Zotarolimus Eluting Coronary Stent System cardiac death/MI incidence to the Driver® cardiac death/MI incidence on the Endeavor® on-label patients. This non-inferiority analysis will be performed yearly through 3 years (with descriptive treatment comparisons following through 5 years of follow-up), with the primary interest of showing non-inferiority of Endeavor® to Driver® at 1 year. The Endeavor® patients will be obtained from the US post-marketing and OUS PROTECT studies; the Driver® patients will be obtained from the Endeavor II clinical study (589, 586, and 579 Driver® patients are evaluable at 1, 2 and 3-years post-procedure).

The null hypothesis (H_0) for this endpoint is that the incidence in patients treated with the Endeavor® Zotarolimus Eluting Coronary Stent System ($\pi_{ENDEAVOR}$) will exceed the endpoint incidence by 50% or more for patients treated with Driver® (π_{DRIVER}). The non-inferiority alternative hypothesis (H_1) is that $\pi_{ENDEAVOR}$ will be less than π_{DRIVER} plus a non-inferiority margin approximately 50% of π_{DRIVER}. Thus,

$$H_0: \pi_{ENDEAVOR} \geq \pi_{DRIVER} + \delta$$
$$H_1: \pi_{ENDEAVOR} < \pi_{DRIVER} + \delta.$$

Based on Endeavor II, π_{DRIVER} is estimated to be 4.6%, 5.8%, and 6.7% at 1, 2 and 3-years post-procedure, respectively (these are the point estimates of π_{DRIVER} from Endeavor II). The test of non-inferiority will be carried out using the Farrington-Manning test on the treatment difference. The Driver® patients will be obtained from the Endeavor II study; the Endeavor® patients will be obtained from the combined US post-marketing and PROTECT OUS studies.

The table below presents power at a one-sided α of 0.05 for expected evaluable sample sizes and the 1-, 2-, and 3-year post-procedure anticipated results. Power is presented for all patients and for

the on-label patients (assuming there are at least 1,900 evaluable on-label Endeavor® patients from the US post-marketing and OUS PROTECT studies combined at each time point; such a sample size is expected with 2000 patients enrolled in US post-marketing study) as analyses will be conducted for all patients and on the subgroup of on-label patients.

Time	$\pi_{ENDEAVOR}$	π_{DRIVER}	δ	All Patients (6,000 Endeavor®, ~600 Driver®)	On-Label Patients (At least 1900 Endeavor®, ~600 Driver®)
				Power (1-β)	Power (1-β)
1-year	4.6%	4.6%	2.30%	89%	80%
2-year	5.8%	5.8%	2.90%	94%	87%
3-year	6.7%	6.7%	3.35%	96%	91%

3.5.2 Interim Analysis

Given the patients in this study are obtained from other clinical trials, there is no planned interim analysis for this trial.

3.5.3 Statistical Analysis

Unless otherwise specified, the analysis described below will be performed on all patients and then on *on-label* patients. Also, analyses will be carried out through 5 years post-procedure, unless otherwise specified. All analyses will be performed by using widely accepted statistical or graphical software.

Prior to performing the statistical analyses comparing treatments outlined below, assessment of the poolability (or i.e., comparability) of Endeavor US post-marketing and PROTECT OUS on-label patients will be carried out. Specifically, Endeavor® on-label patients from the two studies will be pooled prior to carrying out the analyses outlined below if there is no significant difference between the two studies with respect to the clinical endpoint in question at the 0.05 level of significance, adjusting for the clinically relevant baseline covariates of age, gender, reference vessel diameter, percent diameter stenosis, lesion class, hyperlipidemia status, smoking status, history of diabetes mellitus, minimal lumen diameter, and lesion length. If poolability is not met, discussions with the FDA will be conducted to discuss how to proceed with the analysis.

The analysis, detailed below, will consist of two primary assessments:

a. Estimation of definite/probable Endeavor® stent thrombosis (ARC definition) rate during the 12-24, 24-36, 36-48 and 48-60 month periods post-procedure (patients will be obtained from the Endeavor US post-marketing and PROTECT OUS studies);
b. Comparison of Endeavor® to Driver® on cardiac death/MI rate at the end of each of 1, 2, 3, 4, and 5 years post-procedure, with the primary interest being at 1-year post-procedure (Driver® patients will be obtained from the Endeavor II study);

An important secondary analysis will be:
Comparison of Endeavor® to Cypher® on definite/probable stent thrombosis (ARC definition) rate at the end of each of 1, 2, 3, 4, and 5y ears post-procedure (Cypher® patients will be obtained from the OUS PROTECT Study).

Baseline Analysis:

Clinically relevant baseline variables will be tabulated and compared between patients allocated to treatment with the Endeavor®, Cypher® or Driver® stent in order to evaluate the homogeneity of treatments on baseline characteristics. Categorical variables will be evaluated by using chi-square or Fisher's exact tests, whereas continuous variables will be evaluated by Wilcoxon rank-sum tests.

Analysis on Stent Thrombosis (Definite/Probable According to ARC Definition)

The number and percentage of patients with stent thrombosis (definite/probable according to the ARC definition) during the periods from 12-24, 24-36, 36-48 and 48-60 months post-procedure will be presented. One-sided upper exact binomial 95% confidence intervals (CIs) of each percentage will be calculated. If the this upper 95% CI is below 1%, the resulting percentage will be considered to be statistically significantly below 1%. For each time period, patients entering the time-period without stent thrombosis and who have complete 12-month follow-up, or a thrombosis during the 12-month time period, will be included in the analysis. The incidence of endpoint of stent thrombosis during each time period will also be evaluated according to the method of Kaplan-Meier, with a one-sided upper 95% CI of the Kaplan-Meier estimate. If this upper 95% CI is below 1%, the resulting Kaplan-Meier estimate of the incidence will be considered to be statistically significantly below 1%. All patients entering the time period without stent thrombosis will be included in the Kaplan-Meier analysis; patients without an event in the time period will be censored at the time of withdrawal or at 12 months after the start of the time period, whichever is earlier.

At the end of each of 1, 2, 3, 4, and 5 years post-procedure, the time to the endpoint of stent thrombosis (definite/probable according to the ARC definition) will be evaluated for Endeavor® and Cypher® stent groups separately according to the method of Kaplan-Meier, and the two-sided log-rank test will be applied to compare the time-to-endpoint between the Endeavor® and Cypher® stent groups in a superiority manner. Patients from the Endeavor® group will be obtained from the Endeavor US post-marketing and PROTECT OUS studies; patients from Cypher® will be obtained from PROTECT OUS. Hazard ratios and corresponding two-sided 95% confidence intervals will be determined by using a Cox proportional hazards model. A statistically significant treatment difference will be declared if the two-sided P-value from the log-rank is less than 0.05. The analysis will be performed according to the intention-to-treat principle (all enrolled patients), where patients without the event will be censored at the end of the time period being evaluated or at the time of premature withdrawal, whichever is earlier. Analysis will be also performed on all patients with complete follow-up at each time point.

For the thrombosis analysis on all patients, an assessment of the treatment-by-on/off-label status interaction on time to stent thrombosis will be performed using Cox proportional hazards regression. The Cox model will contain the main effects treatment and label status (on vs. off) and the interaction of treatment with on/off-label status. A 0.10 level of significance will be used to declare a significant interaction. If the interaction is significant, Kaplan-Meier estimates of thrombosis rates will be presented for each treatment within each label status to help assess the nature of the interaction.

Analysis on Cardiac Death/MI

For the co-primary composite endpoint of cardiac death/MI, non-inferiority of Endeavor® to Driver® will be assessed using the Farrington-Manning test on the treatment difference at the end of each of 1, 2, and 3 years post-procedure, using the time point-specific non-inferiority margins discussed above. The primary interest is the 1-year post-procedure time point. The tests will be conducted at the one-sided 0.05 level of significance. Patients from the Endeavor® group will be

obtained from the Endeavor US post-marketing and PROTECT OUS studies; patients from Driver® will be obtained from the Endeavor II study. Due to the fact that the Endeavor® and Driver® patients are from two different studies, there is a possibility of treatment imbalance on clinically relevant baseline characteristics. If there are baseline imbalances between the two groups (at a two-sided 0.05 level of significance) due to the non-randomized nature of group membership, then the treatment difference confidence interval on cardiac death/MI rate will be calculated as follows: For each individual a propensity score for group (Endeavor®, Driver®) membership will be calculated using logistic regression, with "group" as the outcome and clinically relevant baseline variables as the independent variables. Patients will then be categorized into quintiles based on this propensity score. A one-sided upper 95% confidence interval of the treatment difference (Endeavor® minus Driver®) in cardiac death/MI rates adjusted for propensity score quintile will be calculated as follows (Koch et al., 1989):

$$\frac{\sum_{h=1}^{n} w_h \left(p_{ha} - p_{hc}\right)}{\sum_{h=1}^{n} w_h} - 1.645 \frac{\left[\sum_{h=1}^{n} w_h^2 \left(SE_{ha}^2 + SE_{hc}^2\right)\right]^{1/2}}{\sum_{h=1}^{n} w_h},$$

where h = propensity strata; a = Endeavor; c = Driver;
p_{ha}, p_{hc} = sample proportions; n_{ha}, n_{hc} = sample sizes;
$w_h = \frac{n_{ha} n_{hc}}{n_{ha} + n_{hc}}$; $SE_{ha}^2 = \frac{p_{ha}(1 - p_{ha})}{n_{ha} - 1}$; and $SE_{hc}^2 = \frac{p_{hc}(1 - p_{hc})}{n_{hc} - 1}$

If the upper one-sided confidence limit is less than the pre-specified non-inferiority margin δ, then Endeavor® will be considered not inferior to Driver® on cardiac death/MI rate. If non-inferiority is claimed at the one-sided 0.05 level of significance, a superiority test of difference between the two groups will then be carried out using the log-rank test (stratified by propensity score quintile, if necessary).

As a secondary safety analysis, the Kaplan-Meier estimate of the treatment difference in cardiac death/MI rate (Endeavor® minus Driver®) and its upper one-sided 95% confidence interval will be calculated, stratified by propensity score quintile if necessary. If this upper limit of the confidence interval of the difference is below the non-inferiority margin δ, Endeavor® will be considered not inferior to Driver® on cardiac death/MI incidence; if this upper limit is below 0, Endeavor® will be considered superior to Driver® on cardiac death/MI incidence.

For the 4- and 5-year post-procedure time points, time to cardiac death/MI will be compared descriptively between Endeavor® and Driver® patients (no formal non-inferiority testing) using the log-rank test. Kaplan-Meier estimates of the cardiac death/MI rate will be presented for each treatment. The treatment difference in cardiac death/MI rates and its two-sided 95% confidence interval will be provided using the Kaplan-Meier approach.

Time to cardiac death/MI will also be compared descriptively between Endeavor® and Cypher® patients using the log-rank test yearly through 5 years post-procedure. Kaplan-Meier estimates of the cardiac death/MI rate will be presented for each treatment. The treatment difference in cardiac death/MI rates and its two-sided 95% confidence interval will be provided using the Kaplan-Meier approach at each time point.

Time-to-event secondary endpoints will be compared between treatments (Endeavor® vs. Cypher® and Endeavor® vs. Driver®, when possible) in a similar manner as for stent thrombosis. Other dichotomous secondary endpoints will be compared between treatments using the chi-square test.

As further secondary analysis, (a) descriptive assessment of the Endeavor® stent thrombosis rate during each of the 0-12, 12-24, 24-36, 36-48 and 48-60 month periods post-procedure, (b)

descriptive comparisons between Endeavor® and Cypher® (Kaplan-Meier estimates of the treatments' event rates and of the treatment difference in event rates, two-sided 95% confidence intervals of this treatment difference, and the log-rank test comparing treatments) on stent thrombosis at the end of each of 1, 2, 3, 4, and 5 years post-procedure, and (c) descriptive assessment of Endeavor® on cardiac death/MI at the end of each of 1, 2, 3, 4, and 5 years post-procedure, will be performed for the following subgroups of the intent-to-treat population:

Demographics

- Age (age < 65 years; age ≥ 65 years)
- Sex (male, female, transgender)
- Race and ethnicity

Patient characteristics

- Patients with diabetes, stratified by insulin-requiring or noninsulin-requiring
- Patients with renal insufficiency, stratified by creatinine clearance (CrCl) using the Cockcroft-Gault equation (CrCl > 60 mL/min, CrCl ≥ 30 and ≤ 60 mL/min, CrCl < 30 mL/min)
- Left ventricular (LV) dysfunction (ejection fraction < 30%, 30-40%, > 40%)
- Patients with 3 vessel disease
- Patients with 2 vessel disease including proximal left anterior descending coronary artery disease

Lesion characteristics

- Lesions in the setting of acute ST elevation myocardial infarction (STEMI)
- Percutaneous coronary interventions within 36 hours of non-STEMI ACS
- Lesion length (≤ 20 mm, 21-30 mm, 31-40 mm, > 40 mm)
- Vessel diameter (2.0 - ≤ 2.5 mm; 2.6 – 2.9 mm; 3.0 - ≤ 3.5 mm, and > 3.5 mm)
- Ostial lesions
- Bifurcation lesions
- Trifurcation lesions (i.e., left main coronary artery, left circumflex coronary artery, left anterior descending artery, and ramus intermedius)
- Thrombus-containing lesions
- Lesions with residual dissection post stenting
- Left main coronary artery (LMCA) lesions
  - Include whether disease was ostial, mid, or terminal and whether or not it involved the ostial LAD +/- LCFX
- Chronic total occlusions (CTO)
- Saphenous vein grafts (SVGs)
- Arterial grafts (internal mammary artery, radial artery, gastroepiploic artery)
- Post-brachytherapy
- In-stent restenosis (ISR) (BMS)
- In-stent restenosis (ISR) (DES)
- Overlapping BMS
- Overlapping DES
- Overlapping BMS and DES
- Non-overlapped multiple stents (in the same vessel or in different vessels)
- Intravascular ultrasound guidance for initial stent deployment

Details on procedures to account for missing, unused or spurious data, and deviation(s) from this analysis plan will be described in a separate Statistical Analysis Plan (SAP). This SAP will be finalized before the database is locked.

3.6 Number of Centers

It is anticipated that up to 100 enrolling centers from the United States will participate in this clinical trial.

4. PATIENT SELECTION

Whenever the investigator is prepared to treat the patient in his/her best interest with a drug eluting stent in accordance with the applicable guidelines on percutaneous coronary interventions, manufacturer's Instructions for Use, national reimbursement policy, Declaration of Helsinki, Code of Federal regulations etc, the patient should be considered for inclusion in this study.

The study specific in- and exclusion criteria are:

4.1 Inclusion criteria

1. Patient is > 18 years of age (or minimum age as required by local regulations).
2. The patient has consented to participate and has authorized the collection and release of his medical information by signing the "Patient Informed Consent Form".
3. All lesions requiring interventions (target lesions - one to a maximum of four) in one or more native coronary arteries are amenable for implantation of one or more Endeavor® Zotarolimus Eluting Coronary Stent System
4. Patient indication, lesion length and vessel diameter of the target lesion(s) are according to the 'Indications for Use' as mentioned in the 'Instructions for Use' that comes with every Endeavor® Zotarolimus Eluting Coronary Stent System*.
5. The patient is willing and able to cooperate with study procedures and required follow up visits.

* Please check the 'Instructions for Use' that comes with the product. Please be aware that the 'Instructions for Use' may be subject to change in the course of the study.

4.2 Exclusion Criteria

1 Women with known pregnancy or who are lactating.
2 Planned elective surgery necessitating discontinuation of anti-platelet therapy within the regular planned period of anti-platelet administration.
3 Patients expected not to be compliant with the anti-platelet and/or anticoagulation therapy regimen.
4 Previous brachy-therapy.
5 Previous implantation of a drug eluting stent.
6 Previous implantation of a bare metal stent in the preceding year.
7 Simultaneous or planned intervention on other non cardiac vessels, including but not limited to renal artery or carotid artery.
8 Current medical condition with a life expectancy of less than 3 years.
9 Manifest acute severe heart failure (Killip class III-IV).
10 The patient is currently, and during the first 3 years of the U.S. Postmarketing trial, participating in another investigational device or drug study that clinically interferes with the U.S. Postmarketing-study endpoints; or requires coronary angiography or other coronary artery imaging procedures. The patient may only be enrolled in the U.S. Postmarketing-study once.
11 Patients with medical conditions that preclude the follow-up as defined in the protocol or that otherwise limits participation in this study.
12 Patients on warfarin or similar anti-coagulant therapy.
13 Patients with hypersensitivity or allergies to one of the drugs or components indicated in the Instructions for Use.
14 Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.
15 Patients in whom anti-platelet and/or anticoagulation therapy is contraindicated.
16 Transplant patients.

5. STUDY PREPARATION PROCEDURES

5.1 Investigator / Site selection

For this study, the following investigator/site selection criteria are applicable:

- Center must have sufficient patient population.
- Investigator should have adequate dedicated staff that has time to manage the study.
- Center must be willing to comply with the protocol and data requirements.
- Center has preferably demonstrated experience with conducting clinical (device) trials that comply with applicable regulatory standards.
- Center has an Internet connection with sufficient speed of data transfer.
- Endeavor stents are available from hospital stock.
- Center willing to participate in study with follow-up of patients for 5 years.

All investigators will be appropriately qualified practitioners legally entitled to practice, and experienced in the diagnosis and treatment of patients requiring a percutaneous coronary intervention (PCI) procedure with a Drug Eluting Stent.

5.2 Review

5.2.1 Institutional Review Board

Written approval from the Institutional Review Board (IRB) with authority for the participating site will be obtained prior to the start of the study.

The investigator is responsible for submitting all required documents to their IRB. At a minimum the following documents will be submitted:

- Clinical Investigation Plan (CIP)
- Patient Informed Consent documents in the local language
- Patient pocket card with physician's contact details
- Any other written information to be provided to the patients in the local language
- Other documents will be submitted as per local requirements.

If requested, a copy of the 'Instructions for Use' for Endeavor® Zotarolimus Eluting Coronary Stent System can also be provided by the investigator to the IRB. After obtaining IRB approval, the investigator will submit the approval letter indicating the approved version of the CIP, Patient Informed Consent, and any other reviewed documentation to Medtronic CardioVascular and/or its designee for review.

5.2.2 Informed consent procedure

All patients must give informed consent prior to enrollment in the study. Informed consent will be obtained prior to the performance of any study related test that is outside of the normal clinical practice. The patient informed consent explains that already available clinical data from patient files may be used for the study. In other words, when certain tests are performed as a standard procedure in the hospital, these may be taken into account for the baseline eligibility, without the need to have a prior patient informed consent. Patients must give informed consent before the study specific procedure.

The process for obtaining informed consent shall:

- Avoid any coercion of or undue influence of patients to participate,
- Not waive or appear to waive patient's legal rights,
- Use language that is non-technical and understandable to the patient or his/her legal representative,
- Provide ample time for the patient to consider participation,

- Include dated signatures of the patient or the patient's legal representative (or impartial witness according to IRB requirements) and the investigator,
- Show how informed consent will be obtained and recorded in circumstances in which the patient is unable to give it.

A patient informed consent document will be given to each patient, including an explanation of the study, duration, expected benefits and risks or inconveniences, explanation of alternatives, medical record access and patient anonymity, if data is used for publications or submission for reimbursement support. The principal investigator may delegate the responsibility to obtain informed consent to one or more of the staff members. This will have to be documented. A sample of the patient informed consent form is presented in Appendix 12.1.

The signed consent forms will be retained by the investigator and made available (for review only) to study monitors, auditors or inspectors on request.

A copy of the signed and dated informed consent form will be provided to the patient.

In the event that the patient is unable to provide written informed consent, verbal consent from the patient or written assent from a legally acceptable representative will be accepted to facilitate enrolment. The legal representative may provide written consent on behalf of the patient only after having been fully informed about the study. Where a patient is providing verbal consent, an impartial witness must be present during the entire informed consent discussion. Once consent has been given, the witness must sign and personally date the consent form, to confirm that the information contained within the informed consent and any further information provided by the investigator, was explained to and apparently understood by the patient and that consent was freely given. Where a patient has initially verbally consented or a patient's legally acceptable representative has assented on behalf of the patient, written consent should be sought from the patient as soon as, in the investigator's opinion, the patient is capable of understanding the process and capable of signing the consent form.

5.2.3 General study and regulatory requirements

The post-market release study will be conducted according to the Declaration of Helsinki, ISO 14155, 21 CFR 822 and applicable local regulations. The adverse event collection will be focused on clinical events specific to drug eluting stents (see also section 6.4).The participating investigator is responsible for adhering to this Clinical Investigation Plan, the Declaration of Helsinki, ISO 14155, 21 CFR 822, the agreement and the regulatory requirements.

Prior to enrolling any patients in the study, all requirements need to be fulfilled. Each study site must have written documentation of site/investigator readiness, including but not limited to IRB approval, and a signed Investigator Agreement. The investigators shall agree to this investigational plan and any amendments and indicate their approval by signing and dating the Investigator's Agreement.

5.3 Training requirements

A representative of Medtronic and/or the Contract Research Organization will provide training on the study documents and the Electronic Data Capture system. Key site personnel will be trained on the Clinical Investigational Plan, Informed Consent Procedure, and the web-based data-collection system. Training records will be maintained in the investigator site file and in the sponsor file at Medtronic and/or its designee.

5.4 Study material and site readiness

Data collected on each patient will be recorded on a web-based electronic Case Report Form (eCRF). The password for the electronic CRF will only be distributed to investigational centers where the sponsor or the CRO has written documentation of site readiness.
Medtronic and/or the designated CRO will be responsible for site management during the study including sending requests to solve electronic Data Clarification Forms that have been sent to the sites based on monitoring or database queries.

The following documentation must be in place before site initiation both at the participating site and at Medtronic or the CRO before patient enrollment begins:
IRB approval
Signed Investigator Agreement

5.5 Devices Accountability

5.5.1 Device Traceability and Disposition

The Endeavor® Zotarolimus Eluting Coronary Stent will be obtained by the centers according to routine hospital procedures for commercial products. The device will be used within the intended approved indication. Existing approved procedures for commercial product regarding distribution, shipment, storage, handling, and return of these devices will be followed. For clinical study related purposes, the model and serial number of all stents used will be documented in the eCRF.

6. STUDY METHODS

6.1 Point of Enrollment

Point of enrollment in this study is the moment when the device is introduced into the guide catheter. Enrollment will occur after confirming that the signed informed consent has been obtained, the patient and the target lesion(s) have met all of the inclusion and none of the exclusion criteria, and prior to any percutaneous treatment of any of the target lesions.

Since analysis will be by Intention-to-treat, patients in whom delivery of one of more study stents failed or patients in whom no attempt is made to deliver a study stent should be included and followed up.

All reportable events occurring after the enrollment, irrespective of whether the stent implantation procedure has actually started, must be documented in the eCRF.

6.2 Implant or Procedure Aspects

6.2.1 Study Procedures

Patients will need to have an indication for placement of a drug-eluting stent according to the 'Instructions for Use' of the Endeavor® stent, which is provided with the product. It is highly recommended that all consecutive patients who meet the inclusion and exclusion criteria should be enrolled.

6.2.2 Stent Implantation Procedure

The stenting procedure should be performed according to the 'Instructions for Use' that is being provided with each Endeavor® Zotarolimus Eluting Coronary Stent System.

Preferably a stent length should be selected so that the lesion can be covered with a single stent in order to avoid the use of multiple stents.

Optional: in case IVUS is being performed during the stent implantation procedure, investigators are requested to enter key parameters in the eCRF.

For treatment of in-stent restenosis, especially when of a focal nature, balloon angioplasty eventually with a cutting balloon is recommended. Additional stent implantation should be avoided. If, at the discretion of the operator, stent implantation is required, either the assigned study stent, or any other bare or drug eluting stent is recommended but the stent from the control arm.

Investigators are requested to carefully document the stent implantation procedure angiography for later usage by the Clinical Event Committee. Angiograms should be retrievable during the duration of the study.

6.2.3 Anti-platelet Therapy

The following anti-platelet therapy is recommended for this trial:

Aspirin: 75 mg daily for 3 days prior to the procedure, or a peri-procedural loading dose of 250-500 mg. Aspirin (at least 75 mg daily) should be continued indefinitely.

Clopidogrel: 75 mg for 3 days prior to the procedure, or a peri-procedural loading dose between 300-600 mg.

Clopidogrel should be prescribed for minimally for 3 months (as per manufacturer's Instructions for Use) and it is recommended to continue this maximally for 12 months (as per ACC/AHA/ SCAI guidelines). Clopidogrel administration may be continued for a longer time period according to physician's and/ or center decision.

If a patient develops a sensitivity or intolerance to clopidogrel subsequent to enrollment, the patient may be given ticlopidine (250 mg BID).

In the decision for the duration of clopidogrel administration, the investigators should take into consideration:
The Manufacturer's Instructions for Use of the Endeavor stent recommends clopidogrel administration for minimally 3 months,
The European Society of Cardiology guidelines for Percutaneous Interventions recommend 6-12 months clopidogrel administration after DES 32,
ACC/AHA/SCAI guideline recommendation that dual anti-platelet therapy be continued for 12 months in patients who are not at high risk for bleeding [33],
Individual patient characteristics.

Administration of less widely-used anti-platelet drugs, such as cilostazol, is discouraged.

The investigator is free to restart or extend the duration of clopidogrel administration if during the follow-up period a new PCI is performed.

During each follow up visit, the investigator's assessment of patient compliance with anti-platelet therapy will be documented [27].

All other co-medication use is at the investigators discretion and will therefore be done according to hospital routine.

6.2.4 Data Collection Time Intervals

This study does not require any specific test or procedure that falls outside a standard stenting procedure as routinely done in the hospital, except for the follow-up schedule that might have more contact moments, and an extra ECG at the 3 years follow-up visit. These clinical follow-ups can be done by phone or preferably by outpatient clinic visit.

Table 3 summarizes what data will be collected prospectively within this study.

ECG
Pre-procedure and post-procedure electrocardiograms will be collected and sent to the CRO by pre-paid courier envelopes.

An ECG will also be collected at the 3-year follow-up visit. The ECG can be performed by a referring center or general practitioner.

Additionally, printouts of ECGs will be collected for death or any suspected myocardial infarction or suspected stent thrombosis that occurs after the index procedure for adjudication purposes by a Clinical Event Committee (CEC).

Angiography
Visual estimation of lesion characteristics in relation to the index procedure will be done by the operator and recorded on the e-CRF.

There is no mandatory angiographic follow-up in the protocol. Investigators are advised to perform angiograms only on a clinically driven basis, i.e. in case of symptoms or demonstrable ischemia. Systematic control angiograms should be avoided.

Baseline and event angiograms will be collected that are related to a study primary or main secondary endpoint, including but not limited to death, (suspected) myocardial infarction or stent thrombosis.

Angiograms of TLR and TVR will be collected, irrespective whether the (re)-intervention was performed in relation to a study primary endpoint, for qualitative review by the angiographic core lab for presence of a stent thrombosis.

Cardiac Biomarkers
Before the procedure, and preferably within 72 hours of the procedure, a creatine kinase (CK) enzyme, creatine kinase myocardial-band (CK-MB) isoenzyme test and Troponin will be obtained. Post-procedure, as a minimum at least one blood sample should be taken for measurement of CK, CK-MB and Troponin. If total CK values are within normal ranges, CK-MB measurements may not be performed per hospital standards.

If a Myocardial Infarction (Non-Q waves or Q waves) has occurred after procedure, CK, CK-MB and Troponin values will be collected on a Myocardial Infarction Form for adjudication purposes by the Clinical Event Committee.

MACCE
Data regarding Major Adverse Cardiac and Cerebral Events (MACCE), which are expected Serious Adverse Events, will be recorded in the eCRF within 10 working days after the investigator becomes aware of the event.

Note: Percutaneous procedures within 6 weeks post-procedure, and indicated to be staged procedures, will not be counted as revascularizations.

Staged Procedures/ TLR/ non TLR
Data regarding Staged Procedures/ TLR/ non TLR will be recorded in the CRF at hospital discharge and throughout the follow-up period.

Bleeding Complications
Data regarding bleeding complications including strokes will be recorded in the eCRF at hospital discharge and throughout the follow-up period. The eCRF will request all information to classify according to the Charisma, TIMI and Gusto following definitions.

Stroke
For strokes, confirmation of the diagnosis by a neurologist and imaging through computed tomography or magnetic resonance is recommended.

Follow-up
Follow-up assessments will be done at:
Day 0 = day of randomization
30 ± 5 days
6 mo ± 14 days
1 yr ± 30 days
1½ yrs ± 30 days
2 yrs ± 30 days
2½ yrs ± 30 days
3 yrs ± 30 days
4 yrs ± 30 days

5 yrs ± 30 days

These clinical follow-ups can be done by phone or preferably by outpatient clinic visit. The patient should be carefully interviewed regarding hospitalizations, myocardial infarctions, coronary angiographies/ interventions as well as compliance regarding clopidogrel intake since the previous follow-up visits.

The maximum follow-up period for each individual patient is 5 years.

Note: MACCE should be recorded in the eCRF within 10 working days after the investigator becomes aware of the event, and not be postponed until the next follow-up visit is due.

Note: compliance to the follow-up schedule is essential to enable an analysis of the results in a scientifically sound and meaningful way. If, for whatever reason, the patient follow-up cannot be scheduled within the time window or occurred outside the time window, it is still essential to document the patient data at a date as close as possible to the calculated follow-up date. Patients Lost-To-Follow-Up should be avoided as much as possible and investigators are urged to do their utmost best to maintain patient's follow-up compliance. Contacting the patient's general practitioner or referring cardiologist should be considered in case the patient cannot be reached in order to obtain information about the patient's health status and documented in the patient's file. Several attempts over a period of time should have been made to contact the patient, family- or referring physician before documenting a patient LTFU. Death registry databases should be consulted where these databases are available and accessible to treating physicians.

Table 3: Summary of study procedures

	Baseline	Procedure	Discharge	Follow-up [4]
Eligibility criteria	X	-	-	-
Demographics	X	-	-	-
Cardiac Risk Factors	X	-	-	-
Current Cardiac Status	X	-	X	X
Angiographic Lesion Characteristics	X	X	-	-
Patient Informed Consent		X (before procedure)		
Randomization		X		
Procedure data	-	X	-	-
Anti-platelet medication	-	X	X	X
MACCE / non TLR / non TVR / bleeding complications	-	X	X	X
Cardiac biomarkers [1]	-	Xpre Xpost	-	-
ECG	-	Xpre Xpost	-	X [5]
Event related:	-	-	-	-
- Cardiac biomarkers [1]	-	-	X	X
- ECG [2]	-	-	X	X
- Angiogram [3]	-	-	X	X
- Anti-platelet medication			X	X

[1)] If a Myocardial Infarction has occurred after procedure, peak CK, CK-MB and Troponin values will be collected on the Myocardial Infarction Form. These biomarkers will also be collected during the procedure. To classify according to the ARC definitions it is strongly recommended to measure peri-procedural CK and CK-MB values and not only Troponin values.

[2)] Printouts of ECG will be collected for death or any suspected myocardial infarction or suspected stent thrombosis that occurs after the index procedure for adjudication purposes by a Clinical Event Committee (CEC).
[3)] Baseline and event angiograms will be collected for angiographies related to the primary endpoint. For TLR and TVR, the angiogram of the (re)-intervention will be collected.

[4)] Follow-up is planned after about 30 days, 6 months, 1, 1½, 2, 2½, 3, 4 and 5 years. Follow-ups may be conducted by phone.

[5)] Printouts of ECG will also be collected at the 3 years follow-up visit. The ECG can be performed by a referring center or general practitioner. These ECGs should be sent to the CRO by pre-paid courier envelopes.

6.2.5 Description of data variables to be collected

Table 4 summarizes projected data variables to be collected in the electronic-CRF. The list is not all-inclusive; please refer to CRF for further details.
The electronic CRF will have separate pages to capture data on MACCE, tooth extractions and surgical procedures, and separate pages to collect concomitant medication information. The concomitant medication page will be limited to capture data on anti-platelet medication.

Table 4: Data variables and documents to be collected

Visit	Variable
Baseline	• Age • Gender • Race and Ethnicity • Eligibility criteria • Current Cardiac status • Cardiac History • Cardiac Risk factors.
Lesion characteristics	• Vessel • Lesion location • Lesion type • Degree of tortuosity • Degree of calcification • Thrombus present • TIMI flow
Pre-procedure angiography (complete visual estimate in eCRF):	• Reference Vessel Diameter (RVD) in mm • Pre-procedure Minimum Lumen Diameter (MLD) in mm • Lesion length in mm
Procedure	• Date of Procedure • Number of stents used • Study Stent details • Stent implantation techniques • Anti-platelet medication
Post procedure final result	• Diameter Stenosis (%)
Hospital Discharge	• Date of discharge • Any new MACCE event since the procedure • Current Cardiac status

Visit	Variable
	• Anti-Platelet Medication • Provide copy of ECG
Follow-up (30 days, 6 months, 1, 1½, 2, 2½, 3, 4, and 5 years)	• Date of follow-up visit • Type of follow-up visit (telephone or routine clinic visit) • MACCE events • Current Cardiac status • Change in Anti-platelet Medication • ECG (at 3 years follow-up)
In case a Death event occurred	In case of death, please provide, if available a copy of: • hospital discharge letter • death note / autopsy report • multiple ECGs related to event • all available lab results • all angiograms (procedure and event related) • cath lab report / technical worksheet
In case a Myocardial Infarction occurred	In case of a myocardial infarction, please provide, if available a copy of: • hospital discharge letter • multiple ECGs related to event • all available lab results • all angiograms (procedure and event related) • cath lab report / technical worksheet
In case a Stent thrombosis occurred	In case of a (suspected) stent thrombosis, please provide, if available a copy of: • hospital discharge letter • multiple ECGs related to event • all lab results • all angiograms (procedure and event related) • cath lab report / technical worksheet
In case of Bleeding complications	In case of a bleeding complication, please provide, if available a copy of: • hospital discharge letter • relevant lab results (HGB, HCT)
In case of Stroke	• Stroke form should be completed • MRI or CT-scan
In case of PCI	• For any surgical or percutaneous TL or non-TL intervention, the revascularization form should be completed. Angiograms will be collected for all TLR and TVR.

6.3 Adverse Events Reporting Requirements

6.3.1 Study Reporting Requirements

In accordance with the primary and secondary endpoints of this study, adverse event collection is mainly focused on the collection of Major Adverse Cardiac and Cerebral Events (MACCE) events as this is a widely accepted parameter to assess the clinical performance of coronary stents [1-14]. The safety and efficacy of Endeavor has been assessed in clinical studies in which extensive data has been collected related to safety and efficacy. This study will also collect data related to stent delivery performance, complaints/device malfunctions and stent thrombosis, irrespective of whether it is related to a MACCE.

The reporting of product complaints and malfunctions should be done by the investigator through the eCRF system.

All product complaints and malfunctions related to the Endeavor® Zotarolimus Eluting Coronary Stent System should be reported to your local Endeavor representative as a Complaint after occurrence. In case of product complaints or malfunctions, the devices/accessories need to be returned (if possible) to:

Field Assurance
Medtronic CardioVascular
3576 Unocal Place
Santa Rosa, CA 95403

Events need to be reported according to the table below:

Table 5: Adverse Event reporting requirements

Major Adverse Cardiac and Cerebral Events (MACCE)	
Investigator submit to:	
Medtronic by eCRF	**Within 10 working days** after the investigator first learns of the event.
IRB	Submit to IRB per local reporting requirement.
Sponsor submit to:	
FDA	Submit to FDA per reporting requirement.
Major Adverse Cardiac and Cerebral Events (MACCE) classified as life-threatening or device-related, Product Complaints or Malfunctions	

Investigator submit to:	
Medtronic by eCRF*	**Within 2 working days** after the investigator first learns of the event.
IRB	Submit to IRB per local reporting requirement.
Sponsor submit to:	
FDA	Submit to FDA per reporting requirement.

6.3.2 Clinical Event Committee

For this study, a Clinical Event Committee (CEC) will consist of multiple cardiologists who are not participants in the study. At the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. The CEC will meet regularly to review and adjudicate all clinical events in which the required minimum data is available. If needed, the adjudication committee will require collection of additional source documentation from the clinical centers by the CRO. The procedures by which the CEC will operate will be documented in a separate manual.

6.4 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) is composed of an uneven number of members (physicians from the fields of cardiology and interventional cardiology and at least one bio-statistician), who are not directly involved in the conduct of the trial. The DSMB will review the study on a periodic basis. Based on the safety data, the DSMB may recommend modifying or stopping the trial. All final decisions, regarding trial modifications rest with the Steering Committee. No formal statistical rule for stopping the trial will be defined.

6.5 Patient accountability

6.5.1 Criteria and procedures for stopping data collection

Stop of data collection for patients in the study will occur in the following cases:

- Withdrawal of consent by patient
- Physician's determination that it is in patient's best interest to be discontinued from the study
- Patient lost-to-follow-up
- Patient death
- Study stop

In case of patient death investigators are urged to obtain consent from family member(s) for post mortem examination.

6.5.2 Documentation of withdrawal, or missed follow-up

Patients may withdraw from the study at any time and for any reason. If a patient decides to withdraw from the study, the investigator will document the reason for withdrawal and indicate any rationale for the withdrawal from the study in the patient's file.

A missed follow-up visit will be documented by the investigator and reported in the eCRF, including the reason for the missed follow-up visit in the patient's file.

6.6 Clinical Investigation Plan Changes

When necessary during the progress of the project the Clinical Investigation Plan (CIP) will be updated. CIP updates or amendments need to be approved by Medtronic and the Principal Investigators (see contact information details).
Medtronic is responsible for obtaining regulatory authority approval and notification of CIP updates or amendments (if applicable). The investigator is responsible for submission of CIP

updates or amendments to the local IRB, and obtaining the required approvals, before implementing the amendment if needed.

7. QUALITY CONTROL PROCEDURES

7.1 Procedures for database management

7.1.1 Data review, processing and internal review

Data collected on each patient will be recorded on a web-based electronic Case Report Form (eCRF). A paper version of the eCRFs may be printed at the sites to use as a working copy. Instructions for proper completion of the eCRF and how the web-based system is used will be provided to the clinical site.

The investigator or an authorized member of the investigational team must sign all completed eCRFs, by using an electronic signature (the electronic signatures will be provided by Medtronic at the start of the study).

The clinical study team at the Contract Research Organization is responsible for assuring that the investigator has completed the eCRFs correctly. Data will be checked for consistency and completeness on a regular basis, both manually as well as by using computer software capabilities of the clinical database. Electronic Data Clarification Forms will be used to document the recovery of incomplete, inconsistent, or missing data.

7.1.2 Treatment of data and source data verification

The investigator is responsible for ensuring that all sections of each eCRF are complete and correct and that those entries can be verified against source data.

The investigator(s) and study personnel must be available to the CRO clinical study team. This availability is of particular importance for the completion and clarification of the data on the case report forms and regulatory responsibilities. Access to the patient records and other source data must be provided to study monitors, auditors, IRB members and/or regulatory agencies.

7.1.3 Source documents

The hospital files (electronic or paper), will constitute source data. In case a follow-up has been performed by phone, the investigator needs to record as a minimum the date of contact in the patient's hospital file as well as reason for withdrawal and actions to trace lost to follow-up patients.

7.2 Monitoring procedures

7.2.1 Site initiation visit

The initiation visit will be performed after it has been verified that the site is prepared for the study and that the requirements for patient enrollment are completed, and prior to or at the same time the first patient is enrolled. See section 9.2.1 for documentation that must be in place at the participating site before patient enrollment begins. Documentation of the training of key site personnel will be collected during the site initiation visit.

7.2.2 Periodic Monitoring visits

In order to ensure a high degree of data quality all clinical sites will be monitored at least once a year, unless no patients are enrolled.

These site-monitoring visits will be conducted to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, to verify that records and documents are being properly maintained for the duration

of the study. The monitor will perform source data verification by reviewing original patient documents.

The aim is to monitor the source data of approximately 30% patients and the Patient Informed Consents of all patients. Furthermore 100% of all deaths and reports of (suspected) myocardial infarctions and stent thrombosis will be monitored with source documents, which need to be provided to the Clinical Event Committee (CEC), for accuracy and completeness.

7.2.3 Study Close Out

The CRO will notify and inform the sites with a study closure letter. No specific Study Close Out visit will be performed. During the last monitoring visit the monitor will perform a site file review and discuss the study close out procedures with the site personnel. This can also be done by phone in the study closure period. The investigator and site personnel will be responsible for notifying the Ethics Committee (if required), checking the site files for completion and filing the study documentation for the required retention period (see section 9.2.5).

7.3 Registry suspension or early termination

7.3.1 Definitions

Early Termination of the Study: Closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the study or a single center.
Study Suspension: A temporary postponement of study activities related to enrollment and distribution of the product if applicable. This is possible for the whole study or a single center.

7.3.2 Criteria for Early Termination or Suspension

If a center is terminated or suspended, no additional enrollments will be allowed at the center. Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Non compliance to obtain patient informed consent
- Non compliance to the inclusion/exclusion criteria
- Failure to follow patients per scheduled follow-ups
- Failure to submit data in a timely manner
- IRB approval expiration
- IRB suspension of the center

7.3.3 Arrangements for Early Termination or Suspension

If the study is terminated prematurely or suspended:

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons, and inform the U.S. FDA
- The IRBs will also be promptly informed and provided with the reasons(s) for termination or suspension by the sponsor or by the clinical investigator.
- The investigator will promptly inform the patients and the personal physician of the patients, assure appropriate therapy and follow-up for the patients.
- In case of early termination the investigator agreement will be terminated.

If the investigator (or IRB) terminates or suspends the investigation without prior agreement of Medtronic:

- The investigator will promptly inform Medtronic and the IRB, and provide a detailed written explanation of the termination or suspension.
- The investigator will inform the institution

- The investigator will promptly inform the patients and the personal physician of the patients, assure appropriate therapy and follow-up for the patients.
- Medtronic will inform the regulatory authority
- In case of early termination the investigator agreement will be terminated.

7.3.4 Patient follow-up in case of early termination

In case of early termination, the patients need to be followed until at least 30-days after the index procedure.

8. DATA REPORTING

8.1 Reporting of data

8.1.1 Patient confidentiality and disclosure of data

All records and other information about patients participating in this study will be treated as confidential. The sponsor, Medtronic and the CRO will collect data and monitor study records. Auditors, IRB members, or the U.S. FDA may also have access to the study records. Participating patients will not be identified by name in any published reports about this study.

8.1.2 Publication policy

The results of this study will be made public and are intended to be presented and published. The study will be registered in the clinicaltrials.gov database.
Medtronic will form a publication committee. The committee will develop a final publication plan. The scientific validity and timing of publications will be evaluated in order to maximize the benefits derived from the publication of the clinical data of the study. In general, publications utilizing data will be managed as described below.

Publication Committee
The Publication Committee will be defined during the course of the study and after enrollment is completed. Committee membership will include representatives of the Steering Committee, and the sponsor. The goal of the Committee is to ensure that the study results are published.

The Publication Committee is responsible for overseeing the development of manuscripts/abstracts, plus identifying and appointing the manuscript/abstract first author(s)/writer(s).

The Committee reviews not only main publications, but also ancillary publications. If necessary, specified authorship criteria may be applied for ancillary publications. The Committee may decide that no publications/abstracts will be prepared prior to the end of the study, also not on individual center data.

Authorship Selection
Authors will be selected on the basis of the following:

- A significant contribution to the design of the clinical study;
- A significant contribution to patient enrollment in the clinical study;
- High quality of data as determined by the clinical study requirements;
- Demonstration of a high level of interest in the outcome of the study, and the ability to write, review, edit, and present the publication;
- A demonstration of a good publication history;
- A willingness to contribute to the publication.

All investigators not listed as co-authors will be acknowledged as investigators and will be individually listed according to the guidelines of the applicable scientific journal. All publications and presentations of data from the Endeavor US Postmarketing registry should use the phrase following the listed authors “for the Endeavor US Postmarketing registry investigators”.

Review and Communication Guidelines
Investigators will receive communication regarding the authorship selection, the publication co-authors and to which scientific platform the publication will be submitted.
Prior to submission of a publication (abstracts and manuscripts), the Publication Committee and all co-authors will review and authorize the publication (contents and platform).

9. PROJECT MANAGEMENT

9.1 Staff

9.1.1 Monitors, incl. contact information

A list of monitors will be filed separately in the Clinical Project File at the sponsor.
Each center will be provided with contact details of the monitor and contact person/ contact number/ mail address for each CRO.

9.2 Records and reports

9.2.1 Investigator records

The investigator is responsible for the preparation and retention of the records cited below. All of the records below, with the exception of patient's hospital file, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or appropriate Patient Study Binder.

- Patient's hospital file
- Clinical Investigation Plan and, if applicable, any amendment
- Instructions For Use
- Blank IRB approved Informed Consent
- Signed and dated informed consent for each patient
- Signed and dated Investigator Agreement
- IRB approval documentation
- Insurance Certificates
- Indemnification agreement, if applicable
- Randomization confirmation for each patient
- Curriculum Vitae, principle investigator only
- Safety reports and the progress reports to the IRB, if required
- Any other records that IRBs or other local regulatory agencies require to be maintained

9.2.2 Investigator reporting responsibilities

The investigator is responsible for completing and signing of all electronic case report forms and adverse event reporting. If any action is taken by an IRB with respect to the study, the information must be forwarded to Medtronic via the CRO.

Table 6: Investigator reporting responsibilities

Report	Submit To	Description
Immediately reportable AEs and MACCE	eCRF system	Reporting according to Table 5.
Premature termination or suspension of the clinical investigation	Medtronic, CRO and Ethics Committee	Provide prompt notification of termination or suspension and reason(s).
Withdrawal of IRB approval	Medtronic and CRO	Notification within five working days.
Study Deviations	eCRF system	The following deviations from the clinical investigational plan and investigator agreement need to be reported: Deviations to protect the life or physical well-being of a patient in an emergency; Deviations from inclusion or exclusion criteria (including failure to obtain informed consent);

Report	Submit To	Description
		Deviation from implantation of study-stent (excluding delivery failure).
eCRF completion	eCRF system	Electronic case report forms should be completed as soon as possible after the visit takes place.

9.2.3 Sponsor records

Medtronic and/or the CRO will maintain the following records:

- All study documents and correspondence which pertains to the study
- Clinical Investigational Plan and, if applicable, any amendments
- List of participating institutions
- Correspondence with authorities as required by national legislation
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Randomization procedure
- Final report of the clinical investigation
- Signed and dated Investigator Agreements
- Copies of all IRB approval documentation
- Instructions for use
- IRB approved informed consent
- Insurance Certificates
- Indemnification agreement, if applicable

Any other records that IRB requires to be maintained.

Depending on the sponsor and CRO responsibilities certain sponsor records may be filed at the CRO during the course of the study.

9.2.4 Sponsor/CRO reporting responsibilities

The following reports will be generated by Medtronic during and after the study:

Table 7: Sponsor and CRO Reports

Report	Submit To	Description
Immediately reportable AEs and MACCE	Investigators IRB U.S. FDA	Notification during the course of the study when appropriate (based on perceived risk), and where required by relevant local authorities and IRBs. The CRO is responsible for reporting to investigators and IRBs, and Medtronic is responsible for reporting to relevant authorities.
Premature termination or suspension of the clinical investigation	Investigators IRB U.S. FDA	The CRO will provide prompt notification of termination or suspension and reason(s) to investigator and Ethics Committee. The sponsor will provide prompt notification of termination or suspension and reason(s) to the U.S. FDA
Patient enrollment completed	Investigators IRBs Relevant Authorities	The CRO will notify the investigators within 30 working days of the completion of the enrollment. Investigators will inform their IRBs, when required.

Report	Submit To	Description
Final report	Investigators IRBs Relevant Authorities	Medtronic or the CRO will provide all investigators with a copy of the final report of the study. Investigators will inform their IRBs, when required. Medtronic will inform the relevant authorities, when required.

9.2.5 Records retention and inspection

Sponsor records and reports will be stored at Medtronic and/or the CRO during the course of the study. Site specific records will only be stored at the CRO during the course of the study. After the closure of the study, all records and reports will be archived by Medtronic permanently.

The investigator must be willing to give access to study monitors, auditors, IRB members and FDA inspectors, and have appropriate facilities to retain relevant study documents.

Investigators records will be retained for at least two years after the formal discontinuation of clinical development of the device, and according to the local requirements of the country.

10. RISK AND BENEFITS

10.1 Risks

For more detailed information on the risks of stent implantation, including a complete list of warnings, precautions and potential adverse events, please refer to the Instructions for Use for Endeavor.

10.2 Possible benefits

10.2.1 Anticipated clinical benefits

Trial patients implanted with an Endeavor stent will receive the same medical treatment as if they were not to participate in this clinical study. Participation contributes to expand the knowledge base with respect to the use of Endeavor in a broad patient population, treated with an anti-platelet regimen according to the physician's preference, and without the interference of a per protocol angiographic evaluation.

10.2.2 Balance of anticipated clinical benefits against the risk

This study will collect data prospectively on patients that receive the Endeavor® stent and treatment will be applied according to the 'Indication for Use'. The treatment will be performed according to routine hospital practice. No additional tests will be performed, apart from an extra ECG during the 3 years follow-up visit. The study will therefore not put any additional risk to the patient.

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12. APPENDICES

12.1 Sample of Patient Informed Consent

Protect Trial: An international study in which data will be collected of patients who are suitable for stenting and who will be treated with the Endeavor Zotarolimus-Eluting Coronary Stent System.

Dear Patient,

Your physician has asked you to participate in a clinical study based upon your cardiac medical history. You as a patient have to give permission in writing for participation into this project. Please read this information carefully. Your physician will be happy to answer any questions you may have regarding the study or any information presented here.

Background
Your doctor will have explained to you that you have a problem with narrowing in one or more of your coronary arteries (blood vessels which supply blood to the muscle of your heart). A narrowing can stop the heart muscle from receiving enough blood rich in oxygen, which may cause you to have chest pain (angina) and/or shortness of breath during exercise or even at rest. If a coronary artery is completely blocked then a part of the heart can be damaged and a myocardial infarction (heart attack) may occur.

One commonly used treatment to treat your condition is to insert a small metal tube (stent) in the coronary artery.

What is a stent procedure?
A stent is a small, tubular metal device that is placed in the narrow section of the artery and is intended to serve as a support to hold the arterial walls open. A stent is tightly placed on a balloon-catheter and inserted into the coronary artery. Once a stent is placed at the site of the narrowing, inflating the balloon expands the stent. After the stent has been expanded to the required diameter, the balloon is deflated and then withdrawn while the stent remains in the artery. Once a stent has been implanted, it cannot be removed.
In the recent years, drug eluting stents have been developed to reduce the chance of a re-narrowing of the stent after implantation. Studies have demonstrated that drug eluting stents have a lower chance of re-narrowing than a stent without a drug on it. The drug is released into the artery wall from the stent during the first weeks after implantation. The drug will act locally where the stent is implanted

Objective of the study
In this study the safety of Endeavor® drug eluting stent will be evaluated in a large patient population. Approximately 2000 patients will participate in this study at upto 100 hospitals in the United States.

The stents that will be used in this study is the Medtronic Endeavor® Zotarolimus Eluting Coronary Stent System that is commercially available in the United States.

Your physician will implant a drug-eluting stent according to standard stenting procedures as described above. If you decide to participate in this study, your narrowed artery(ies) will therefore be treated as is routinely done for all other patients. This procedure consists of a stent procedure as described above. In case additional stents need to be implanted during the 3 years after the initial procedure, your physician will aim to use the same stent model.

Medical check-ups
You will be contacted for medical check-ups at 30 days, 6 months, 1, 1½, 2, 2½, 3, 4 and 5 years after the implantation of the stent(s). It will take more than a year for all 2000 patients in this study to be enrolled in this study.

You should not take part in this study if you will not be available for the check-ups.

The medical check-ups will be performed by telephone or by a visit to the outpatient clinic. Your doctor will ask you a few questions to assess your medical condition. If your doctor thinks it is necessary, he will perform additional tests or request you to undergo additional investigations.

During the 5 years of medical follow-up, an electrocardiogram (ECG) will be made at 3 years through electrodes placed on your chest. This ECG and the specific schedule of the medical check-ups are the only study elements which differ from the treatment you would normally receive after having an Endeavor stent implanted.

Risks and benefits
You will be implanted with one or more Endeavor® Zotarolimus-Eluting Coronary Stent System stent. You will receive the same medical treatment as you would if you decide not participate in this clinical study. Therefore there is no higher risk associated with your participation in this study. The risk associated with stent implantation in general is dependent on the severity of the narrowing(s) in your coronary arteries, your symptoms, and also other factors. Your physician will inform you about the risk in your particular situation.

For this study, only data from your medical files will be gathered and no additional tests will be performed except for the ECG. However, you will have more medical check-ups. Your participation contributes to expand the knowledge base with respect to the Endeavor drug eluting stent in a larger patient population, which may assist physicians in their choice of treating any future patients with drug eluting stents.

Your physician can explain to you the possible risks that are associated with a standard stenting procedure with a drug eluting stent.

Alternative treatment
The alternative treatment, outside the one suggested within this study, includes amongst others stenting with a stent without a drug, another type of drug eluting stent, or medical treatment.

Pregnancy
Pregnant woman cannot participate into this clinical study. All woman of child bearing potential should have a negative pregnancy test at the beginning of the study. In case a female patient becomes pregnant during the study, she should immediately report this to her physician. The risks for the unborn child are still unknown.

Compensation for illness or injury
If you are physically injured as a result of your participation in this study, reasonable and appropriate medical treatment will be provided. You and your medical insurance is responsible for the costs of such care.

You do not waive any of your rights by signing this form.

Compensation and additional costs
You will not receive any compensation for your participation in this clinical investigation (including follow up), nor will you be reimbursed for any costs associated with your participation, such as travel expenses.

Participation is voluntary
Your participation in this study is entirely voluntary. You are free to refuse participation and you are free to discontinue participation in the study at any time without fear of penalty or loss of medical care.
In addition, you will be notified of any significant new findings that may develop during the course of the study, which may relate to your willingness to continue your participation.
Your physician or the sponsor may decide to terminate your participation in the study at any time without your prior consent. If this happens you will be notified and the reasons explained to you.

Confidentiality of your information
While participating in this study, personal information, including medical and health data, will be collected from your medical records. These data will be used and processed manually and by computer by Medtronic (meaning the Medtronic, Inc. group of companies) and/or it`s designee. Other designated parties that are involved in the study, including third party data processors, the institution in which you are treated, your physician(s), IRB (Institutional Review Board), and the U.S. FDA may also be granted access to your personal information in order to comply with legal and regulatory requirements. Your data may be communicated to the above-mentioned parties located in the United States as well as the European Economic Area, Japan and Canada..

Your personal data are collected for medical research purposes, to gather information on the device and its performance during and after this study and may be used for additional scientific research, educational purposes and publications as well as for future health studies.

Your confidential personal information will be anonymized and key-coded, unless it may be impossible to anonymize it, for instance, where your name cannot be removed from the data carrier, such as an angiogram, or in order for Medtronic to comply with its reporting obligations. In all cases, your personal information will be handled at all times in accordance with appropriate confidentiality standards and all applicable data protection and privacy laws.

You are entitled to access the personal information collected about you and to have inaccuracies corrected.

Problems or questions
In case of any question about the investigation (e.g. risks, side effects, injury etc.), you can always contact one of the following doctors:

_____
_____
_____

PATIENT INFORMED CONSENT FORM SIGNATURE SHEET

For participation in the Endeavor U.S. Postmarketing study study: A U.S. based study in which data will be collected of patients who are suitable for stenting and who will be treated with one or more Endeavor® stents.

I have read and understood the patient information of this study and my physician has answered all my questions regarding the study.

I had sufficient time to consider my participation into this study and I am aware that participation into this study is completely voluntary.

I realize that I may decide to refuse participation or stop participation at any time without affecting the quality of my health care or the relationship with my physician.

I understand and agree that personal information about me will be collected from my medical records, used and processed (manually and by computer) by the manufacturer of a medical device used in my treatment or any other designated party that is involved in the study (e.g. hospital, physician, regulatory authorities, ethics committees).

I authorize and instruct my physician(s) and institution to release the necessary personal information about me.

I understand that I am entitled to access the personal information collected about me and to have inaccuracies corrected.

I have received a copy of the Patient Information and hereby I agree to participate voluntarily in and comply with this study.

You may agree or disagree that your personal physician is informed on your participation in this study. Please check one option below indicating your choice:

☐ I agree that my personal physician is informed about my participation in this study

☐ I disagree that my personal physician is informed about my participation in this study

I agree to participate in this study.

Patient (or Legal Representative if patient is unable to give consent):

_____	_____	_____
Name	Signature	Date

Investigator or designated person by investigator:
I have conducted the informed consent discussion.

_____	_____	_____
Name	Signature	Date

If patient, or patient's legally acceptable representative, is unable to read:

I have attended the entire informed consent discussion. I attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legally acceptable representative. Informed consent was freely given by the patient or the patient's legally acceptable representative.

Impartial Witness:

_____	_____	_____
Name	Signature	Date

12.2 Investigator and institutions list

The list with participating institutions will be available in the eCRF system, and updated on a regular basis.

12.3 Definitions

Abrupt Closure	Abrupt closure is defined as the occurrence of new (during the index procedure) severely reduced flow (TIMI grade 0 or 1) within the target vessel that persists and requires rescue by a non-assigned treatment strategy (including emergency surgery), or results in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" (due to microvascular flow limitation), in which the epicardial artery is patent but has reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application does reverse the closure. **Subabrupt closure**: defined as abrupt closure that occurs after the index procedure is completed (and the patient left the catheterization laboratory) and before the 1 month follow-up. **Threatened abrupt closure**: defined as a grade B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.
Acute Success	**Device Success**: Attainment of <50% residual stenosis of the target lesion using only the assigned device. **Lesion Success**: Attainment of <50% residual stenosis of the target lesion using any percutaneous method. **Procedure Success**: Attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.
Bleeding complications	Bleeding complications will be adjudicated according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO), Thrombolysis in Myocardial Infarction (TIMI) and by the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) definitions.
Calcification	Calcification is defined as readily apparent radiopacities within the vascular wall at the site of the stenosis and is classified **as none/mild**, **moderate** (radiopacities noted only during the cardiac cycle before contrast injection), and **severe** (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen).
Cerebrovascular Accident (CVA) or Stroke	Cerebrovascular accident is defined as an acute focal neurological event regardless of the duration of clinical symptoms confirmed by MR or CT imaging deficits.

De Novo Lesion	De Novo Lesion is defined as a coronary lesion not previously treated.
Death (ARC Definition)	All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.
Death (continued) (ARC Definition)	**Cardiac death** Any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related deaths including those related to concomitant treatment. **Vascular death** Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause. **Non-cardiovascular death** Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.
Dissection Classification (NHLBI – National Heart, Lung, and Blood Institute)	**Type A** Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material. **Type B** Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles. **Type C** Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material. **Type D** Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow. **Type E** Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen. **Type F** Filling defect accompanied by total coronary occlusion.
Emergent Bypass Surgery	Emergent Bypass Surgery is defined as coronary bypass surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

Intracoronary Thrombus	Intracoronary Thrombus is defined as the presence of a filling defect within the lumen, surrounded by contrast material seen in multiple projections in the absence of calcium within the filling defect, or the persistence of contrast material within the lumen or a visible embolization of intraluminal material downstream.
Lesion Classification (American College of Cardiology/ American Heart Association Class)	**Type A** Minimally complex, discrete (length <10 mm), concentric, readily accessible, non-angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus. **Type B** Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present. **Type B1**: One type B characteristic **Type B2**: Two or more type B characteristics **Type C** Severely complex, diffuse (length >2 cm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.
Major Adverse Cardiac Events (MACE)	MACE is defined as death, MI (Q waves and non-Q waves), emergent cardiac bypass surgery, or any target lesion revascularization (repeat PTCA or CABG).
Major Adverse Cardiac and Cerebral Events (MACCE)	MACCE is defined as death, MI (Q waves and non-Q waves), emergent cardiac bypass surgery, or any target lesion revascularization (repeat PTCA or CABG) and stroke.

Myocardial Infarction (ARC Definition)	In percutaneous coronary intervention trials, initial blood sampling of CK (and CKMB or Troponin if CK is elevated) must be performed prior to the index procedure. Repeat samples should be performed at least twice between 8 and 24 hours following the procedure and at least 4 hours apart. Three categories can be distinguished being: Peri – Procedural MI Post – Intervention MI Electrocardiographic Classification
Peri – Procedural MI	*Peri – Procedural MI* is defined as within 48 hours after PCI and within 7 days after CABG. Within this category we distinguish: <u>Peri-procedural</u> Total CK >2 times upper limit of normal (ULN) in the presence of a confirming cardiac specific biomarker (a positive value of CK-MB, Troponin I/T) on any one sample obtained after the procedure. If total CK is not available then CKMB >3 times ULN is considered evidence of peri-procedural MI. If neither CK nor CKMB are available then a Troponin elevation that is >5 times the 99th percentile or diagnostic value for the specific institution is considered evidence of peri-procedural MI. <u>Peri-procedural MI in the setting of evolving MI</u> 1) If the peak total CK (or CK-MB) from the index infarction has not yet been reached: recurrent chest pain lasting >20 minutes (or new ECG changes consistent with MI) AND the peak CK (or CK-MB in absence of CK) level measured within 24 hours after the event is elevated by at least 50% above the previous level. 2) If the elevated CK (or CK-MB) levels from the index infarction are falling or have returned to normal within 24 hours post index PCI: EITHER a new elevation of CK >2 x ULN within 24 hours post index PCI if the CK level has returned to <ULN OR a rise by >50% above the previous nadir level if the CK level has not returned to <ULN.
Post – Intervention MI	*Post – Intervention MI* Within this category we distinguish: <u>Non-procedural related MI (spontaneous MI)</u> (adapted from ESC/ACC guidelines JACC2000) (ref. 1,2) Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI: 1) Typical rise and gradual fall (Troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischemic symptoms;

Electrocardiographic Classification	b) development of new pathologic (defined by Minnesota Code) Q-waves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); 2) pathologic findings of an acute MI. 3) development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event. <u>MI after CABG</u> A definite diagnosis of myocardial infarction is made: 1) Within the first 7 days post-intervention (CABG or Stent) when the two following criteria both are positive: a) Development of new abnormal Q-waves not present on the patient's baseline (i.e. before allocation) ECG. The Minnesota Code for pathologic Q-waves will be used. b) Enzyme changes defined as more than 10% of the ratio of [peak CK-MB/peak total CK] on 3 consecutive samples OR Enzyme changes defined as CKMB >5x ULN. 2) Beyond 7 days after any intervention procedure (CABG or Stent) the standard definition for non-procedural related MI applies. Comment 1: MI after CABG refers to both: studies including CABG as investigational treatment (e.g. Freedom and Syntax studies) (ref. 3) and patients undergoing CABG as a repeat intervention Comment 2: This unusual definition of MI, within 7 days post-intervention, is based on published results from the EAST-study (ref. 4). This study showed electrocardiographic peri-operative QMI to be a weak end-point without prognostic importance in patients treated with bypass surgery. *Electrocardiographic Classification* Within this category we distinguish: <u>Q-waves MI</u> Development of new pathological s in 2 or more contiguous leads (according to the Minnesota code as assessed by the ECG core laboratory) with or without post-procedure CK or CK-MB levels elevated above normal. <u>Non Q-waves MI</u> All MIs not classified as Q-waves
Large Myocardial Infarction	Myocardial Infarction with ST elevation ACS, or discharged with a new Q-waves on the ECG or a CPK >5 ULN

Stent Thrombosis (ARC Definition)	Stent Thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the Cathlab. Timing: • Acute stent thrombosis(1): 0 – 24 hours post stent implantation • Subacute stent thrombosis(1): > 24 hours – 30 days post stent implantation • Late stent thrombosis(2): > 30 days – 1 year post stent implantation • Very late stent thrombosis(2): > 1 year post stent implantation (1) 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. (2) including 'primary' as well as 'secondary' late stent thrombosis; 'secondary' late stent thrombosis is a stent thrombosis after a target segment revascularization.

Definite stent thrombosis	We recognize three categories of evidence in defining stent thrombosis. Definite stent thrombosis Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation. <u>Angiographic confirmation of stent thrombosis</u> Thrombolysis In Myocardial Infarction (TIMI) flow is: A. TIMI flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus(*). B. TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus(*). AND at least one of the following criteria has been fulfilled within a 48 hours time window: 1. new acute onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes) 2. new ischemic ECG changes suggestive of acute ischemia 3. typical rise and fall in cardiac biomarkers (refer to definition non-procedural related MI). Comment: the incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion). (*) Intracoronary thrombus [Ellis et al., Mabin et al., Capone et al.] (ref. 5,6,7) *<u>Non-occlusive thrombus:</u>* Intracoronary thrombus is defined as a (spheric, ovoid or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream. *<u>Occlusive thrombus:</u>* A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch). <u>Pathologic confirmation of stent thrombosis</u> Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis	*Probable stent thrombosis* Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases: 1) Any unexplained death within the first 30 days. 2) Irrespective of the time after the index procedure any MI (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	*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.
Target Lesion Revascularization (TLR) (ARC Definition)	TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs should be classified prospectively as clinically indicated or not clinically indicated by the investigator prior to repeat angiography. An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement. The target lesion is defined as the treated segment starting 5 mm proximal to the stent and ending 5 mm distal to the stent.
Target Vessel Revascularization (TVR) (ARC Definition)	TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. (e.g.: if the original lesion is the first obtuse marginal branch, the target vessel includes the left main coronary artery, the circumflex coronary artery and its branches). Comment: in three-vessel treatment every repeat revascularization becomes TVR.

	Within the categories TLR and TVR we distinguish: Clinically indicated TLR / TVR A revascularization is clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥50% (corelab QCA assessment) **and** if one of the following occurs: 1. A positive history of recurrent angina pectoris presumably related to the target vessel. 2. Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel. 3. Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve). The results of the test must be documented in the Case Report Form. A TLR/TVR with a diameter stenosis ≥70% in the absence of the above mentioned ischemic signs or symptoms is also considered clinically indicated. Comment: clinically indicated is a documented, provisional decision to re-intervene based on clinical symptoms and/or results of non invasive functional testing, before any coronary imaging. These criteria are intended to determine clinical indications for re-intervention in patients undergoing routine angiographic follow-up. In the patient cohorts assigned to clinical follow-up only, or in studies without routine angiographic follow-up, all revascularizations are considered clinically indicated. Not clinically indicated TLR / TVR are reinterventions for: 1. all stenoses <50% in the presence or absence of ischemic signs or symptoms; 2. all stenoses ≥50% but <70% without ischemic signs or symptoms.
Non Target Lesion Revascularization (Non TLR) (ARC Definition)	Any revascularization in a lesion other than the target lesion is considered a non-TLR.
Non Target Vessel Revascularization (Non TVR) (ARC Definition)	Any revascularization in a vessel other than the target vessel is considered a non-TVR.

Target Vessel Failure (TVF)	TVF is defined as target vessel revascularization (defined below), recurrent Q or Non Q-Waves myocardial infarction, or cardiac death that could not be clearly attributed to a vessel other than the target vessel. Target vessel failure is a more conservative and broader category and includes any target vessel revascularization as well as any recurrent MI or any cardiac death that cannot be clearly attributed to a non-target vessel. Target vessel failure, thus, 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. Target vessel failure will be reported when: 1. Recurrent MI occurs in territory not clearly other than that of the target vessel. 2. Cardiac death not clearly due to a non-target vessel endpoint. 3. Target vessel revascularization is determined.
TIMI classification	**TIMI 0** - No perfusion **TIMI 1** - Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run. **TIMI 2** - Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel. **TIMI 3** - Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

Note: if the ARC definitions listed in this table will be updated throughout the study, the latest version may be used.

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8.0 Summary of Safety and Effectiveness Data

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8.0 Summary of Safety and Effectiveness Data

8.1 General Information

Product Generic Name:	Drug-Eluting Coronary Stent System (NIQ)
Product Trade Name:	Endeavor Over-the-Wire (OTW) Zotarolimus-Eluting Coronary Stent System
	Endeavor Rapid Exchange (RX) Zotarolimus-Eluting Coronary Stent System
	Endeavor Multi Exchange II (MX^2) Zotarolimus-Eluting Coronary Stent System
Applicant's Name and Address:	Medtronic Vascular 3576 Unocal Place Santa Rosa, CA 95403
Premarket Approval Application (PMA) Number:	P060033
Date of Panel Recommendation:	To be completed by FDA
Date of Notice of Approval to Applicant:	To be completed by FDA

8.2 Indications For Use

The Endeavor Zotarolimus-Eluting Coronary Stent System (hereafter referred to as the Endeavor stent system) is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5mm to ≤ 3.5mm.

8.3 Contraindications

Use of the Endeavor stent system is contraindicated for use in patients with:

- Known hypersensitivity to zotarolimus or structurally-related compounds.
- Known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Known hypersensitivity to the polymer or its individual components (see details in Section 8.5: Product Description below).

Coronary Artery Stenting is contraindicated for use in:

- Patients in whom anti-platelet and/or anticoagulant therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

8.4 Warnings and Precautions

The warnings and precautions can be found in the Endeavor stent system labeling.

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8.5 Product Description

The Endeavor stent system is a device / drug combination product comprised of device components (Driver™ Coronary Stent and Micro-Driver™ Coronary Stent and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus and phosphorylcholine (PC) contained in a polymer coating). The characteristics of the Endeavor stent system are described in Table 8-1.

Table 8-1: The Endeavor Stent System Product Description

	Endeavor Rapid Exchange (RX) Delivery System	Endeavor Over-The-Wire (OTW) Delivery System	Endeavor Multi Exchange II (MX^2) Delivery System
Available Stent lengths (mm)*	8, 9, 12, 14, 15, 18, 24, 30		
Available Stent diameters (mm)**	2.5, 3.0, 3.5		
Stent Material	A cobalt based alloy (MP35N) – the Driver & Micro-Driver Stents		
Drug Component	A spray coating of polymer carrier loaded with zotarolimus is applied to the stent at a drug loading of 10µg/mm stent length. The maximum nominal drug content on the longest stent (30mm) is 300µg.		
Delivery System Working Length (cm)	135	135	138
Delivery System Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25cm from tip. Designed for guidewire ≤0.014”.	Y-Connector (Side arm for access to balloon inflation/ deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤0.014”	Single access port to inflation lumen. Guidewire exits through a Z-component located on the proximal shaft. Designed for guidewire ≤0.014”.
Stent Delivery Balloon	A semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. There are proximal and distal pillows formed on either side of the stent which aid in holding the stent in position Two radiopaque balloon markers are located on the distal section of the inner member and are positioned to mark the working length of the balloon.		
Balloon Inflation Pressure	Nominal Inflation Pressure: 9 ATM; Rated Burst Inflation Pressure: 16 ATM		
Guide Catheter Compatibility	0.056” minimum (5F)	0.056” minimum (5F)	0.064” minimum (6F)
Distal Section OD	Distal = 2.7F	Distal = 2.7F	Distal = 2.7F
	Proximal = 3.0F	Proximal = 3.0F	Middle = 3.0F
			Proximal = 3.8F
Proximal OD	2.2F	3.3F	2.3F x 4.2F (Oval)

* 2.5 mm diameter stents are not available in 9 and 15 mm lengths
** 3.0 and 3.5 mm diameter stents are not available in 8 and 14 mm lengths

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8.5.1 Device Component Description

The device component consists of the Driver™ Coronary Stent or Micro-Driver™ Coronary Stent pre-mounted onto one of three delivery systems; Over-The-Wire (OTW), Rapid Exchange (RX) or Multi Exchange II (MX^2) Delivery Systems. Each delivery system provides a means for delivering the stent through the coronary vasculature and, once in the desired location, expands the stent through balloon inflation. The delivery systems utilized for the Endeavor product are similar in materials, design and construction to the approved Driver (P030009, approved October 1, 2003; Driver MX^2 P030009/S001, approved on August 4, 2004; Driver RX, P030009/S003, approved on December 22, 2005) and Micro-Driver (P030009/S002, approved on April 21, 2006) delivery systems.

The Endeavor stent is made of the cobalt alloy MP35N conforming to ASTM F562. The modular stent segments are created from a single ring formed into a repeating pattern of crowns and struts. The appropriate ring is formed into alternating upper and lower crowns with seven (2.5 mm diameters) or ten (3.0 – 3.5 mm diameters) crowns per end, connected by axial struts in a sinusoidal pattern. The stent is crimped onto various size delivery catheter balloons, with diameters of 2.5mm, 3.0mm or 3.5mm.

The Endeavor stent system contains 10 µg zotarolimus per millimeter of stent length for all diameters. Because an identical dose (10µg/mm zotarolimus per mm stent length) is used for the entire Endeavor 2.5 – 3.5 mm diameter range, the total drug per stent is a function of stent length, irrespective of stent diameter.

The Endeavor MX^2 delivery system was not used in the Endeavor clinical investigations (Endeavor I to IV). The Endeavor MX^2 utilizes a modified shaft to facilitate the multi-exchange feature of the delivery system.

The distal section of the Endeavor MX^2 Zotarolimus-Eluting Coronary Stent System, including the stent, balloon, drug coating and stent interfaces are identical to that of the Endeavor RX and OTW delivery systems which were studied clinically. Appropriate pre-clinical testing was provided to support the Endeavor MX^2 delivery system. Acute and long term safety and performance data is provided in the PMA application (ENDEAVOR I to IV clinical investigations, over 2000 patients) to support the clinical safety and efficacy of the Endeavor stent mounted on the Endeavor balloon.

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8.5.2 Drug Component Description

The drug component of the Endeavor coronary stent system consists of zotarolimus (the active ingredient) and Phosphorylcholine (PC) polymer (the inactive ingredient).

8.5.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the Endeavor stent is zotarolimus. It is a tetrazole-containing macrocyclic immunosuppressant. The Chemical name of zotarolimus is: [3S-[3R*[S*(1R*,3S*,4R*)],6S*, 7E,9S*,10S*,12S*,14R*,15E,17E,19E, 21R* ,23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27, 32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazoyl-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown below (Figure 8-1).

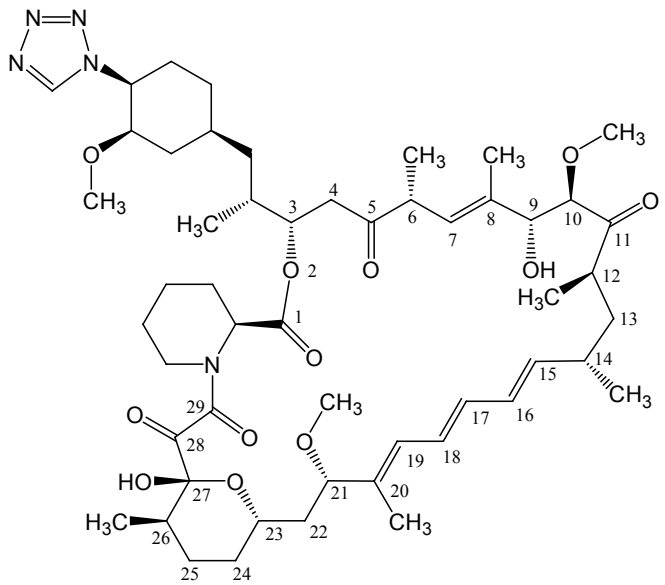

Figure 8-1: Chemical Structure of zotarolimus

Zotarolimus has extremely low water solubility and is a lipophilic compound but is freely soluble in Propylene glycol, Acetone, Toluene, Acetonitrile, Ethanol, Benzyl alcohol and DMSO. The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

Zotarolimus does not have any ionizable group(s) in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

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8.5.2.2 Inactive Ingredients

The only inactive ingredient in the Endeavor stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for zotarolimus. The PC polymer consists of 2-Methacryloyloxyethyl phosphorylcholine that is synthesized and then used in the preparation of cross-linked polymer membranes with lauryl methacrylate, hydroxypropyl methacrylate and trimethoxysilylpropyl methacrylate (crosslinker) co-monomers. The PC polymer contains a biocompatible component which mimics the body's own chemistry, a hydrophobic component for adhesion and stability, and a crosslinking component for robustness.

The molecular weight of PC polymer was estimated using viscometry and resulted in values of Mw ranging from 160,000 to 270,000. These figures were supported by light scattering values of Mw (g/mol) ranging from 100,000 to 200,000.

PC polymer in a solvent carrier (ethanol) is applied to the Driver stent to form the base layer coat of the Endeavor stent. The polymer is also mixed with the drug zotarolimus and then applied to the base layer-coated stents. Finally, a drug-free overspray of PC polymer is applied after the stent has been coated with the drug/polymer formulation and it has been crimped onto the balloon. The drug/polymer coating is applied to the entire surface (i.e. luminal and abluminal) of the stent. The structural formula of the polymer is shown in Figure 8-2.

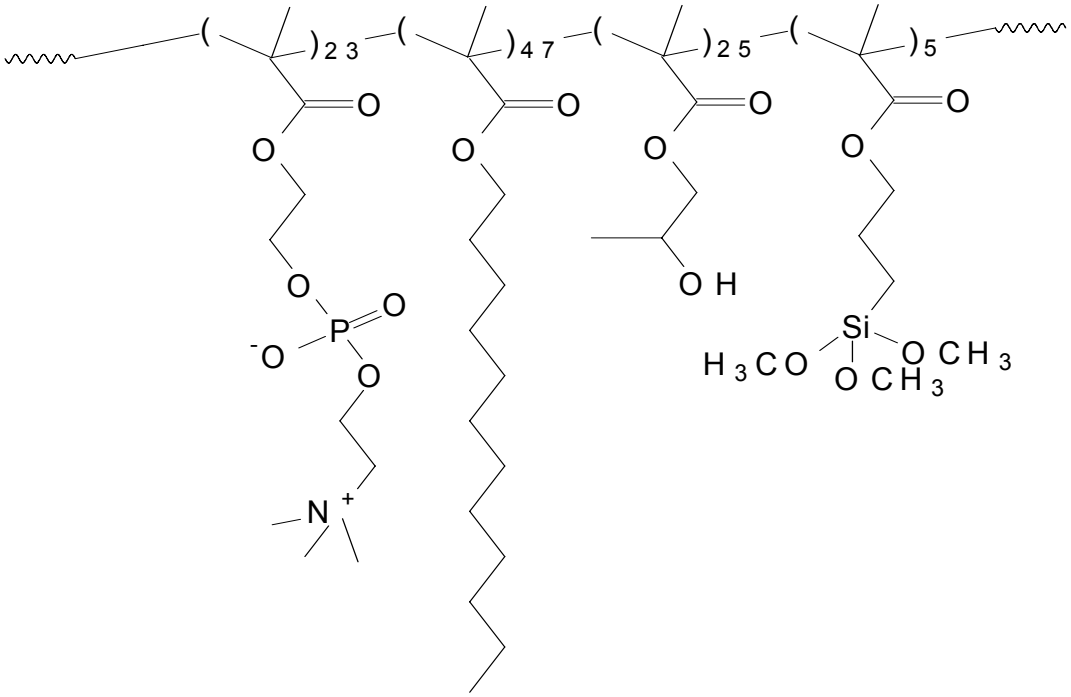

Figure 8-2: Chemical Structure of PC Polymer

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Product Matrix and Zotarolimus Content

Table 8-2: Endeavor Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number OTW	Product Number RX	Product Number MX[2]	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg) [24]
EN25008W	EN25008UX	EN25008MX	2.50	8	84
EN30009W	EN30009UX	EN30009MX	3.00	9	90
EN35009W	EN35009UX	EN35009MX	3.50	9	90
EN25012W	EN25012UX	EN25012MX	2.50	12	120
EN30012W	EN30012UX	EN30012MX	3.00	12	120
EN35012W	EN35012UX	EN35012MX	3.50	12	120
EN25014W	EN25014UX	EN25014MX	2.50	14	144
EN30015W	EN30015UX	EN30015MX	3.00	15	150
EN35015W	EN35015UX	EN35015MX	3.50	15	150
EN25018W	EN25018UX	EN25018MX	2.50	18	180
EN30018W	EN30018UX	EN30018MX	3.00	18	180
EN35018W	EN35018UX	EN35018MX	3.50	18	180
EN25024W	EN25024UX	EN25024MX	2.50	24	240
EN30024W	EN30024UX	EN30024MX	3.00	24	240
EN35024W	EN35024UX	EN35024MX	3.50	24	240
EN25030W	EN25030UX	EN25030MX	2.50	30	300
EN30030W	EN30030UX	EN30030MX	3.00	30	300
EN35030W	EN35030UX	EN35030MX	3.50	30	300

8.5.3 Mechanism of Action

The mechanism (or mechanisms) by which the Endeavor stent system affects neointimal production as seen in clinical studies has not been established conclusively. *In vitro*, zotarolimus inhibited growth factor-induced proliferation of human coronary artery smooth muscle cells and also demonstrated binding affinity with FKBP-12 (binding protein). The suggested mechanism of action of zotarolimus is to bind to FKBP-12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR activity leads to inhibition of cell cycle progression from the G1 to the S phase.

[24] Note the 8 mm and 14 mm stent lengths have a total nominal drug content of 84 µg and 144 µg respectively since the actual stent length for the 8 mm stent is 8.4 mm and the actual stent length for the 14 mm stent is 14.4 mm.

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8.6 Alternative Practices and Procedures

Treatment of patients with coronary artery disease may include exercise, diet, drug therapy, percutaneous coronary interventions (such as angioplasty, bare metal stents. coated stents, and other drug eluting stents), and coronary artery bypass surgery (CABG).

8.7 Marketing History

The Endeavor Zotarolimus-Eluting Coronary Stent System is commercially available in the following countries:

• Albania	• Brazil	• Germany	• Lebanon	• Pakistan	• Sudan
• Algeria	• Bulgaria	• Ghana	• Libya	• Panama	• Sweden
• Antigua and Barbuda	• Cayman Islands	• Greece	• Liechtenstein	• Paraguay	• Switzerland
• Argentina	• Chile	• Guatemala	• Lithuania	• Peru	• Syria
• Armenia	• China	• Honduras	• Luxembourg	• Poland	• Thailand
• Aruba	• Colombia	• Hong Kong	• Malaysia	• Portugal	• Trinidad and Tabago
• Australia	• Costa Rica	• Hungary	• Malta	• Qatar	• Tunisia
• Austria	• Cyprus	• Iceland	• Mauritius	• Romania	• Turkey
• Bahamas	• Czech Republic	• India	• Mexico	• Russia	• Uganda
• Bahrain	• Denmark	• Iran	• Morocco	• Saudi Arabia	• United Arab Emirates
• Bangladesh	• Dominican Republic	• Ireland	• Mozambique	• Senegal	• United Kingdom
• Barbados	• Ecuador	• Israel	• Nepal	• Serbia & Montenegro	• Uruguay
• Belgium	• Egypt	• Italy	• Netherlands	• Singapore	• Venezuela
• Belize	• El Salvador	• Jamaica	• New Zealand	• Slovakia	• Virginia Islands (British)
• Bermuda	• Estonia	• Jordan	• Nicaragua	• Slovenia	• Yemen
• Bolivia	• Finland	• Kenya	• Nigeria	• South Africa	• Zimbabwe
• Bosnia-Herzegovina	• France	• Kuwait	• Norway	• South Korea	
• Botswana	• Georgia	• Latvia	• Oman	• Spain	

As of February 28, 2007, approximately 248,000 Endeavor Zotarolimus-Eluting Coronary Stent Systems have been distributed outside of the U.S. No products have been withdrawn from the market in any country for any reason.

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8.8 Summary of Non-Clinical Studies

A series of non-clinical laboratory studies were performed, pertaining to the stent and the stent delivery system (i.e. the stent mounted on either the Endeavor OTW, RX and MX^2 stent delivery system), the polymer substance [i.e., Phosphorylcholine (PC)], the drug substance (i.e., zotarolimus), and the finished combination product (i.e., Endeavor Zotarolimus-Eluting Coronary Stent System).

8.8.1 Biocompatibility Studies

A series of GLP biocompatibility tests and USP Physicochemical tests were conducted to demonstrate that the components of the Endeavor Zotarolimus-Eluting Coronary Stent System (OTW, RX and MX^2) are non-toxic. Tests were conducted on ethylene oxide-sterilized Endeavor coated stents, stent delivery systems (finished product) and polymer-only coated stainless steel (SS) coupons. These test articles were processed in the same manner as the finished Endeavor product. The polymer only coated coupons did not include drug substance but were manufactured to simulate the processing of Endeavor Zotarolimus-Eluting Coronary Stent System with equivalent surface treatment, cross-linking and sterilization processes utilized. In all of these test systems, the materials were non-reactive and met all acceptance criteria. The results of the biocompatibility studies indicated that the Endeavor stent system was biologically safe and acceptable for clinical use.

All biocompatibility testing was conducted in accordance with Good Laboratory Practices Regulations (21 CFR § 58) and with consideration of the following guidances:

- Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices; published by the Interventional Cardiology Devices Branch, Division of Cardiovascular, Respiratory and Neurology Devices, Office of Device Evaluation, CDRH/FDA, in May 1995.
- Guidance for Industry and FDA Staff, Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. Document issued on January 13, 2005.
- International Standard ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and Testing.

Table 8-3 provides a summary of the biocompatibility testing conducted in support of the Endeavor Zotarolimus-Eluting Coronary Stent System.

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Table 8-3: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Cytotoxicity	ISO 10993-5: *In Vitro* Cytotoxicity (L929 MEM Elution)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-cytotoxic)
Pyrogenicity	ISO-10993-11: Systemic Toxicity (Material Mediated Rabbit, Injection)	• Endeavor stent and delivery systems	Pass (non-pyrogenic)
Sensitization	ISO-10993-10: Sensitization (Guinea pig Maximization)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-sensitizing)
Acute Intracutaneous Reactivity	ISO-10993-10: Irritation (Injection)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non- irritant)
Acute Systemic Toxicity	ISO-10993-11: Systemic Toxicity (Acute)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-toxic)
Hemocompatability	ISO-10993-4: *In Vivo* Thromboresistance	• Endeavor stent and delivery systems	Pass (non-thrombogenic)
	ISO-10993-4: C3a Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)
	ISO-10993-4: SC5b9 Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)
	ISO-10993-4: Plasma Recalcification	• Endeavor stent and delivery systems	Pass (no significant change in coagulation time)
	ISO-10993-4: *In Vitro* Hemolysis Study	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-hemolytic)
	ISO-10993-4: White Blood Cell Morphology	• Endeavor stent and delivery systems	Pass (no change in WBC morphologically)
Genotoxicity	ISO-10993-3: Bacterial Reverse Mutation (AMES)	• Endeavor stent	Pass (non-mutagenic)
	ISO-10993-3: *In Vitro* Chromosomal Aberration in Mammalian Cells	• Endeavor stent	Pass (non-clastogenic)
	ISO-10993-3: *In Vivo* Mouse Bone Marrow	• Endeavor stent	Pass (non-mutagenic)

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Table 8-3: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
	Micronucleus Test		
Material Characterization (USP Physicochemical Testing)	USP Physicochemical Extracts <661> (Aqueous)	• Balloon Material • Polyethylene Sheath • PC Polymer-only Coated Coupons	Pass

In vivo animal testing conducted on the Endeavor Zotarolimus-Eluting Coronary Stent System evaluated the effects of multiple doses and device exposure in a porcine coronary or rabbit iliac artery model for up to 180 days, in lieu of ISO 10993 sub-chronic and muscle implantation testing. The *in vivo* results indicated that the Endeavor Zotarolimus-Eluting Coronary Stent System was biologically safe and acceptable for clinical use. The significant animal studies are summarized separately in Section 8.8.6 – Animal Studies.

Formal carcinogenicity and reproductive toxicity testing was not conducted on the Endeavor Zotarolimus-Eluting Coronary Stent System. An appropriate rationale has been provided to demonstrate why the carcinogenic potential of the Endeavor stent system is minimal based on the quantities of materials present and the limited period of zotarolimus release. The genotoxicity and reproductive toxicity of zotarolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*.

Medtronic Vascular provided a letter from the drug substance manufacturer, Abbott Laboratories Inc., authorizing FDA access to a Drug Master File (DMF) in support of this application. *In vivo* and *in vitro* pharmacology and toxicology studies as well as animal and human pharmacokinetic studies were conducted on zotarolimus to provide information about systemic and regional toxicity, distribution profiles, end-organ disposition, drug metabolism and potential drug-drug interactions.

There is no evidence to suggest that any chemical interactions occur between the PC polymer and zotarolimus drug under established processing and storage conditions that would lead to the formation of covalent bonds or that would alter the structure of the drug in any way to form a new intermediate or molecular entity.

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8.8.2 In Vivo Pharmacokinetics

Endeavor US Pharmacokinetic (PK) study was conducted to evaluate the pharmacokinetic profile of the Endeavor Zotarolimus-Eluting Coronary Stent System in eligible patients.

8.8.2.1 The Endeavor US PK Registry

The Endeavor US PK Registry was a prospective, multi-center, single-arm, open-label study designed to assess the acute pharmacokinetics and safety of zotarolimus administered using the Medtronic Endeavor Zotarolimus-Eluting CSS for the treatment of single *de novo* lesions in native coronary arteries. Pharmacokinetic evaluation was conducted on all patients participating in the Endeavor US PK trial. Forty-three (43) patients received the Endeavor Zotarolimus-Eluting CSS; six patients received overlapping stents.

Blood samples (5 mL) were collected till 30 days post-procedure. Selected pharmacokinetic parameters for the Endeavor US PK study analysis are provided in Table 8-4.

Table 8-4: Endeavor US PK Results

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	1.584	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
$AUC_{0\text{-last}}$	(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
$AUC_{0\text{-inf}}$	(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
$t_{½}$‡	(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
Cmax Maximum blood concentration
Tmax Time to Cmax
$AUC_{0\text{-last}}$ (AUC) Area under the blood concentration-time curve from time 0 to time of last measurable concentration
$AUC_{0\text{-inf}}$ AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).
t½ Harmonic mean half-life
CL/F Mean apparent clearance

a. Primary dose groups
‡ Harmonic mean ± pseudo-standard deviation
† No SD was reported when N ≤ 2
§ Mean only
# N = 6

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The results in Table 1.3-4 show that pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 2), 180, 240 and 300 µg, following the implantation of Endeavor Zotarolimus-Eluting Stents as illustrated by dose proportional increases in Cmax, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$. Mean apparent clearance and harmonic mean half-life for the primary dose groups ranged from 2.8 to 3.5 L/h and 57.5 to 59.7 hours, respectively. The mean time to reach peak systemic concentration (Tmax) ranged from 1.2 to 1.5 hours after stent implantation. Additionally, this study showed that zotarolimus is released gradually into the systemic circulation without any evidence of dose dumping.

8.8.2.2 Drug Interactions

While no specific clinical data are available, drugs, like sirolimus, that act through the same binding protein (FKBP) may interfere with the efficacy of zotarolimus. Zotarolimus is metabolized by cytochrome P450 3A4 (CYP3A4), a human cytochrome P450 enzyme. Strong inhibitors of CYP3A4 (e.g., ketoconazole) might cause increased zotarolimus exposure to levels associated with systemic effects, especially if multiple stents are deployed. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

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8.8.3 In Vitro Engineering Testing

In vitro engineering testing, in accordance with FDA's "Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems" (January 13, 2005) and "Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents" (May 1995), was conducted on the Endeavor stent mounted on the OTW, RX, and/ or MX^2 delivery systems.

Some *in vitro* engineering tests were performed on the uncoated, bare metal version of the Endeavor stent since there was no change to the stent substrate. An appropriate rationale was provided where the testing of the bare metal stent provided a worst case or representative condition for the attributes evaluated.

Additional tests were conducted to support the integrity of the coating on the Endeavor stent system and are summarized separately in Section 8.8.4 - Coating Characterization Testing.

The *in vitro* engineering studies conducted are summarized in Table 8-5. "Pass" denotes that the test results met product specifications and/or the recommendations in the above-referenced guidance documents.

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Table 8-5: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
	Stent Material Specification Conformance Testing	
Material Characterization	Chemical analysis was conducted on the Co-Ni-Cr-Mo alloy provided by the material supplier to confirm both chemical analysis and inclusion/ impurity content as provided by ASTM F562 "Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy for Surgical Implant Applications."	Pass
Surface Contamination	SEM analysis was conducted to detect evidence of surface contaminants or impurities. Results of SEM evaluation showed no evidence of contamination above the specified limits.	Pass
Mechanical Properties	Testing was conducted to characterize the following properties of the annealed Co-Ni-Cr-Mo alloy bars: 0.2% offset yield strength, ultimate tensile strength, percent elongation, and reduction of area. Bars were machined from barstock conforming to ASTM F562. The bars were tensile tested to failure while engineering stress and strain were continuously recorded. The results were in conformance with ASTM F562.	Pass
Stent Corrosion Resistance	Endeavor stents were tested according to ASTM F2129 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibilty of Small Implant Devices" to demonstrate that the finished stents exhibit corrosion and repassivation characteristics comparable to marketed Driver stents. Results were comparable to the control stents and met product specification requirements. Testing was also conducted to evaluate the relative susceptibility to pitting/crevice corrosion of the Endeavor stent utilizing the corrosion techniques outlined in ASTM F746 and using sample preparation techniques in accordance with ASTM F2129. Results were comparable to marketed Driver stents and met product specification requirements.	Pass
Fretting Corrosion	Overlapped bare metal Driver or Micro-Driver stents were evaluated post fatigue testing to determine the potential for fretting corrosion. The results met all acceptance criteria and indicated that the stents possess a high resistance to fretting corrosion.	Pass
Galvanic Corrosion	Testing was conducted on marketed Driver stents (MP35N) overlapped with marketed S7 (316L stainless steel) stents to determine the potential for galvanic corrosion. The results met all acceptance criteria and indicated a high resistance to galvanic corrosion.	Pass

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Table 8-5: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Stent Dimensional and Functional Attributes		
Stent Dimensional Verification	Testing was conducted to measure and optically inspect the stent to document that stent dimensional and visual specifications do not deviate from product specifications. All product met specifications.	Pass
Percent Surface Area	This value is calculated using stent nominal dimensional values and is based on the ratio of stent area to the area of the vessel. Metal to artery percentage ratios were calculated for all of the stent diameters recommended in the product labeling, with the highest surface to artery ratio (18.6%) occurring when the stent is deployed to the nominal diameter (2.5 mm) for the seven crown stent design and (19.9%) occurring when the stent is deployed to the nominal diameter (3.0 mm) for the ten crown stent design.	N/A Characterization only
Foreshortening	The length of the stents were measured prior to and after expansion to the largest nominal diameter. All stents met product specifications.	Pass
Stent Recoil	Testing was conducted to quantify the amount of elastic recoil for the stent and correlate this parameter to the recommended sizing procedures. The stent delivery system was inflated to nominal pressure and the stent was removed allowing for recoil to occur. The inner diameter at each end of the stent was recorded. Recoil was calculated by subtracting the recoiled stent inner diameter from the pre-recoil inner diameter. All stents met the acceptance criteria after balloon inflation to nominal pressure.	Pass
Stent Integrity	Testing was conducted to determine if the plastic deformation experienced by the stent when expanded from the compressed profile to the final maximum deployed diameter can produce crack initiation for the stent. Samples were deployed to their largest possible diameters by inflating each delivery system to nominal plus 0.5mm. Each stent was examined at 40X magnification for potential cracks. All samples met the acceptance criteria with no visible cracks or notches.	Pass
Radial Stiffness and Radial Strength	Testing was conducted to determine stent resistance to radial load. The stents were deployed to nominal stent diameter and placed in a radial crush tester. All samples met the acceptance criteria.	Pass
Stent Expansion/ Coating Evaluation	Testing was conducted to provide a qualitative comparison of Endeavor coating in the pre-deployed, deployed to nominal and deployed to maximum diameter conditions using 60 – 80X optical microscopy. A qualitative comparison of coating integrity was also performed pre- and post tracking through a tortuous anatomy using 60 – 80X optical microscopy and SEM.	N/A Characterization only See note at end of table*
Coating Stress Analysis	A stress analysis, using a Finite element analysis (FEA), demonstrated that the addition of a coating to a Driver or Micro-Driver stent will not change the critical location of stresses during expansion and during *in vivo* loading. Additionally the coating stress analysis showed that the critical stress location within the coating is in the same location found on a bare stent.	Pass

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Table 8-5: Stent and Delivery Catheter Engineering Testing

Test	Description of Test		Conclusion
Fatigue Analysis (FEA)	An in-depth analysis of the stent was conducted to ensure that the implant conditions to which the stent will be subjected would not result in failure due to fatigue. The FEA evaluated the structural integrity of the stent when subjected to the expected loading conditions generated in coronary arteries. The analysis took into account manufacturing, delivery, implantation and clinical loading over the implant life, and predicted that fatigue failures will not likely occur.		Pass
Accelerated Durability Testing	This testing was conducted to determine the fatigue integrity of a stent under accelerated cycling designed to model *in vivo* conditions. Stents were deployed up to the largest intended diameter and tested through a simulated 10 year life. After the completion of the ten year simulated durability testing, the stents were visually inspected using 60 – 80X optical microscopy for cracking or breaks. All units tested were free of any cracks or breaks. There were no stent failures noted after 420 million cycles (equivalent to 10 years *in vivo*). Additionally, Endeavor stents were analyzed using SEM post accelerated durability testing.		Pass * see note at end of table
Magnetic Resonance Imaging (MRI) Safety and Compatibility	Non-clinical testing on single and overlapped stents has demonstrated the Endeavor Zotarolimus-eluting coronary stent is MR Conditional. It can be scanned safely under the following conditions:		N/A
	Single Stenting (Stent Length 30mm)	**Overlapped Stenting (Total Length 55mm)**	
	Static magnetic field of 3 - Tesla	Static magnetic field of 3 - Tesla	
	Spatial gradient field of 525 Gauss/cm	Spatial gradient field of 720 Gauss/cm	
	Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of scanning	Maximum whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning	
	In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of MR scanning in a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.	In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.	
	The Endeavor stent should not move or migrate when exposed to MR scanning immediately post-implantation.		

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Table 8-5: Stent and Delivery Catheter Engineering Testing

Test	Description of Test		Conclusion
	The image artifact extends approximately 9 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR system with a send-receive RF body coil.	The image artifact extends approximately 10 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR system with a send-receive RF body coil.	
Radiopacity	The radiopacity of the Endeavor stent system was evaluated at delivery, deployment and after implantation in an *in vivo* animal study and radiopacity characteristics were sufficiently comparable to marketed cobalt alloy stents.		Pass
Stent ID Uniformity	This test was conducted to demonstrate that the deployed internal diameter of the Endeavor stent system is consistent with labeling. Each stent was deployed to nominal pressure, and the stent inner diameter was measured at each end. The results indicated that the Endeavor stent system expands uniformly at all diameters and maintains this uniformity upon withdrawal of the balloon.		Pass
Delivery System Dimensional and Functional Attributes			
Delivery, Deployment, and Retraction	*In vitro* testing was conducted to evaluate delivery, deployment, and retraction of the Endeavor stent delivery system through a simulated tortuous path according to the instructions for use. All results indicated that the system performed as intended and no damage to the stent was noted.		N/A Characterization only
Balloon Maximum Pressure	This test was conducted to demonstrate that the Endeavor stent system (with mounted stent) will not experience balloon, shaft, proximal adaptation or proximal/distal seal loss of integrity at or below the pressure required to expand the stent to its labeled diameter. Stent delivery systems were initially pressurized to 90 psi. The cycle was then repeated, increasing inflation pressure by 15 psi each cycle until failure. The results demonstrate with 95% confidence that at least 99.9% of the delivery systems will not experience loss of integrity at or below the rated burst pressure.		Pass
Balloon Fatigue	Endeavor stent systems were required to complete 10 unconstrained pressurization cycles to Rated Burst Pressure (RBP). The stent/balloon burst results show statistically that, with 95% confidence, 90% of the delivery systems will not experience balloon, shaft, or proximal/ distal seal loss of integrity at or below the maximum recommended RBP.		Pass
Stent Diameter vs. Balloon Pressure (Compliance)	Testing was performed to determine how the stent inner diameter varies with applied inflation pressures. The stent sizing results verify that the stent systems meet the labeled compliance curves.		N/A Characterization for product labeling
Catheter Bond Strength	Testing was performed to confirm the bond strength specifications for the Endeavor stent delivery system. All bonds were loaded into the tensile tester and pulled to failure. All samples met the acceptance criteria.		Pass

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Table 8-5: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Stent / Catheter Crossing Profile	Endeavor stents and delivery systems were tested to verify the crossing profile per label claims. All samples met product specifications.	Pass
Balloon Inflation and Deflation Time	Endeavor delivery systems were tested for inflation/deflation times. All samples met the product specification.	Pass
Stent Securement	• Testing was conducted to assess the force required to displace a crimped Endeavor stent from the Endeavor delivery system by both forward and reverse motion. All stent systems met the stent securement specification. • Testing was performed to characterize the performance of the Endeavor stent system (undeployed) to cross a simulated lesion post tracking through a tortuous artery model. The Endeavor product performed as intended. • To further characterize the performance of the Endeavor stent system undeployed stents were tracked through a tortuous artery model and withdrawn through the recommended guide catheter. The Endeavor product performed as intended.	Pass
Balloon Deflatability	This test was performed to provide assurance that the deflated delivery system balloons will release from the expanded stent without interference. All samples met specification.	Pass
Catheter Body Maximum Pressure	Testing was conducted on the Endeavor stent delivery systems to determine the ability of the catheter shaft to withstand inflation to balloon rated burst pressure. All samples met the product specification.	Pass

***Note:** Microcracks were observed in the drug/ polymer coating layer of all samples both pre- and post simulated use and pre- and post durability testing. The location of microcracks did not appear to change from the pre- to the post- deployed state. Microcracks were not observed in the cross-linked polymer base layer (i.e. the coating layer that remains implanted post drug exhaustion) after durability testing. Areas of apparent coating loss were observed on the inner and outer stent diameters; however areas of coating loss were predominantly on the ID surface of the stent.

8.8.4 Coating Characterization Testing

The following methods were developed to characterize and set initial specifications for the Endeavor stent system. The coating characterization testing conducted on the Endeavor stent system includes those tests summarized in Table 8-6.

Table 8-6: Coating Characterization Testing

Test	Description of Test
Materials Analysis – Polymer	Polymer components were tested to ensure conformity to raw materials specifications and incoming inspection procedures.
Chemical Analysis – Polymer	Assays were conducted to determine residual monomer content, residual solvent levels and water content.
Chemical Analysis – Drug	Drug substance was tested to ensure conformity to incoming Certificate of Analysis.
Total Drug Content	Assay was conducted to quantitatively determine the total amount of drug substance, zotarolimus, on the Endeavor stent system.

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Test	Description of Test
Dose Density	Dose per mm was calculated.
Drug Content along Stent Length	Testing was conducted to characterize the uniformity of distribution of drug along the length of the Endeavor stent system.
Total Drug Related Substances	Assays were conducted to quantitatively determine the type and amount of impurities and degradation products on the Endeavor stent system.
Coating Thickness	Testing was conducted to describe the coating thickness along the length of the stent.
In Vitro Elution	Assay was developed to measure the *in vitro* release kinetics of zotarolimus from the Endeavor stent system.
Particulates	Particulate levels were determined for the Endeavor stent system post tracking and deployment. All samples met product specifications.

Medtronic Vascular provided a letter from the polymer manufacturer, Biocompatibles Ltd., authorizing access to a Master File (MAF) in support of this submission.

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8.8.5 Chemistry Manufacturing and Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on Endeavor stents as part of CMC. This testing is summarized in Table 8-7. Information to support the stability of the Endeavor stent is summarized separately in Section 8.8.7 – Stability below.

Table 8-7: CMC Release Testing

Test	Description of Test
Material Analysis – Polymer	The polymer was tested to ensure conformity to specifications. The polymer met specifications prior to utilization in finished goods.
Drug Identity	Assay was conducted to verify the identity of the drug substance, zotarolimus, on the Endeavor stent system. The product met specifications established for finished goods release.
Drug Content/Impurities	Assays were conducted to quantitatively verify the amount of drug and the type and amount of impurities on the Endeavor stent system. The product met specifications established for finished goods release.
Drug Content Uniformity	Multiple stents were assayed to verify the uniformity of the drug content between the individual stents was within specifications established for finished good release.
Residual Solvents	Assay was conducted on the Endeavor stent system to verify that residual levels of solvents used in the manufacturing process were below acceptable limits established for finished goods release.
In Vitro Elution	The *in vitro* release profile for zotarolimus was measured on the Endeavor stent system. Specifications were based on the elution characteristics of stents evaluated in the clinical investigation. The product met specifications established for finished goods release.
Particulates	Particulate levels were monitored to verify that they remain below acceptable levels as established in the product specifications.

8.8.6 Animal Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials. Consequently, a series of animal studies were conducted to evaluate safety, proof of concept and overall product performance.

Medtronic Vascular conducted a series of animal studies evaluating various Zotarolimus-Eluting stent formulations (e.g., drug dosages), polymer-coated control stents and/or bare metal control stents. These studies were conducted in coronary arteries of pigs, or iliac arteries of rabbits. Data from these studies served as the basis for the dose selection for the Endeavor stent system used in the Endeavor clinical studies and provided an assessment of the safety of the product over a range of timepoints.

The intravascular safety and biocompatibility of zotarolimus-eluting stents were evaluated in a series of animal studies in a porcine model of stent-mediated vascular injury. Non-GLP studies were conducted in order to provide additional background data for non-safety related areas. All study phases (feasibility, safety, pharmacokinetic and

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acute) are represented by studies that were conducted in accordance with § 21CFR 58 (Good Laboratory Practices), except where noted. The results of these studies support the safety and biocompatibility of the Endeavor stent system. Summaries of the major animal studies performed to support product safety are included in Table 8-8.

Table 8-8: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS102	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS GLP: Yes	**Diameter:** • 3.0, 3.5, 4.0 mm **Lengths:** • 12, 18 mm	Domestic Swine Test and Control: 15 (LAD, LCX, RCA) One stent / vessel Animals received both test and control	Test: 32 Control: 20	7 days	• Angiographic patency • Histologic and histomorphometric evaluation of single and overlapping stents • Cell proliferation • Acute delivery
FS135	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	**Diameter:** • 2.25, 2.5mm **Lengths:** • 8 mm	Juvenile Yorkshire Swine Test and Control: 21 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 24 Control: 20 Control (Polymer Coated Stents): 12	28 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose and Endeavor stent systems • Acute Delivery • Chronic vascular response at 28 days
FS99	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	**Diameter:** • 2.5, 3.0, 3.5, 4.0 mm **Lengths:** • 12, 18 mm	Domestic Swine Test and Control : 51 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 99 Control: 64 Control (Polymer Coated Stents): 13	28 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose, single and overlapping stents • Acute Delivery • Chronic vascular response at 28 days
FS100	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	**Diameter:** • 2.5, 3.0, 3.5, 4.0 mm **Lengths:** • **12mm**	Yucatan Miniswine Test & Control: 31 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 58 Control: 43 Control (Polymer Coated Stents): 9	90 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose, single and overlapping stents • Acute Delivery • Chronic vascular response at 90 days

Table 8-8: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS101	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	**Diameter:** • 2.5, 3.0, 3.5, 4.0 mm **Lengths:** • 12mm	Yucatan Miniswine Test & Control: 30 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 55 Control: 40 Control (Polymer Coated Stents): 11	180 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose, single and overlapping stents • Acute Delivery • Chronic vascular response at 180 days
FS114	Test Article: zotarolimus-eluting Endeavor stent system GLP: Yes	**Diameter:** • 3.0mm **Lengths:** • 12mm	Domestic Swine (LAD, LCX, RCA) One stent per vessel.	48	1, 2, 3, 5, 7, 10, 14 and 28 days	Evaluation of drug release rate, arterial drug levels & systemic drug levels over time.
FS161	Test Article: zotarolimus-eluting Endeavor stent system Control: BMS GLP: Yes	**Diameter:** • 3.0mm **Lengths:** 15mm	Juvenile Yorkshire Swine Test and Control: 22 divided into 3 test and 1 control arms (LAD, LCX, RCA) One stent per vessel	Test: Endeavor RX: 6 Endeavor OTW: 5 Endeavor MX2: 6 Control: Driver OTW: 5	ACT level: 0, 3, 6, 9 and 11 days Angiography: 11 days	• Microscopic evaluation of the overall subacute tissue reaction of the vessel and the surrounding myocardium; examination of the thrombogenicity of the stent and delivery device at 11-days post-stenting • Acute delivery • Angiographic patency • Histologic and histomorphometric evaluation of test and controls • ACT levels at time of implant, 3, 6, and 9 days post-implant, at explant

BMS = bare metal stent – Driver for these studies.

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8.8.7 Stability

Manufacturing site-specific stability studies were conducted to establish a shelf-life/expiration date for the Endeavor Zotarolimus-Eluting Coronary Stent System. Testing to establish package integrity and functional testing of the stent system were conducted on aged product. Testing evaluation included drug identity, assay, degradants, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents, and endotoxins. Appropriate engineering tests were also performed on aged product and compared to baseline to ensure that the Endeavor stent system performed acceptably. The data generated support a shelf life of one year.

8.8.8 Sterilization

The Endeavor Zotarolimus-Eluting Coronary Stent System (OTW, RX, and MX^2 delivery systems) is sterilized using ethylene oxide sterilization, and has been validated per AAMI/ISO 11135:1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization."

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The amount of bacterial endotoxins was verified to be within the specification limit for the Endeavor stent delivery systems.

8.9 Overview of Clinical Studies

ENDEAVOR IV was a randomized, single-blind, controlled U.S. study of the safety and performance of the Endeavor Zotarolimus-Eluting Coronary Stent in patients with single *de novo* coronary artery lesions. A total of 1548 patients at 80 U.S. sites were enrolled with patients randomized to receive Endeavor or the Taxus stent in 1:1 ratio. The primary endpoint for the study was target vessel failure (TVF) at nine months post-procedure. The secondary endpoints for this trial include: acute success (device, lesion, and procedure); Major Adverse Cardiac Event (MACE) rate at 30 days, 6, 9, and 12 months post-procedure; percent diameter stenosis (%DS), late lumen loss, late loss index, angiographic binary restenosis (ABR) rate and minimum luminal diameter (MLD) at eight month angiographic follow-up (in a subset of patients); neointimal hyperplastic volume and percent volume obstruction (%VO) at 8 months post-procedure as measured by intravascular ultrasound (IVUS) in a subset of patients; target site revascularization (TSR) rate and clinically-driven TSR rate at 9 months post-procedure; and target vessel revascularization (TVR) rate and clinically-driven TVR rate at 9 months post-procedure. After the procedure, patients received clopidogrel for a minimum of 6 months and aspirin indefinitely. Follow-up through 9 months is available, and subsequent follow-up is ongoing for 12 months and will be conducted yearly thereafter through five years.

ENDEAVOR III was a randomized, single-blind, controlled U.S. study of the safety and performance of the Endeavor Stent in patients with single *de novo* coronary artery lesions. A total of 436 patients at 29 U.S. sites were enrolled with patients randomized to receive Endeavor or the Cypher stent in 3:1 ratio. The primary endpoint for the study was in-segment late lumen loss at eight months post-procedure. The secondary endpoints for this trial included: in-stent late lumen loss at eight months; device success; lesion success; procedure success; Major Adverse Cardiac Event (MACE) rate at 30 days, 6, 9, and 12 months post-procedure; as well as the eight month angiographic and IVUS parameters and the nine month clinical

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assessments in all patients. After the procedure, patients received clopidogrel for a minimum of three months and aspirin indefinitely. Follow-up through 24 months is available, and yearly follow-up for clinical parameters through five years is ongoing.

ENDEAVOR II was a multi-center, double-blind, randomized controlled supporting study of the safety and performance of the Zotarolimus-Eluting stent. A total of 1197 patients in 72 countries were enrolled. Patients in each cohort were randomized (1: l) to receive the Endeavor or the control (Driver BMS) stent. The primary analytical subset for this trial was the Intent-to-Treat population. The primary endpoint for this study was Target Vessel Failure (TVF) at nine months post-procedure. The secondary endpoint of the study included clinical assessments for all patients through nine months and the angiographic and IVUS parameters in a subset of patients at eight months. After the procedure, patients received clopidogrel for three months and aspirin indefinitely. Follow-up through 36 months is available, and yearly follow- up for clinical parameters through five years is ongoing.

ENDEAVOR I was the first-in-man study for the Endeavor stent system. Endeavor I was a non-randomized, prospective, single arm feasibility study. In brief, 100 patients were enrolled at eight clinical research sites in Australia and New Zealand. The primary endpoint was 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (by QCA) at four months. Follow-up through 48 months is currently available and follow-up for clinical parameters through five years is ongoing.

8.10 Potential Adverse Effects of the Product on Health

8.10.1 Observed Adverse Events

Observed adverse event experience comes from four clinical studies: ENDEAVOR IV, ENDEAVOR III, ENDEAVOR II, and the ENDEAVOR I study.

Principal adverse events are shown in Table 8-9 below.

Table 8-9: Principal Adverse Events

Description of Event	ENDEAVOR IV to 270 days		Endeavor III to 720 days		Endeavor II to 1080 days		Endeavor I to 1440 days
	Endeavor (N=773 patients)	Control (N=775 patients)	Endeavor (N=323 patients)	Control (N=113 patients)	Endeavor (N=598 patients)	Control (N=599 patients)	Endeavor (N=100 patients)
In-Hospital							
MACE	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Myocardial Infarction (Q wave or Non-Q wave)	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
Q wave MI	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.3% (2/596)	0.0% (0/100)
Non-Q wave MI	0.5% (4/773)	1.9% (15/775)	0.6% (2/323)	3.5% (4/113)	2.3% (14/597)	2.3% (14/596)	0.0% (0/100)
Target Lesion Revascularization	0.4% (3/773)	0.5% (4/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
TL-CABG	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TL-PTCA	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Revascularization non Target Lesion	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-CABG	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-PTCA	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Target Vessel Revascularization	0.4% (3/773)	0.6%(5/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Failure	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Perforation	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)

Table 8-9: Principal Adverse Events

Description of Event	ENDEAVOR IV to 270 days		Endeavor III to 720 days		Endeavor II to 1080 days		Endeavor I to 1440 days
	Endeavor (N=773 patients)	Control (N=775 patients)	Endeavor (N=323 patients)	Control (N=113 patients)	Endeavor (N=598 patients)	Control (N=599 patients)	Endeavor (N=100 patients)
Stent Thrombosis (acute)	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.3% (2/597)	0.3% (2/596)	0.0% (0/100)
Cerebrovascular Accident (CVA)	0.1% (1/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Out-of-Hospital							
MACE	4.7% (35/740)	3.0% (22/734)	8.6% (27/313)	8.9% (10/112)	9.5% (55/577)	18.7% (108/579)	7.2% (7/97)
Death	0.7% (5/740)	0.8% (6/734)	1.6% (5/313)	4.5% (5/112)	3.1% (18/577)	4.5% (26/579)	4.1% (4/97)
Myocardial Infarction (Q wave or Non-Q wave)	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.7% (4/577)	1.6% (9/579)	1.0% (1/97)
Q wave MI	0.0% (0/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.7% (4/579)	0.0% (0/97)
Non-Q wave MI	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.5% (3/577)	0.9% (5/579)	1.0% (1/97)
Target Lesion Revascularization	3.8% (28/740)	2.2% (16/734)	7.0% (22/313)	4.5% (5/112)	6.8% (39/577)	14.3% (83/579)	3.1% (3/97)
TL-CABG	0.4% (3/740)	0.4% (3/734)	1.3% (4/313)	0.0% (0/112)	0.5% (3/577)	1.0% (6/579)	1.0% (1/97)
TL-PTCA	3.5% (26/740)	1.8% (13/734)	5.8% (18/313)	4.5% (5/112)	6.4% (37/577)	13.5% (78/579)	3.1% (3/97)
Target Vessel Revascularization non Target Lesion	2.0% (15/740)	2.6% (19/734)	8.3% (26/313)	6.3% (7/112)	2.9% (17/577)	4.8% (28/579)	2.1% (2/97)
TV/non-TL-CABG	0.4% (3/740)	0.1% (1/734)	1.0% (3/313)	0.0% (0/112)	0.2% (1/577)	0.3% (2/579)	1.0% (1/97)
TV/non-TL-PTCA	1.8% (13/740)	2.5% (18/734)	7.7% (24/313)	6.3% (7/112)	2.8% (16/577)	4.7% (27/579)	1.0% (1/97)
Target Vessel Revascularization	5.1%	4.4%	13.7%	9.8%	9.0% (52/577)	17.4%	5.2% (5/97)

Table 8-9: Principal Adverse Events

Description of Event	ENDEAVOR IV to 270 days		Endeavor III to 720 days		Endeavor II to 1080 days		Endeavor I to 1440 days
	Endeavor (N=773 patients)	Control (N=775 patients)	Endeavor (N=323 patients)	Control (N=113 patients)	Endeavor (N=598 patients)	Control (N=599 patients)	Endeavor (N=100 patients)
	(38/740)	(32/734)	(43/313)	(11/112)		(101/579)	
Target Vessel Failure	5.8% (43/740)	4.8% (35/734)	13.7% (43/313)	10.7% (12/112)	10.4% (60/577)	19.2% (111/579)	5.2% (5/97)
Stent Thrombosis (sub-acute/<30 days)	0.1% (1/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.9% (5/579)	1.0% (1/97)
Stent Thrombosis (late /≥ 30 days)	0.4% (3/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.0% (0/577)	0.0% (0/579)	0.0% (0/97)
Cerebrovascular Accident (CVA)	0.5% (4/740)	0.5% (4/734)	0.6% (2/313)	0.9% (1/112)	1.0% (6/577)	1.2% (7/579)	1.0% (1/97)

N = The maximum number of eligible patients
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization.
ENDEAVOR IV: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR III: The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
ENDEAVOR II: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR I: The primary endpoint is 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months.

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In the ENDEAVOR IV trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. In the ENDEAVOR III trial all enrolled patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluation at 8-months. In the ENDEAVOR II trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. Rates of incomplete stent apposition are shown in Table 8-10 for ENDEAVOR II, ENDEAVOR III and ENDEAVOR IV trials.

Table 8-10: Frequency of Incomplete Apposition (ENDEAVOR II, ENDEAVOR III and ENDEAVOR IV)

	ENDEAVOR II Trial		ENDEAVOR III Trial		ENDEAVOR IV Trial	
	Endeavor Stent (N=169)	Control Stent (N=159)	Endeavor Stent (N=323)	Control Stent (N=113)	Endeavor Stent (N=164)	Control Stent (N=164)
Incomplete Stent Apposition Rate at Post-Procedure	24.8% (36/145)	19.6% (28/143)	12.4% (31/251)	17.7% (17/96)	12.5% (17/136)	11.8% (15/127)
Incomplete Stent Apposition Rate at 8 Month Follow-up	16.8% (21/125)	14.5% (16/110)	7.5% (17/226)	17.1% (13/76)	10.0% (12/120)	14.7% (17/116)
Resolved	7.0% (8/114)	6.7% (7/104)	5.8% (11/189)	7.4% (5/68)	3.8% (4/106)	2.1% (2/95)
Persistent	17.5% (20/114)	14.4% (15/104)	7.9% (15/189)	11.8% (8/68)	8.5% (9/106)	10.5% (10/95)
Late Acquired	0% (0/114)	0% (0/104)	0.5% (1/189)	5.9% (4/68)	0.9% (1/106)	3.2% (3/95)

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8.10.2 Potential Adverse Events

Risks associated with using this product are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks (in alphabetical order) may include, but are not limited to, the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias
- Balloon rupture
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Infection or fever
- Myocardial infarction (MI)
- Peripheral ischemia / peripheral nerve injury
- Restenosis of the stented artery
- Shock / pulmonary edema
- Stent deformation, collapse, or fracture
- Stent migration
- Stent misplacement
- Stroke / transient ischemic attack
- Thrombosis (acute and subacute)
- Unstable angina

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted.

The adverse events that have been associated with the intravenous injection of zotarolimus in humans include:

- Anemia
- Circumoral paresthesia
- Diarrhea
- Dry Skin
- Headache
- Hematuria

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- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

In addition, thirty-day Adverse Event information was provided on over 2000 patients treated with the Endeavor Zotarolimus-Eluting CSS to support the safety profile of zotarolimus. There may be other potential adverse events that are unforeseen at this time.

8.11 Summary of Clinical Studies

8.11.1 ENDEAVOR IV Clinical Trial

Objective: To demonstrate the equivalence in safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Taxus Paclitaxel-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5-3.5 mm

Conclusion: Based on acute procedural results, 8-month angiographic, and 9-month clinical follow-up the Endeavor Zotarolimus-Eluting CSS has demonstrated similar safety and efficacy compared to the Taxus control stent. The non-inferiority of the Endeavor stent to the Taxus stent with respect to TVF rate was demonstrated in this study.

Design: This was a prospective, multi-center, randomized, two-arm, single-blind trial that enrolled 1548 patients with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to treatment by percutaneous stenting.

Follow-up was performed at 30 days, 6, 8, and 9 months, and will be performed at 12 months, then annually thereafter out to 5 years. Angiography and IVUS evaluations were performed immediately post-procedure and at 8 months post-procedure for the first 328 consecutively enrolled patients (combined from all sites). In addition, patients at all sites receiving two or more stents at the target lesion had angiographic and IVUS evaluations immediately post-procedure and at 8 months post-procedure (known as the Multi-stent subset).

Demographics: The analysis population of this report consisted of 1548 patients. Baseline demographics and clinical characteristics showed a mean age of 63.5 years for patients in the Endeavor arm and 63.6 years for patients in the Taxus arm. The Endeavor group had 66.9% (517/773) male enrollment and the Taxus group had 68.5% (531/775) male enrollment. In the Endeavor arm, 28.2% (218/773) of patients had prior percutaneous coronary revascularization compared to 29.5% (229/775) of subjects in the Taxus arm. In the Endeavor group, 31.2% (241/773) of patients had a history of diabetes mellitus compared to 30.5% (236/775) of patients in the Taxus group.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by study personnel at the clinical sites. Angiographic and IVUS outcomes were assessed at designated core laboratories. Clinical events were adjudicated by an independent Clinical Events Committee and the trial was monitored by an independent Data Monitoring Committee.

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Results: The effectiveness and safety results for Endeavor and Taxus are presented in Table 1.3-12. At 270 days, the cumulative incidence of MACE for the Endeavor patients was 5.7% (42/740) compared to the Taxus patients which was 5.7% (42/734). The Kaplan-Meier estimate of freedom from MACE at 270 days for Endeavor patients was 94.4%; for Taxus patients it was 94.5%.

The incidence of the primary endpoint of TVF at 270 days for Endeavor was 6.8% (50/740) and for Taxus it was 7.4% (54/734) (p=0.685). The incidence of TLR at 270 days post-index procedure for the Endeavor arm was 4.2% (31/740); for Taxus it was 2.7% (20/734) (p=0.154).

In Table 8-11 the outcome of the primary endpoint from the ENDEAVOR IV trial is summarized.

Table 8-11: Primary endpoint from ENDEAVOR IV

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
ENDEAVOR IV	Target Vessel Failure at 9 months post-procedure	Endeavor	6.8% (50/740)	0.0005
		Taxus	7.4% (54/734)	

* P-value is for the test of Non-Inferiority.

Table 8-12 summarizes the principal effectiveness and safety results of the ENDEAVOR IV Trial through 9 months.

Table 8-12: Principal Effectiveness and Safety Results- ITT population

Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Lesion Success	99.6% (767/770)	99.2% (766/772)	0.4%[-0.4%, 1.1%]	0.507
Device Success	97.3% (751/772)	97.9% (757/773)	-0.7%[-2.2%, 0.9%]	0.412
Procedure Success	98.7% (760/770)	96.8% (747/772)	1.9% [0.5%, 3.4%]	0.015
Device-Specific Procedure Success	96.5% (745/772)	95.6% (739/773)	0.9% [-1.0%, 2.8%]	0.433
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.62±0.43 (763)	2.61±0.44 (763)	0.01 [-0.04, 0.05]	0.703
In-Segment	2.22±0.47 (770)	2.19±0.50 (772)	0.03 [-0.02, 0.08]	0.196
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	5.50±9.61 (763)	5.01±10.49 (763)	0.48 [-0.53, 1.49]	0.348
In-Segment	20.47±9.54 (770)	20.97±11.12 (772)	-0.50 [-1.53, 0.54]	0.344
Eight-Month Follow-Up MLD (mm)				

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Table 8-12: Principal Effectiveness and Safety Results- ITT population

Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
In-Stent	1.95±0.61 (143)	2.25±0.61 (135)	-0.30 [-0.45, -0.16]	<0.001
In-Segment	1.80±0.55 (144)	1.98±0.56 (135)	-0.18 [-0.31, -0.05]	0.008
Eight-Month Follow-up %DS				
In-Stent	26.41±19.74 (143)	16.09±17.99 (135)	10.32 [5.85, 14.79]	<.001
In-Segment	32.28±17.02 (144)	26.61±15.52 (135)	5.68 [1.83, 9.52]	0.004
Eight-Month Late Loss (mm)				
In-Stent	0.67±0.49 (142)	0.42±0.50 (135)	0.25 [0.13, 0.37]	<.001
In-Segment	0.36±0.47 (143)	0.23±0.45 (135)	0.13 [0.02, 0.23]	0.023
Eight-Month Binary Restenosis				
In-Stent	13.3% (19/143)	6.7% (9/135)	6.6% [-0.4%, 13.6%]	0.075
In-Segment	15.3% (22/144)	10.4% (14/135)	4.9% [-2.9%, 12.7%]	0.284
Eight-Month Volume Obstruction (%)	15.72±10.40 (74)	9.88±9.24 (77)	5.84 [2.68, 9.00]	<.001
Eight-Month Minimal Lumen Area (mm^2)	4.62±1.82 (113)	5.50±2.14 (109)	-0.87 [-1.39, -0.35]	0.001
Eight-Month NIH Volume (mm^3)	24.14±19.38 (74)	14.88±16.62 (77)	9.26 [3.46, 15.06]	0.002
In-Hospital MACE	0.9% (7/773)	2.6% (20/775)	-1.7% [-3.0%, -0.4%]	0.018
MACE to 30 Days	1.2% (9/770)	3.0% (23/771)	-1.8% [-3.2%, -0.4%]	0.019
MACE to 270 Days	5.7% (42/740)	5.7% (42/734)	-0.0% [-2.4%, 2.3%]	1.000
Death to 270 Days	0.7% (5/740)	0.8% (6/734)	-0.1% [-1.0%, 0.7%]	0.773
Vascular Complications to 270 Days	0.5% (4/740)	0.8% (6/734)	-0.3% [-1.1%, 0.6%]	0.546
Major Bleeding to 270 Days	1.6% (12/740)	2.9% (21/734)	-1.2% [-2.8%, 0.3%]	0.116
Early Stent Thrombosis to 30 Days	0.4% (3/770)	0.1% (1/771)	0.3% [-0.2%, 0.8%]	0.374
Late Stent Thrombosis to 270 days	0.4% (3/740)	0.0% (0/734)	0.4% [-0.1%, 0.9%]	0.250
Cerebrovascular Accident (CVA) to 270 Days	0.7% (5/740)	0.5% (4/734)	0.1% [-0.7%, 0.9%]	1.000
Perforation to 270 Days	0.1% (1/740)	0.4% (3/734)	-0.3% [-0.8%, 0.3%]	0.372

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Table 8-12: Principal Effectiveness and Safety Results- ITT population

Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Target Vessel Revascularization to 30 days	0.4% (3/770)	0.9% (7/771)	-0.5% [-1.3%, 0.3%]	0.342
Target Vessel Revascularization to 270 days	5.5% (41/740)	5.0% (37/734)	0.5% [-1.8%, 2.8%]	0.727
Target Vessel Failure to 30 days	1.0% (8/770)	3.0% (23/771)	-1.9% [-3.3%, -0.5%]	0.010
Target Vessel Failure to 270 days	6.8% (50/740)	7.4% (54/734)	-0.6% [-3.2%, 2.0%]	0.685
Target Lesion Revascularization to 30 days	0.4% (3/770)	0.8% (6/771)	-0.4% [-1.1%, 0.4%]	0.507
Target Lesion Revascularization to 270 days	4.2% (31/740)	2.7% (20/734)	1.5% [-0.4%, 3.3%]	0.154

Kaplan-Meier Estimate	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	P-value†
*MACE-Free at 270 days	94.4%	94.5%	0.952
*TLR-Free at 270 days	95.8%	97.3%	0.127
*TVR-Free at 270 days	94.4%	95.0%	0.682
*TVF-Free at 270 days	93.3%	92.8%	0.626

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – TAXUS.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.

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Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free– No Death, MI, emergent CABG or target lesion revascularization

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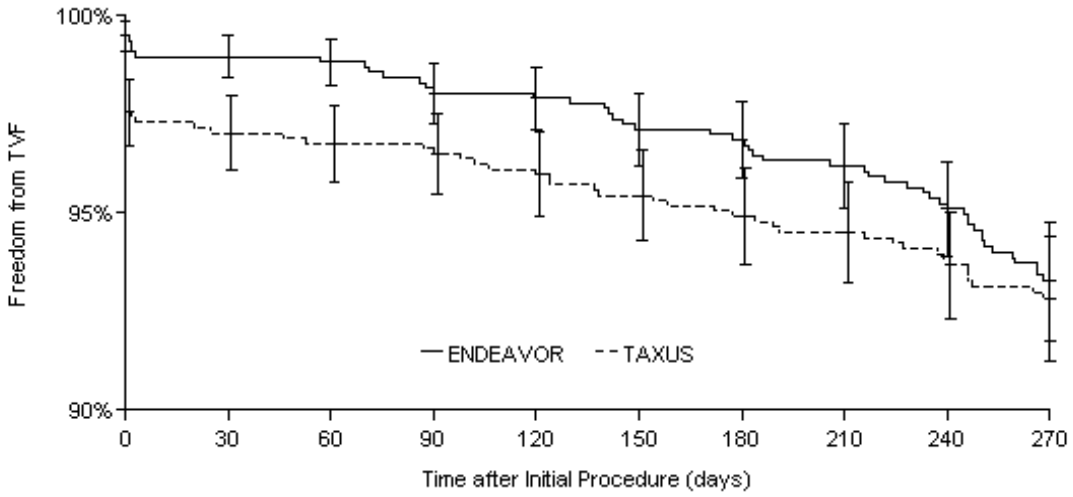

TVF	0	7	14	21	30	60	90	120	150	180	210	240	270
ENDEAVOR													
# Entered	773	769	760	760	760	756	750	744	743	736	728	718	703
# Censored	0	5	0	0	4	5	0	0	1	6	5	7	118
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	4	4	0	0	0	1	6	1	6	2	5	8	13
% Survived	99.5%	99.0%	99.0%	99.0%	99.0%	98.8%	98.0%	97.9%	97.1%	96.9%	96.2%	95.1%	93.3%
SE	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.6%	0.6%	0.7%	0.8%	1.0%
TAXUS													
# Entered	775	755	748	748	747	744	735	732	726	720	710	694	683
# Censored	1	5	0	0	2	7	1	2	2	6	13	5	105
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	19	2	0	1	1	2	2	4	4	4	3	6	6
% Survived	97.5%	97.3%	97.3%	97.2%	97.0%	96.8%	96.5%	96.0%	95.4%	94.9%	94.5%	93.7%	92.8%
SE	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.7%	0.7%	0.8%	0.8%	0.8%	0.9%	1.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Log-Rank	0.24	1	0.626									
	Wilcoxon	0.43	1	0.511									

Figure 8-3: Survival Free from Target Vessel Failure at 270 days (ITT)

8.11.2 ENDEAVOR III Clinical Trial

Objective: To demonstrate the equivalency in in-segment late lumen loss at 8 months between the Endeavor Zotarolimus-Eluting CSS (coated with 10 µg/mm zotarolimus) and the Cypher Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter.

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Conclusion: As demonstrated in this clinical trial, the Endeavor stent was shown to have higher device success rate, a favorable safety profile (lower peri-procedural myocardial infarctions and no stent thrombosis) and comparable clinical efficacy (target lesion revascularization), despite higher restenosis and angiographic late loss. The criterion for non-inferiority of the Endeavor stent to the Cypher stent was not met with regard to the 8-month in-segment late lumen loss.

Design: This was a prospective, multi-center, single-blind, parallel, two-arm, randomized, controlled study that enrolled 436 patients with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to treatment by percutaneous stenting.

Follow-up was performed at 30 days, 6, 8, 9, 12 months and 2 year, and will be performed annually thereafter out to five years post-procedure. All study patients enrolled were scheduled to have angiographic and intravascular ultrasound (IVUS) follow-up at eight months post-index procedure.

Demographics: Of the 436 enrolled patients, baseline demographics and clinical characteristics showed a mean age of 61.4 years in the Endeavor arm and 61.7 years in the Cypher arm. The Endeavor group had 65.3% (211/323) male enrollment and the Cypher group had 81.4% (92/113) male enrollment. In the Endeavor arm, 22.6% (73/323) had prior percutaneous coronary revascularization compared to 16.8% (19/113) in the Cypher arm. In the Endeavor group, 29.7% (96/323) of patients had a history of diabetes mellitus compared to 28.3% (32/113) of patients in the Cypher arm.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by study personnel at the study sites. Angiographic and IVUS outcomes were assessed at designated core laboratories. Clinical events were adjudicated by an independent Clinical Events Committee and the trial was monitored by an independent Data Monitoring Committee.

Results: The effectiveness and safety results for Endeavor and Cypher are presented in Table 8-14. Baseline angiographic results were obtained for 436 enrolled patients on whom treatment was attempted. Follow up angiographic results were obtained for 371 patients with qualified angiographic films at the eight-month follow-up period. Safety measure measures were obtained for patients with follow-up information before the lower window of the follow-up period or with an incidence of the corresponding safety measure prior to the time of interest.

The mean and standard deviation for the primary endpoint of In-Segment Late Lumen Loss at eight months for the Endeavor arm was 0.36 ±0.46 (mm) and for the Cypher arm it was 0.13 ±0.33 (mm). The mean and standard deviation for the secondary endpoint of In-Stent Late Lumen Loss at eight months for the Endeavor group was 0.62±0.49 (mm) and for the Cypher group it was 0.15± 0.34 (mm). The rate of In-Stent Binary Restenosis at eight months for the Endeavor arm was 9.7% (27/277); for the Cypher arm it was 2.1% (2/94).

In Table 8-13 the outcome of the primary endpoint from the ENDEAVOR III trial is summarized.

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Table 8-13: Primary endpoint from ENDEAVOR III

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
ENDEAVOR III	In-segment Late Lumen Loss at 8 months post-procedure (mm)	Endeavor	0.36 ± 0.46	0.791*
		Cypher	0.13 ± 0.33	

* P-value is for the test of Non-Inferiority.

Effectiveness measures were reported for 436 patients with available baseline angiographic data. The lesion success rate was 100.0% (323/323) for patients in the Endeavor arm and 99.1% (112/113) for patients in the Cypher arm. The device success rate was 98.8% (319/323) for patients in Endeavor arm and 94.7% (107/113) for patients in the Cypher group. The procedure success rate was 99.4% (321/323) for patients in the Endeavor arm and 95.6% (108/113) for patients in the Cypher arm. The Device-Specific Procedure Success, defined as device success and no in-hospital MACE, rate for Endeavor arm patients was 98.1% (317/323) and 91.2% (103/113) for Cypher patients.

Additionally, in-hospital incidence of MACE was 0.6% (2/323) for patients in the Endeavor arm and 3.5% (4/113) for patients in the Cypher arm. Incidence of MACE at 720 days was 9.3% (29/313) for patients in the Endeavor group and 11.6% (13/112) for patients in the Cypher group.

The cumulative incidence of TLR at 720 days post-index procedure for Endeavor was 7.0% (22/313); for Cypher it was 4.5% (5/112). The cumulative incidence of TVR at 720 days post-index procedure for Endeavor was 13.7% (43/313); for Cypher it was 9.8% (11/112). The cumulative incidence of TVF at 720 days post-index procedure for Endeavor was 14.4% (45/313); for Cypher it was 13.4% (15/112).

The Kaplan-Meier estimate of freedom from MACE at 720 days for the Endeavor arm was 90.9%; for the Cypher arm it was 88.5%.

Table 8-14 summarizes the principal effectiveness and safety results of the ENDEAVOR III Trial through 24 months.

Table 8-14: Principal Effectiveness and Safety Results through 720 Days for ENDEAVOR III

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Lesion Success	100.0% (323/323)	99.1% (112/113)	0.9% [-0.8%,2.6%]	0.259
Device Success	98.8% (319/323)	94.7% (107/113)	4.1% [-0.2%,8.4%]	0.022
Procedure Success	99.4% (321/323)	95.6% (108/113)	3.8% [-0.1%,7.7%]	0.014
Device-Specific Procedure Success	98.1% (317/323)	91.2% (103/113)	7.0% [1.6%,12.4%]	0.002
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.67±0.42 (323)	2.67±0.40 (112)	0.00 [-0.09,0.09]	0.993
In-Segment	2.27±0.45 (323)	2.28±0.47 (113)	-0.01 [-0.11,0.09]	0.836

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Table 8-14: Principal Effectiveness and Safety Results through 720 Days for ENDEAVOR III

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	4.33±9.77 (323)	5.92±9.07 (112)	-1.59 [-3.66,0.48]	0.132
In-Segment	19.38±9.25 (323)	20.17±11.74 (113)	-0.78 [-2.92,1.36]	0.522
Eight-Month Follow-Up MLD (mm)				
In-Stent	2.06±0.57 (277)	2.52±0.56 (94)	-0.46 [-0.60,-0.33]	<0.001
In-Segment	1.91±0.53 (277)	2.16±0.50 (94)	-0.25 [-0.37,-0.13]	<0.001
Eight-Month Follow-up %DS				
In-Stent	24.90±17.45 (277)	11.01±15.91 (94)	13.89 [9.88,17.90]	<0.001
In-Segment	30.42±15.57 (277)	23.86±13.87 (94)	6.56 [3.01,10.12]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.49 (277)	0.15±0.34 (94)	0.47 [0.36,0.58]	<0.001
In-Segment	0.36±0.46 (277)	0.13±0.33 (94)	0.24 [0.13,0.34]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.7% (27/277)	2.1% (2/94)	7.6% [3.1%,12.2%]	0.014
In-Segment	12.3% (34/277)	4.3% (4/94)	8.0% [2.4%,13.6%]	0.029
Eight-Month Volume Obstruction (%)	15.94±10.94 (187)	2.66±3.11 (61)	13.27 [10.48,16.07]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.89±1.96 (209)	5.77±1.97 (66)	-0.88 [-1.43,-0.34]	0.002
Eight-Month NIH Volume (mm^3)	24.09±21.16 (209)	3.74±5.20 (67)	20.36 [15.21,25.50]	<0.001
In-Hospital MACE	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 30 Days	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 270 Days	7.5% (24/321)	7.1% (8/113)	0.4% [-5.1%,5.9%]	1.000
MACE to 360 Days	7.8% (25/320)	8.0% (9/112)	-0.2% [-6.1%,5.6%]	1.000
MACE to 720 Days	9.3% (29/313)	11.6% (13/112)	-2.3% [-9.1%,4.4%]	0.465
Death to 720 Days	1.6% (5/313)	4.5% (5/112)	-2.9% [-6.9%,1.2%]	0.138
Vascular Complications to 720 Days	1.9% (6/313)	5.4% (6/112)	-3.4% [-7.9%,1.0%]	0.090
Major Bleeding to 720 Days	2.2% (7/313)	6.3% (7/112)	-4.0% [-8.8%,0.8%]	0.060
Early Stent Thrombosis to 30 Days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Late Stent Thrombosis to 270 days	0.0% (0/321)	0.0% (0/113)	0.0% [--,--]	--
Late Stent Thrombosis to 360 days	0.0% (0/320)	0.0% (0/112)	0.0% [--,--]	--

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Table 8-14: Principal Effectiveness and Safety Results through 720 Days for ENDEAVOR III

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Late Stent Thrombosis to 720 days	0.0% (0/313)	0.0% (0/112)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 720 Days	0.6% (2/313)	0.9% (1/112)	-0.3% [-2.2%,1.7%]	1.000
Perforation to 720 Days	0.0% (0/313)	0.9% (1/112)	-0.9% [-2.6%,0.8%]	0.264
Target Vessel Revascularization to 30 days	0.0% (0/323)	0.9% (1/113)	-0.9% [-2.6%,0.8%]	0.259
Target Vessel Revascularization to 270 days	11.2% (36/321)	8.0% (9/113)	3.3% [-2.8%,9.3%]	0.375
Target Vessel Revascularization to 360 days	12.2% (39/320)	8.0% (9/112)	4.2% [-2.0%,10.3%]	0.295
Target Vessel Revascularization to 720 days	13.7% (43/313)	9.8% (11/112)	3.9% [-2.8%,10.6%]	0.325
Target Vessel Failure to 30 days	0.6% (2/323)	4.4% (5/113)	-3.8% [-7.7%,0.1%]	0.014
Target Vessel Failure to 270 days	11.8% (38/321)	11.5% (13/113)	0.3% [-6.5%,7.2%]	1.000
Target Vessel Failure to 360 days	12.8% (41/320)	11.6% (13/112)	1.2% [-5.8%,8.2%]	0.868
Target Vessel Failure to 720 days	14.4% (45/313)	13.4% (15/112)	1.0% [-6.4%,8.4%]	0.875
Target Lesion Revascularization to 30 days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Target Lesion Revascularization to 270 days	6.2% (20/321)	3.5% (4/113)	2.7% [-1.6%,7.0%]	0.346
Target Lesion Revascularization to 360 days	6.6% (21/320)	3.6% (4/112)	3.0% [-1.4%,7.4%]	0.347
Target Lesion Revascularization to 720 days	7.0% (22/313)	4.5% (5/112)	2.6% [-2.2%,7.3%]	0.498

Kaplan-Meier Estimate	ENDEAVOR III (N= 323 Patients)	CYPHER™ (N= 113 Patients)	P-value†
*MACE-Free at 720 days	90.9%	88.5%	0.464
*TLR-Free at 720 days	93.0%	95.5%	0.336
*TVR-Free at 720 days	86.4%	90.2%	0.304
*TVF-Free at 720 days	85.8%	86.7%	0.867

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – CYPHER.
CI = Confidence interval
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.

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Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as:
100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 30 days after index procedure 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair.
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel.
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free – No Death, MI, emergent CABG or target lesion revascularization.

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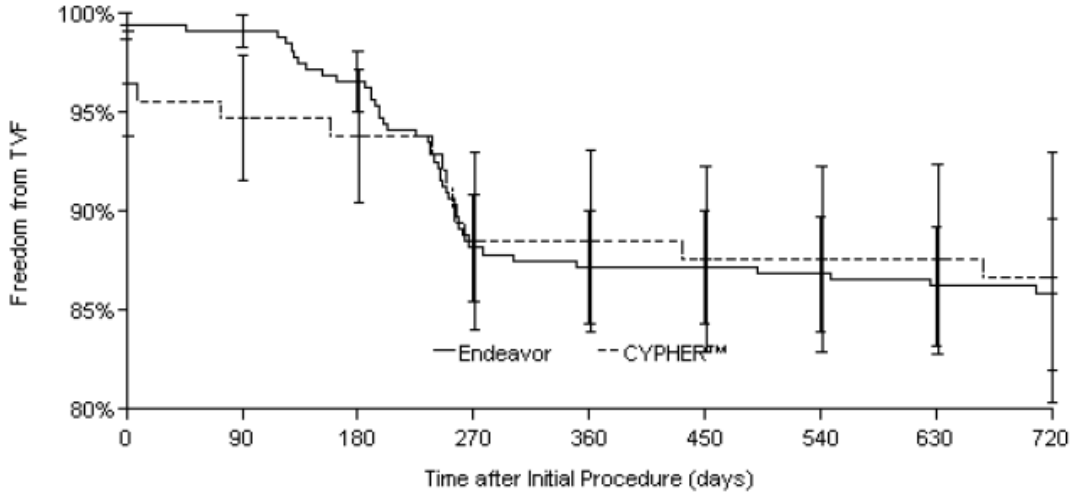

TVF	0	90	180	270	360	450	540	630	720
Endeavor									
# Entered	323	321	318	310	281	274	268	264	262
# Censored	0	2	0	2	4	6	3	0	102
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	2	1	8	27	3	0	1	2	1
% Survived	99.4%	99.1%	96.6%	88.1%	87.2%	87.2%	86.9%	86.2%	85.8%
SE	0.4%	0.5%	1.0%	1.8%	1.9%	1.9%	1.9%	2.0%	2.6%
CYPHER™									
# Entered	113	109	107	106	100	98	97	97	95
# Censored	0	0	0	0	2	0	0	2	38
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	4	2	1	6	0	1	0	0	1
% Survived	96.5%	94.7%	93.8%	88.5%	88.5%	87.6%	87.6%	87.6%	86.7%
SE	1.7%	2.1%	2.3%	3.0%	3.0%	3.1%	3.1%	3.2%	4.2%

Figure 8-4: Survival Free from Target Vessel Failure at 720 days (ITT)

8.11.3 ENDEAVOR II Clinical Trial

Objective: To demonstrate the safety and efficacy of the Endeavor Zotarolimus-Eluting CSS (coated with 10 µg/mm zotarolimus) compared to the Driver Stent for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter.

Conclusion: Based on acute procedural results, 8-month angiographic, and 36-month clinical follow-up, the Endeavor Zotarolimus-Eluting CSS has demonstrated similar safety and superior efficacy compared with the uncoated Driver control stent.

Design: This was a prospective, multi-center, double-blind, two-arm randomized controlled trial that enrolled 1197 patients with symptomatic ischemic heart disease attributed to stenotic lesions of the native coronary arteries that are amendable to treatment by percutaneous stenting.

Demographics: Of the 1197 enrolled patients, treatment was attempted on 1193. Baseline demographics and clinical characteristics showed a mean age of 61.58 years for patients

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in the Endeavor arm and 61.89 years for patients in the Driver arm. The Endeavor group had 77.2% (461/597) male enrollment and the Driver group had 75.3% (449/596) male enrollment. In the Endeavor arm, 21.7% (129/595) of patients had prior percutaneous coronary revascularization compared to 18.0% (107/594) of subjects in the Driver arm. In the Endeavor group, 18.2% (108/595) of patients had a history of diabetes mellitus compared to 22.2% (132/595) of patients in the Driver group.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by study personnel at the study sites. Angiographic and IVUS outcomes were assessed at designated core laboratories. Clinical events were adjudicated by an independent Clinical Events Committee and the trial was monitored by an independent Data Monitoring Committee. Additionally, pharmacokinetic (PK) analysis was conducted on 106 patients at selected sites.

Results: The effectiveness and safety results for Endeavor and Driver are presented in Table 8-16. At 1080 days, the cumulative incidence of MACE for the Endeavor patients was 12.0% (69/577) compared to the Driver patients which was 20.7% (120/579). The Kaplan-Meier estimate of freedom from MACE at 1080 days for Endeavor patients was 88.3%; for Driver patients it was 79.6%.

Additionally, in-hospital incidence of MACE was 2.5% (15/597) for patients in the Endeavor group and 2.9% (17/596) for patients in the Driver group. Incidence of MACE at 270 days was 7.3% (43/592) for patients in the Endeavor arm and 14.4% (85/591) for patients in the Driver arm.

The cumulative incidence of the primary endpoint of TVF at 270 days for Endeavor was 7.9% (47/592) and for Driver it was 15.1% (89/591) ($p<0.001$). The cumulative incidence of TLR at 270 days post-index procedure for the Endeavor arm was 4.6% (27/592); for Driver it was 11.8% (70/591) ($p<0.001$).

In Table 8-15 the outcome of the primary endpoint from the ENDEAVOR II trial is summarized.

Table 8-15: Primary endpoint from ENDEAVOR II

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
ENDEAVOR II	**Target Vessel Failure at 9 months post-procedure**	**Endeavor Driver**	**7.9% (47/592) 15.1% (89/591)**	**< 0.001**

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Table 8-16 summarizes the principal effectiveness and safety results of the ENDEAVOR II Trial through 24 months.

Table 8-16: Principal Effectiveness and Safety Results for ENDEAVOR II through 1080 Days

Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
Lesion Success	99.7% (587/589)	100.0% (590/590)	-0.3% [-0.8%,0.1%]	0.249
Device Success	98.8% (585/592)	99.2% (586/591)	-0.3% [-1.5%,0.8%]	0.773
Procedure Success	97.3% (573/589)	97.1% (573/590)	0.2% [-1.7%,2.0%]	1.000
Device-Specific Procedure Success	96.5% (571/592)	96.4% (570/591)	0.0% [-2.1%,2.1%]	1.000
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.59±0.43 (588)	2.61±0.44 (589)	-0.02 [-0.07,0.03]	0.436
In-Segment	2.21±0.49 (589)	2.24±0.49 (590)	-0.03 [-0.09,0.03]	0.302
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	6.04±10.43 (588)	6.23±10.03 (589)	-0.18 [-1.36,0.99]	0.757
In-Segment	20.39±10.26 (589)	20.11±9.38 (590)	0.28 [-0.84,1.41]	0.622
Eight-Month Follow-Up MLD (mm)				
In-Stent	1.99±0.56 (264)	1.62±0.70 (265)	0.37 [0.26,0.48]	<0.001
In-Segment	1.86±0.55 (264)	1.56±0.67 (265)	0.30 [0.19,0.40]	<0.001
Eight-Month Follow-up %DS				
In-Stent	27.91±17.30 (264)	42.24±21.73 (265)	-14.33 [-17.68,-10.97]	<0.001
In-Segment	32.67±16.27 (264)	44.33±20.45 (265)	-11.66 [-14.82,-8.50]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.46 (264)	1.03±0.59 (263)	-0.41 [-0.50,-0.32]	<0.001
In-Segment	0.36±0.46 (264)	0.72±0.61 (263)	-0.36 [-0.45,-0.27]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.5% (25/264)	33.2% (88/265)	-23.7% [-30.4%,-17.1%]	<0.001
In-Segment	13.3% (35/264)	34.7% (92/265)	-21.5% [-28.5%,-14.4%]	<0.001
Eight-Month Volume Obstruction (%)	17.34±10.27 (90)	29.55±17.58 (81)	-12.22 [-16.51,-7.92]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.99±1.66 (122)	3.98±1.72 (107)	1.01 [0.57,1.45]	<0.001
Eight-Month NIH Volume (mm^3)	30.15±21.66 (90)	53.51±39.80 (81)	-23.36 [-32.91,-13.81]	<0.001

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Table 8-16: Principal Effectiveness and Safety Results for ENDEAVOR II through 1080 Days

Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
In-Hospital MACE	2.5% (15/597)	2.9% (17/596)	-0.3% [-2.2%,1.5%]	0.725
MACE to 30 Days	2.9% (17/596)	3.7% (22/594)	-0.9% [-2.9%,1.2%]	0.421
MACE to 270 Days	7.3% (43/592)	14.4% (85/591)	-7.1% [-10.6%,-3.6%]	<0.001
MACE to 360 Days	8.8% (52/590)	15.6% (92/589)	-6.8% [-10.5%,-3.1%]	<0.001
MACE to 720 Days	9.9% (58/587)	18.1% (106/586)	-8.2% [-12.2%,-4.3%]	<0.001
MACE to 1080 Days	12.0% (69/577)	20.7% (120/579)	-8.8% [-13.0%,-4.5%]	<0.001
Death to 1080 Days	3.3% (19/577)	4.5% (26/579)	-1.2% [-3.4%,1.0%]	0.362
Vascular Complications to 1080 Days	0.5% (3/577)	1.2% (7/579)	-0.7% [-1.8%,0.4%]	0.342
Major Bleeding to 1080 Days	1.2% (7/577)	2.4% (14/579)	-1.2% [-2.7%,0.3%]	0.185
Early Stent Thrombosis	0.5% (3/596)	1.2% (7/594)	-0.7% [-1.7%,0.4%]	0.224
Late Stent Thrombosis to 270 days	0.0% (0/592)	0.0% (0/591)	0.0% [--,--]	--
Late Stent Thrombosis to 360 days	0.0% (0/590)	0.0% (0/589)	0.0% [--,--]	--
Late Stent Thrombosis to 720 days	0.0% (0/587)	0.0% (0/586)	0.0% [--,--]	--
Late Stent Thrombosis to 1080 days	0.0% (0/577)	0.0% (0/579)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 1080 Days	1.0% (6/577)	1.2% (7/579)	-0.2% [-1.4%,1.0%]	1.000
Perforation to 1080 Days	0.5% (3/577)	0.3% (2/579)	0.2% [-0.6%,0.9%]	0.686
Target Vessel Revascularization to 30 days	1.2% (7/596)	1.2% (7/594)	-0.0% [-1.2%,1.2%]	1.000
Target Vessel Revascularization to 270 days	5.6% (33/592)	12.5% (74/591)	-6.9% [-10.2%,-3.7%]	<0.001
Target Vessel Revascularization to 360 days	7.5% (44/590)	14.1% (83/589)	-6.6% [-10.2%,-3.1%]	<0.001
Target Vessel Revascularization to 720 days	8.3% (49/587)	16.4% (96/586)	-8.0% [-11.8%,-4.3%]	<0.001
Target Vessel Revascularization to 1080 days	9.5% (55/577)	17.6% (102/579)	-8.1% [-12.0%,-4.2%]	<0.001
Target Vessel Failure to 30 days	3.2% (19/596)	3.7% (22/594)	-0.5% [-2.6%,1.6%]	0.638
Target Vessel Failure to 270 days	7.9% (47/592)	15.1% (89/591)	-7.1% [-10.7%,-3.5%]	<0.001
Target Vessel Failure to 360 days	10.0% (59/590)	16.6% (98/589)	-6.6% [-10.5%,-2.8%]	<0.001

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Table 8-16: Principal Effectiveness and Safety Results for ENDEAVOR II through 1080 Days

Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
Target Vessel Failure to 720 days	11.1% (65/587)	19.8% (116/586)	-8.7% [-12.8%,-4.6%]	<0.001
Target Vessel Failure to 1080 days	12.8% (74/577)	21.4% (124/579)	-8.6% [-12.9%,-4.3%]	<0.001
Target Lesion Revascularization to 30 days	0.8% (5/596)	1.2% (7/594)	-0.3% [-1.5%,0.8%]	0.579
Target Lesion Revascularization to 270 days	4.6% (27/592)	11.8% (70/591)	-7.3% [-10.4%,-4.2%]	<0.001
Target Lesion Revascularization to 360 days	5.9% (35/590)	13.1% (77/589)	-7.1% [-10.5%,-3.8%]	<0.001
Target Lesion Revascularization to 720 days	6.5% (38/587)	14.2% (83/586)	-7.7% [-11.1%,-4.2%]	<0.001
Target Lesion Revascularization to 1080 days	7.3% (42/577)	14.7% (85/579)	-7.4% [-11.0%,-3.8%]	<0.001

Kaplan-Meier Estimate	Endeavor (N=598 patients)	Driver (N=599 patients)	P-value†
*MACE-Free at 1080 days	88.3%	79.6%	<0.001
*TLR-Free at 1080 days	92.8%	85.4%	<0.001
*TVR-Free at 1080 days	90.6%	82.6%	<0.001
*TVF-Free at 1080 days	87.4%	78.9%	<0.001

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter.
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – DRIVER.
CI = Confidence interval
The primary endpoint is Target Vessel Failure at 9 months.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 30 days after index procedure 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair

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Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free – No Death, MI, emergent CABG or target lesion revascularization

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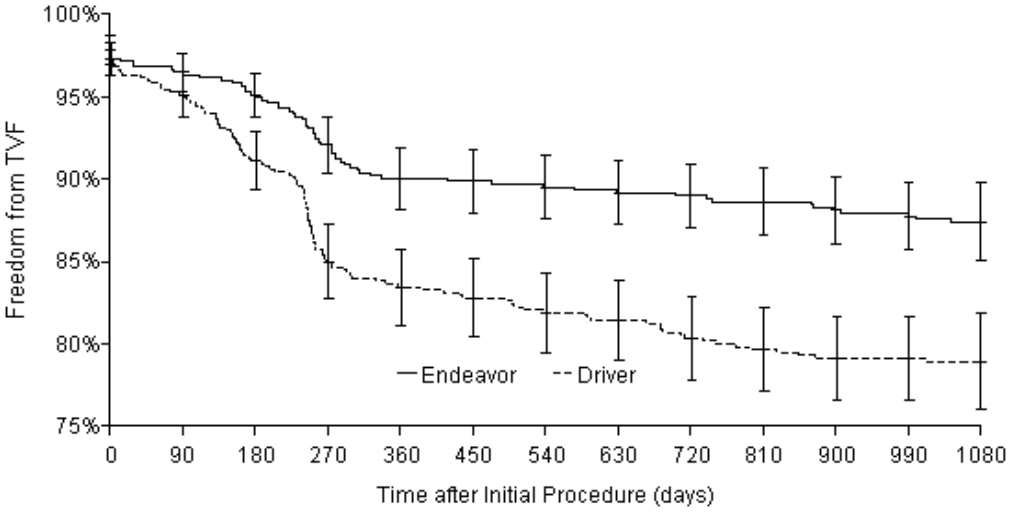

TVF	0	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor													
# Entered	597	584	570	561	541	525	522	519	515	512	503	500	497
# Censored	0	6	1	2	4	2	1	2	2	7	0	1	108
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	13	8	8	18	12	1	2	2	1	2	3	2	2
% Survived	97.8%	96.5%	95.1%	92.1%	90.0%	89.9%	89.5%	89.2%	89.0%	88.6%	88.1%	87.8%	87.4%
SE	0.6%	0.8%	0.9%	1.1%	1.2%	1.3%	1.3%	1.3%	1.3%	1.3%	1.4%	1.4%	1.6%
Driver													
# Entered	596	580	565	540	500	485	478	473	470	460	453	450	448
# Censored	0	2	1	4	6	3	0	0	4	3	0	2	109
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	16	13	24	36	9	4	5	3	6	4	3	0	1
% Survived	97.3%	95.1%	91.1%	85.0%	83.5%	82.8%	81.9%	81.4%	80.3%	79.6%	79.1%	79.1%	78.9%
SE	0.7%	0.9%	1.2%	1.5%	1.5%	1.6%	1.6%	1.6%	1.7%	1.7%	1.7%	1.7%	2.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Wilcoxon	15.19	1	<0.001									
	Log-Rank	15.19	1	<0.001									

Figure 8-5: Survival Free from Target Vessel Failure at 1080 Days (ITT)

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8.11.4 ENDEAVOR I Clinical Trial

Objective: To demonstrate the safety and efficacy of the Endeavor Zotarolimus-Eluting CSS (coated with 10 μg/mm zotarolimus) for the treatment of single *de novo* lesions in native coronary arteries.

Conclusion: The acute clinical results demonstrate 100.0% (100/100) lesion, device, procedure and device-specific preocedure success rates with MACE rates of 1.0% (1/100) at 30 days and 7.2% (7/97) at 48 months post-index procedure. The survival estimate free from the secondary endpoint of TVF at nine months post-index procedure was 98.0%. The survival estimate free from the endpoint of TVF at 48 months post-index procedure was 94.9%. The cumulative incidence of TVF at 48 months was 5.2% (5/97). The survival estimate free from TLR at 48 months post-index procedure was 96.9%, and the cumulative incidence of TLR at 48 months was 3.1% (3/97). Four-month angiographic late loss was 0.22 + 0.43 in-segment and 0.32 + 0.37 in-stent and neointimal hyperplastic volume by IVUS was 6.1 mm^3. Twelve-month angiographic late loss was 0.43 + 0.44 in-segment and 0.58 + 0.44 in-stent for the 92 evaluable patients and neointimal hyperplastic volume by IVUS was 14.2 mm^3.

Design: This was a prospective, multi-center, non-randomized, single-arm study that enrolled 100 subjects with symptomatic ischaemic heart disease attributable to native coronary artery stenoses that were amenable to treatment by percutaneous stenting. Study subjects with multiple vessel disease were allowed but only a single lesion per subject could be treated in this trial.

Demographics: Of the 100 patients enrolled, baseline demographics and clinical characteristics showed a mean age of 58.7 years, 79.0% (79/100) were men, 16.0% (16/100) had a history of diabetes mellitus, and 47% (47/100) had a prior MI. Mean reference vessel diameter pre-procedure was 2.96 ± 0.47 mm, pre-procedure minimal lumen diameter was 0.88 ± 0.33 mm, mean pre-procedure percent diameter stenosis was 70.32% ± 9.80% and the mean lesion length was 10.94 ± 3.13 mm (range 4.26-20.28 mm).

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical study personnel at the study sites. Angiographic and IVUS outcomes were assessed at designated core laboratories. Clinical events were adjudicated by an independent Clinical Events Committee and the trial was monitored by an independent Data Monitoring Committee.

Results: In-hospital incidence of major adverse cardiac events (MACE) was 0%. Incidence of MACE at 30 days was 1% (1/100). One patient had a non-Q wave MI post-index procedure day 10. At both 270 and 360 days, the incidence of MACE was 2% (2/100 and 2/98, respectively). One patient had a target lesion revascularization 112 days post-index procedure. At 720 days post-procedure, the incidence of MACE was 3.1% (3/98). The cumulative incidence of MACE was 6.2% (6/97) at Day 1080 and 7.2% (7/97) at Day 1440. The Kaplan-Meier estimate of freedom from MACE at 1080 days was 93.9% [89.2%, 98.6%]. The cumulative incidence of TVF at 1440 days was 5.2% (5/97). The Kaplan-Meier estimate of freedom from TVF at 1440 days was 94.9%.

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Table 8-17 summarizes the principal effectiveness and safety results of the ENDEAVOR I Trial through 48 months.

Table 8-17: Principal Effectiveness and Safety Results for ENDEAVOR I through 48 months

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Lesion Success	100.0% (100/100)
Device Success	100.0% (100/100)
Procedure Success	100.0% (100/100)
Device-Specific Procedure Success	100.0% (100/100)
Post- Procedure Minimal Lumen Diameter (MLD, in mm)	
In-Stent	2.84±0.35 (100)
In-Segment	2.52±0.42(100)
Post-Procedure % Diameter Stenosis (%DS)	
In-Stent	5.37±7.51 (100)
In-Segment	16.54±8.40 (100)
4-Month Follow-Up MLD (mm)	
In-Stent	2.52±0.44 (98)
In-Segment	2.29±0.46 (98)
4-Month Follow-up %DS	
In-Stent	14.40±13.10 (98)
In-Segment	22.36±12.08 (98)
4-Month Late Loss (mm)	
In-Stent	0.32±0.37 (98)
In-Segment	0.22±0.43 (98)
4-Month Binary Restenosis	
In-Stent	2.0% (2/98)
In-Segment	3.1% (3/98)
4-Month Volume Obstruction (%)	4.46±6.05 (94)
4-Month Minimal Lumen Area (mm^2)	5.96±1.66 (95)
4-Month NIH Volume (mm^3)	6.10±7.39 (94)
12-Month Follow-Up MLD (mm)	
In-Stent	2.26±0.49 (92)
In-Segment	2.08±0.47 (92)
12-Month Follow-up %DS	

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Table 8-17: Principal Effectiveness and Safety Results for ENDEAVOR I through 48 months

Safety & Effectiveness Measures	Endeavor (N=100 patients)
In-Stent	21.75±15.35 (92)
In-Segment	28.00±13.41 (92)
12-Month Late Loss (mm)	
In-Stent	0.58±0.44 (92)
In-Segment	0.43±0.44 (92)
12-Month Binary Restenosis	
In-Stent	4.3% (4/92)
In-Segment	5.4% (5/92)
12-Month Volume Obstruction (%)	9.73±8.50 (86)
12-Month Minimal Lumen Area (mm^2)	5.69±1.74 (86)
12-Month NIH Volume (mm^3)	14.15±11.82 (86)
In-Hospital MACE	0.0% (0/100)
MACE to 30 Days	1.0% (1/100)
MACE to 270 Days	2.0% (2/100)
MACE to 360 Days	2.0% (2/98)
MACE to 720 Days	3.0% (3/99)
MACE to 1080 Days	6.1% (6/98)
MACE to 1440 Days	7.2% (7/97)
Death to 1440 Days	4.1% (4/97)
Vascular Complications to 1440 Days	3.1% (3/97)
Major Bleeding to 1440 Days	2.1% (2/97)
Early Stent Thrombosis	1.0% (1/97)
Late Stent Thrombosis to 270 days	0.0% (0/100)
Late Stent Thrombosis to 360 days	0.0% (0/98)
Late Stent Thrombosis to 720 days	0.0% (0/98)
Late Stent Thrombosis to 1080 days	0.0% (0/97)
Late Stent Thrombosis to 1440 days	0.0% (0/97)
Cerebrovascular Accident (CVA) to 1440 Days	1.0% (1/97)
Perforation to 1440 Days	0.0% (0/97)
Target Vessel Revascularization to 30 days	1.0% (1/100)
Target Vessel Revascularization to 270 days	2.0% (2/100)
Target Vessel Revascularization to 360 days	2.0% (2/98)
Target Vessel Revascularization to 720 days	4.0% (4/99)

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Table 8-17: Principal Effectiveness and Safety Results for ENDEAVOR I through 48 months

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Target Vessel Revascularization to 1080 days	5.1% (5/98)
Target Vessel Revascularization to 1440 days	5.2% (5/97)
Target Vessel Failure to 30 days	1.0% (1/100)
Target Vessel Failure to 270 days	2.0% (2/100)
Target Vessel Failure to 360 days	2.0% (2/99)
Target Vessel Failure to 720 days	4.0% (4/99)
Target Vessel Failure to 1080 days	5.1% (5/98)
Target Vessel Failure to 1440 days	5.2% (5/97)
Target Lesion Revascularization to 30 days	1.0% (1/100)
Target Lesion Revascularization to 270 days	2.0% (2/100)
Target Lesion Revascularization to 360 days	2.0% (2/99)
Target Lesion Revascularization to 720 days	2.0% (2/99)
Target Lesion Revascularization to 1080 days	3.1% (3/98)
Target Lesion Revascularization to 1440 days	3.1% (3/97)

Kaplan-Meier Estimate	Endeavor (N=100 patients)
*MACE-Free at 1440 days	92.9%
*TLR-Free at 1440 days	96.9%
*TVR-Free at 1440 days	94.9%
*TVF-Free at 1440 days	94.9%

N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
The primary endpoint was 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as:
100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.

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Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free – No Death, MI, emergent CABG or target lesion revascularization

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8.11.5 Gender Bias

The gender selection in this series of clinical trials was completely random, and solely based upon exclusion and inclusion criteria. In the ENDEAVOR IV study (conducted in the US), men represented 68.5% of the population. In the ENDEAVOR III study (conducted in the US), men represented 69.5% of the population. In the ENDEAVOR II study (conducted outside of the US), men represented 76.3% of the population. In the ENDEAVOR I feasibility trial (conducted outside of the US), men represented 79.0% of the population. The ratio of men to women in each of these trials is reflective of the underlying distribution of the disease for the given age groups, ethnic groups and stages of disease in these populations. No selection bias on the basis of gender was identified during the review. In addition, no differences in safety or effectiveness were found, with respect to gender.

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8.12 Conclusions Drawn from the Studies

The safety and effectiveness of the Endeavor Zotarolimus-Eluting Coronary Stent System is based on the results obtained from: biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing; and clinical studies. These test results revealed the following:

The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal testing that were conducted demonstrated that the acute and chronic *in vivo* performance characteristics of the product are safe and acceptable for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the zotarolimus/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 12 months.

The clinical testing conducted demonstrated that the product provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

8.13 Panel Recommendation

To be completed by FDA.

8.14 CDRH Decision

To be completed by FDA.

8.15 Approved Specifications

To be completed by FDA

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9.0 Labeling

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9.0 Labeling

The labeling for the Endeavor Zotarolimus-Eluting Coronary Stent System (CSS) consists of an Instructions for Use (IFU) and Patient Guide. Three separate IFUs will be available. There will be one IFU for the Endeavor Over-the-Wire (OTW), one for the Endeavor Rapid Exchange (RX), and one for the Endeavor Multi-Exchange II (MX2) Zotarolimus-Eluting Coronary Stent Systems. The Patient Guide is identical for the Endeavor Over-the-Wire (OTW), Endeavor Rapid Exchange (RX), and Endeavor Multi-Exchange II (MX^2) Zotarolimus-Eluting Coronary Stent Systems.

9.1 Instructions for Use

The IFU will be provided to medical providers in electronic or hard copy format. The IFU content will remain identical regardless of the medium used for distribution. The draft IFUs for each of the Endeavor systems are presented in the following attachments of this section:

- Endeavor Over-the-Wire (OTW) Attachment 9A
- Endeavor Rapid Exchange (RX) Attachment 9B
- Endeavor Multi-Exchange II (MX^2) Attachment 9C

9.2 Patient Guide

The Patient Guide will be available to medical providers in hard copy booklet format. The Patient Guide will not be packaged with the device in order to allow discussions of risks and benefits between physicians and patients prior to procedure. A draft Endeavor Patient Guide is presented in Attachment 9D of this section.

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ATTACHMENT 9A Draft Endeavor Over-the-Wire (OTW) Instructions For Use

Instructions for Use

ENDEAVOR® Zotarolimus-Eluting Coronary Stent System
Over-the-Wire Delivery System

Caution: Federal (USA) law restricts this product to sale by or on the order of a physician

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1.0 Endeavor Zotarolimus-Eluting Coronary Stent System

The **Endeavor** Zotarolimus-Eluting Coronary Stent System (**Endeavor** Coronary Stent System) is a device / drug combination product comprised of device components (Driver® Coronary Stent and Micro-Driver® Coronary Stent and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus contained in a polymer coating).

The characteristics of the **Endeavor** Coronary Stent System are described in **Table 1-1**.

Table 1–1: Device Component Description

Component	Endeavor Zotarolimus-Eluting Over-the-Wire (OTW) Delivery System	
Available Stent Diameters (mm):	2.5	3.0, 3.5
Available Stent Lengths (mm):	8† 12, 14, 18, 24, 30	9†, 12, 15, 18, 24, 30
Stent Material :	A cobalt based alloy (MP35N) – the Driver & Micro-Driver Stents	
Drug Component:	A spray coating of polymer carrier loaded with zotarolimus is applied to the stent at a drug loading of 10 µg/mm stent length. The maximum nominal drug content on the longest stent (30 mm) is 300 µg.	
Delivery System Usable Length:	135 cm	
Delivery System Luer Adapter Ports:	Y-Connector (Side arm for access to balloon inflation/ deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014” (0.36 mm).	
Stent Delivery Balloon:	A semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. There are proximal and distal pillows formed on either side of the stent which aid in holding the stent in position. Two radiopaque balloon markers are located on the distal section of the inner member and are positioned to mark the working length of the balloon.	
Balloon Inflation Pressure:	Nominal Pressure: 9 atm (912 kPa, 9.12 bar) Rated Burst Pressure: 16 atm (1621 kPa, 16.21 bar)	
Guide Catheter Compatibility:	0.056” minimum (5F)	
Distal Section OD:	Distal = 2.7F	
	Proximal = 3.0F	
Proximal OD:	3.3F	

† The 8 mm and 9 mm stent lengths are used for bailout procedures or insufficient lesion coverage.

1.1 Device Component Description

The device component consists of the **Driver** or **Micro-Driver** Balloon-Expandable Coronary Stent pre-mounted onto a stent delivery system (SDS). The range of stent diameters is made possible by varying the element lengths and number of crowns on the stent. The 2.5 mm diameter cobalt-based alloy stent (**Micro-Driver**) has 1.2 mm length elements and seven crowns; the 3.0 and 3.5 mm diameter cobalt-based stents (**Driver**) have 1.0 mm length elements and ten crowns. The stent is crimped on various size delivery catheter balloons, which are sized from 2.5 to 3.5 mm.

1.2 Drug Component Description

The drug component of the **Endeavor** Coronary Stent System consists of zotarolimus (the active ingredient) and Phosphorylcholine (PC) polymer (the inactive ingredient).

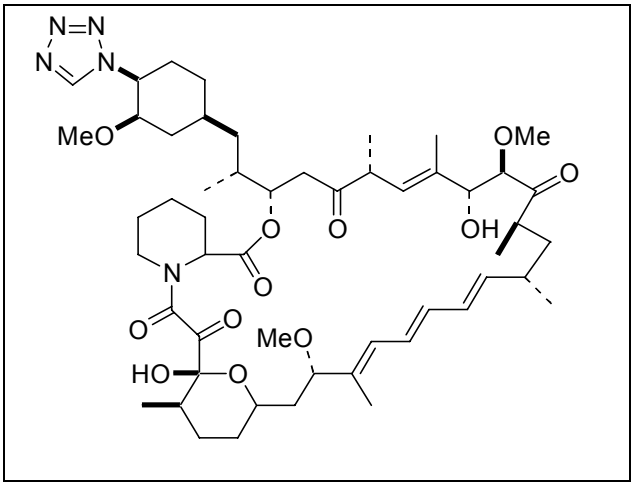
1.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the **Endeavor** Stent is zotarolimus. It is a tetrazole-containing macrocyclic immunosuppressant.

The chemical name of zotarolimus is: [3S-[3R*[S*(1R*,3S*,4R*)],6S*, 7E,9S*,10S*,12S*,14R*,15E,17E,19E, 21R* ,23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27, 32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown below:

Figure 1-1: Zotarolimus Chemical Structure



Zotarolimus has extremely low water solubility and is a lipophilic compound but is freely soluble in Propylene glycol, Acetone, Toluene, Acetonitrile, Ethanol, Benzyl alcohol and DMSO. The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

Zotarolimus does not have any ionizable group(s) in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

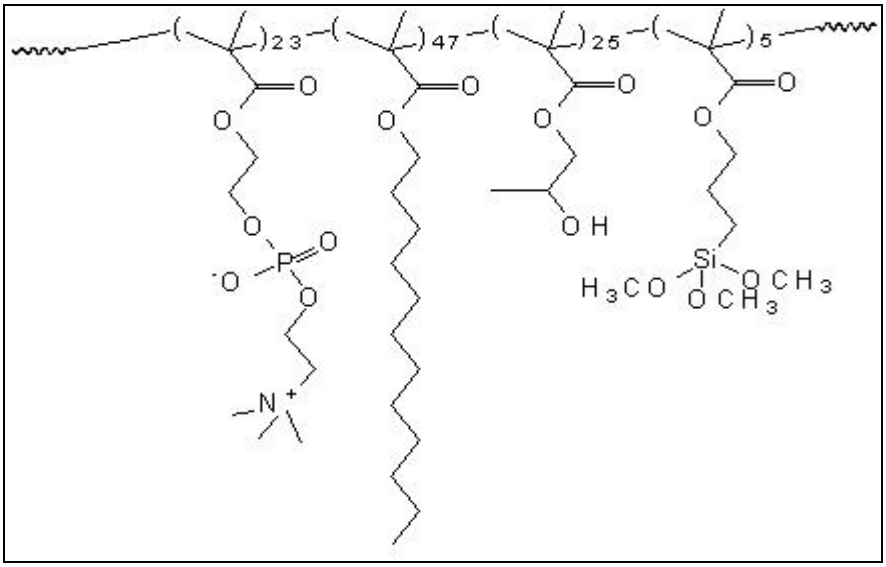
1.2.2 Polymer Component Description

The only inactive ingredient in the **Endeavor** Stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for zotarolimus. The PC polymer consists of 2-Methacryloyloxyethyl phosphorylcholine that is synthesized and then used in the preparation of crosslinked polymer membranes with lauryl methacrylate, hydroxypropyl methacrylate and trimethoxysilylpropyl methacrylate (crosslinker) co-monomers. The PC polymer contains a biocompatible component which mimics the body's own chemistry, a hydrophobic component for adhesion and stability, and a crosslinking component for robustness.

The molecular weight of PC polymer was estimated using viscometry and resulted in values of Mv ranging from 160,000 to 270,000. These figures were supported by light scattering values of Mw (g/mol) ranging from 100,000 to 200,000.

PC polymer in a solvent carrier (ethanol) is applied to the Driver Stent to form the base layer coat of the Endeavor stent. The polymer is also mixed with the drug zotarolimus and then applied to the base layer-coated stents. Finally, a drug-free overspray of PC polymer is applied after the stent has been coated with the drug/polymer formulation and it has been crimped onto the balloon. The drug/polymer coating is applied to the entire surface (i.e. luminal and abluminal) of the stent. The structural formula of the polymer is shown below:

Figure 1-2. PC Polymer Structure*



* PC Technology™ is licensed under patents or patent applications owned by Biocompatibles

1.2.3 Product Matrix and Zotarolimus Content

Table 1–2: Endeavor Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number OTW	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
EN25008W	2.50	8*	84
EN30009W	3.00	9	90
EN35009W	3.50	9	90
EN25012W	2.50	12	120
EN30012W	3.00	12	120
EN35012W	3.50	12	120
EN25014W	2.50	14*	144
EN30015W	3.00	15	150
EN35015W	3.50	15	150
EN25018W	2.50	18	180
EN30018W	3.00	18	180
EN35018W	3.50	18	180
EN25024W	2.50	24	240
EN30024W	3.00	24	240
EN35024W	3.50	24	240
EN25030W	2.50	30	300
EN30030W	3.00	30	300
EN35030W	3.50	30	300

* Note the 8 mm and 14 mm stent lengths have a total nominal drug content of 84 µg and 144 µg respectively since the actual stent length for the 8 mm stent is 8.4 mm and the actual stent length for the 14 mm stent is 14.4 mm

2.0 Indications

The **Endeavor** Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5mm to ≤ 3.5mm.

3.0 Contraindications

Use of the **Endeavor** Zotarolimus-Eluting Coronary Stent System is contraindicated for use in:

- Patients with a known hypersensitivity to zotarolimus or structurally-related compounds..
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Patients with a known hypersensitivity to phosphorylcholine polymer or its individual components (see details in **Section 1.2.2 – Polymer Component Description** for details).

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

4.0 Warnings

- Please ensure that the inner package has not been opened or damaged as this indicates the sterile barrier has been breached.
- The use of this product carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.

5.0 Precautions

5.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Risks and benefits of the stent should be assessed for patients with history of severe reaction to contrast agents.
- Do not expose or wipe the product with organic solvents such as alcohol or detergents.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In the ENDEAVOR I, ENDEAVOR II, and ENDEAVOR III studies, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 12 weeks post-procedure. In ENDEAVOR IV, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 6 months post-procedure in order to ensure proper blinding to the randomized comparator, the Taxus stent. Aspirin was administered pre-procedure and continued indefinitely. Based on empirical data from the Endeavor randomized clinical trials (ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV), approximately 82% of the patients remained on dual antiplatelet therapy at 6 months. See **Section 8, Clinical Studies,** for more specific information.
- It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a drug eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, recommendations of a surgical or dental procedure,and the risks and benefits of the

procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy.

5.3 Use of Multiple Stents

The long-term effects of zotarolimus are currently unknown. In clinical trials of the **Endeavor** Stent, patients were treated with no more than 48 mm of total **Endeavor** Stent, except in situations involving bailout stenting. The extent of the patient's exposure to the drug and polymer coating is directly related to the number of stents and stent length implanted.

When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. Data obtained from in vitro corrosion tests using F562 CoCr alloy stent (Medtronic **Driver** Coronary Stent) in combination with a 316L stainless steel alloy stent (Medtronic **S7** Coronary Stent) do not suggest an increased risk of in vivo corrosion. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.

Potential interactions of the **Endeavor** Stent with other drug-eluting or coated stents have not been evaluated.

5.4 Brachytherapy

The safety and effectiveness of the **Endeavor** Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of the use of brachytherapy to treat in-stent restenosis in an **Endeavor** Stent has not been established. Both vascular brachytherapy and the **Endeavor** Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with **Endeavor** Stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

- There are no adequate and well-controlled studies in pregnant women or men intending to father children.
- The **Endeavor** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

5.6.2 Lactation

It is not known whether zotarolimus is excreted in human milk. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

5.6.3 Gender

Clinical studies of the **Endeavor** Stent did not find any significant differences in safety and effectiveness for male and female patients.

5.6.4 Ethnicity

Clinical studies of the **Endeavor** Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity.

5.6.5 Pediatric Use

The safety and effectiveness of the **Endeavor** Stent in pediatric patients below the age of 18 years have not been established.

5.6.6 Geriatric Use

Clinical studies of the **Endeavor** Stent did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.7 Lesion/Vessel Characteristics

The safety and effectiveness of the **Endeavor** Stent have not yet been established in the following patient populations:

- Patients with unresolved vessel thrombus at the target lesion site
- Patients with reference vessel diameters <2.5 mm or >3.5 mm.
- Patients with lesions located in saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor flow distal to the identified lesions.
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.
- Patients for longer than 48 months of follow-up.
- Patients with severe calcification in the lesion.

5.8 Drug Interactions

While no specific clinical data are available, drugs, like sirolimus, that act through the same binding protein (FKBP) may interfere with the efficacy of zotarolimus. Zotarolimus is metabolized by CYP3A4, a human cytochrome P450 enzyme. Strong inhibitors of CYP3A4 (e.g., ketoconazole) might cause increased zotarolimus exposure to levels associated with systemic effects, especially if multiple stents are deployed. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

5.9 Magnetic Resonance Imaging (MRI)

Non-clinical testing on single and overlapped stents has demonstrated that the Endeavor Zotarolimus-eluting coronary stent is MR Conditional. It can be scanned safely under the following conditions:

Single Stenting (Stent Length 30mm)	Overlapped Stenting (Total Length 55mm)
Static magnetic field of 3 - Tesla	Static magnetic field of 3 - Tesla
Spatial gradient field of 525 Gauss/cm	Spatial gradient field of 720 Gauss/cm
Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of scanning	Maximum whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning
In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of MR scanning in a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.	In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.
The Endeavor stent should not move or migrate when exposed to MR scanning immediately post-implantation.	
The image artifact extends approximately 9 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR system with a send-receive RF body coil.	The image artifact extends approximately 10 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR system with a send-receive RF body coil.

5.10 Stent Handling Precautions

- For single use only. The **Endeavor** Coronary Stent System is provided sterile. Do not resterilize or reuse this product. Note the "Use By" date on the product label. (See Reuse Precaution Statement, Section 13.0). Do not use if package or product has been opened or damaged.
- The foil pouch is not a sterile barrier. The pouch contained within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is not sterile.**
- Do not remove the contents of foil pouch until immediately prior to the use of device.
- Do not remove the stent from the delivery balloon – removal may damage the stent and polymer coating and/or lead to stent embolization. The **Endeavor** Coronary Stent System is intended to perform as a system. The stent is not designed to be crimped onto another delivery device.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the rotating hemostatic valve and guiding catheter hub.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may cause coating damage, contamination or dislodgement of the stent from the delivery system balloon.
- The **Endeavor** Stent must not be exposed to any direct handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug elution.

- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.
- The **Endeavor** Coronary Stent Delivery System should not be used in conjunction with any other stents or for post-dilatation.
- In the event the **Endeavor** Stent is not deployed contact your local Medtronic, Inc. representative for return information.

5.11 Stent Placement Precautions

- The vessel should be pre-dilated with an appropriately sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 12.5 – Delivery Procedure**.
- Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in **Section 12.0 – Operator's Manual**.
- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Device Component Description** in **Table 1-1**).
- Do not induce negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- In smaller or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection.
- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel (see **Precautions – 5.12 Stent/System Removal Precautions**).
- Placement of the stent has the potential to compromise side branch patency.
- Do not attempt to pull an unexpanded stent back through the guiding catheter as dislodgement of the stent from the balloon may occur. Remove as a single unit per instructions in **Precautions – 5.12 Stent/System Removal Precautions**.
- Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure that the stent is in full contact with the arterial wall upon deflation of the balloon.
- Stent retrieval methods (e.g., use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.
- Administration of appropriate anticoagulant, antiplatelet and coronary vasodilator therapy is critical to successful stent implantation.

5.12 Stent/System Removal Precautions

If removal of a stent system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the stent delivery system, and cautiously withdraw the stent delivery system into the guide catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guide catheter, the stent delivery system and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.

When removing the stent delivery system and guiding catheter as a single unit:

- Do not retract the stent delivery system into the guiding catheter. Maintain guidewire placement across the lesion and carefully pull back the stent delivery system until the proximal balloon marker of the stent delivery system is aligned with the distal tip of the guiding catheter.

- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten, allowing safe withdrawal of the stent delivery system into the guiding catheter and the subsequent removal of the delivery system and the guiding catheter from the arterial sheath.

  Failure to follow these steps and/or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent and/or stent delivery system components such as the balloon.

5.13 Post-Procedure

- Care should be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Post-dilatation: All efforts should be made to assure that the stent is not under dilated. If the deployed stent is not fully apposed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2 mm) than the stent. The post-dilatation can be done using a low-profile, high pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. **Do not use the stent delivery balloon for post-dilatation.**
- Non-clinical testing on single and overlapped stents has demonstrated that the **Endeavor** Zotarolimus-eluting coronary stent is MR Conditional (see **Precautions – 5.9 Magnetic Resonance Imaging (MRI)**). MR imaging quality may be compromised if the area of interest is in the same area of the position of the stent.
- Antiplatelet therapy should be administered post-procedure (see **Precautions – 5.2 Pre- and Post-Procedure Antiplatelet Regimen**). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.

6.0 Drug Information

6.1 Mechanisms of Action

The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control.

6.2 Pharmacokinetics of the Endeavor Stent

The pharmacokinetics of zotarolimus delivered from the **Endeavor** Coronary Stent System have been determined in patients with coronary artery disease after stent implantation in the ENDEAVOR US Pharmacokinetic trial. The dose of zotarolimus was calculated from the total implanted stent length; the parameters determined from these patients are provided in **Table 6-1**.

Table 6-1: Zotarolimus Pharmacokinetics in Patients after Implantation of Endeavor-Zotarolimus Eluting Coronary Stents

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	1.584	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
$AUC_{0\text{-last}}$	(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
$AUC_{0\text{-inf}}$	(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
$t_{½}$‡	(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
Cmax Maximum blood concentration
Tmax Time to Cmax
$AUC_{0\text{-last}}$ Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration
$AUC_{0\text{-inf}}$ AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).
t½ Harmonic mean half-life
CL/F Mean apparent clearance

a. Primary dose groups
‡ Harmonic mean ± pseudo-standard deviation
† No SD was reported when N ≤ 2
§ Mean only
# N = 6

The results in **Table 6-1** show that pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 2), 180, 240 and 300 µg, following the implantation of **Endeavor** Zotarolimus-Eluting Stents as illustrated by dose proportional increases in C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$. Mean apparent clearance and harmonic mean half-life for the primary dose groups ranged from 2.8 to 3.5 L/h and 57.5 to 59.7 h, respectively. The mean time to reach peak systemic concentration (Tmax) ranged from 1.2 to 1.5 h after stent implantation.

6.3 Pharmacokinetics following Intravenous Administration of Zotarolimus

Zotarolimus pharmacokinetic activity has been determined following intravenous administration in healthy subjects. **Table 6-2** provides a summary of the pharmacokinetic analysis.

Table 6-2: Pharmacokinetic Parameters (Mean ± standard deviation) in Patients Following Intravenous Administration of Zotarolimus

PK Parameters	Units	**200µg QD** (N = 15)		**400µg QD** (N= 16)		**800µg QD** (N=16)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max}	(ng/mL)	11.41± 1.38¥	11.93 ± 1.25	21.99 ± 3.79	23.31± 3.15	37.72 ± 7.00	41.79 ± 6.68
T_{max}	(h)	1.05 ± 0.04¥	1.03 ± 0.04	1.00 ± 0.14	1.05 ± 0.04	1.03 ± 0.04	1.03 ± 0.05
$AUC_{0\text{-}24}$	(ng•h/mL)	34.19 ± 4.39¥	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
$t_{1/2}$$	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL[b]	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

¥ N = 16; $ Harmonic mean ± pseudo-standard deviation
[b] Clearance data is calculated using compartmental methods. All other data presented in Table 6-2 is calculated using non-compartmental methods.

When administered intravenously for 14 consecutive days, zotarolimus showed dose proportionality. Renal excretion is not a major route of elimination for zotarolimus as approximately 0.1% of the dose was excreted as unchanged drug in the urine per day. In multiple doses of 200, 400 and 800 µg, zotarolimus was generally well tolerated by the subjects. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study.

6.4 Metabolism

Zotarolimus undergoes oxidative metabolism in the liver to form the desmethyl and hydroxylated metabolites of the parent drug. Further metabolism can lead to the formation of hydroxyl-demethyl and dihydroxyl-demethyl metabolites. Enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities, however the IC_{50} values (3 µM and above) are many fold higher than the systemic concentrations expected following implantation of a drug-eluting stent. The anticipated zotarolimus blood levels in stented patients are expected to be less than 0.004 µM, suggesting that clinically significant drug-drug interactions are unlikely.

6.5 Mutagenesis, Carcinogenicity and Reproductive Toxicology

6.5.1 Mutagenesis

Zotarolimus was not genotoxic in a standard battery of tests.

6.5.2 Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of zotarolimus.

6.5.3 Reproductive Toxicology

No effect on fertility or early embryonic development in female rats following the administration of zotarolimus was observed at intravenous dosages up to 100 µg/kg/day (approximately 5 times the maximum blood level and about 11 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus). Administration at a dosage of 300 µg/kg/day (approximately 10 times the maximum blood level and about 28 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus) resulted in embryotoxicity and embryolethality.

For male rats, there was no effect on fertility rate at intravenous dosages up to 300 µg/kg/day (approximately 13 times the maximum blood level and about 50 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus) administered for 28 days prior to mating. No effects on testicular toxicity were observed as a result of chronic exposure when administered for approximately 70 days at dosages of 10 µg/kg/day (approximately 1.3 times the maximum blood level and about 10 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus). Testicular changes observed at higher doses were reversible after 10 weeks.

6.6 Pregnancy

There are no adequate and well-controlled studies in pregnant women with zotarolimus.

Administration of zotarolimus to pregnant female rats in a developmental toxicity study at an intravenous dosage of 60 µg/kg/day (approximately 4 times the maximum blood level and about 5 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus) resulted in embryolethality. Fetal ossification delays were also observed at this dosage, but no major fetal malformations or minor fetal anomalies were observed in this study.

No embryo-fetal effects were observed in pregnant rabbits administered zotarolimus in a developmental toxicity study at intravenous dosages up to 100 µg/kg/day (approximately 19 times the maximum blood level and about 22 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus).

6.7 Lactation

It is not known whether zotarolimus is excreted in human milk. The potential adverse reactions in nursing infants from zotarolimus have not been determined.

7.0 Adverse Events

7.1 Observed Adverse Events

The incidence of adverse events attributed to the drug zotarolimus was determined in intravenous escalating and multiple dose studies. In the single-escalating dose study the proportion of subjects reporting treatment-emergent adverse events was slightly lower among subjects who received doses of zotarolimus than those who received placebo for zotarolimus. The most common treatment-emergent adverse events associated with zotarolimus were injection site reaction, pain, and circumoral paresthesia. There were no serious adverse events reported in this study. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles. There were no apparent differences among the doses with regard to safety. **Table 7-1** provides a summary of the analysis.

Table 7-1: Summary of Treatment-Emergent Adverse Events reported by two or more subjects in any one treatment by Body Systems and COSTART Term in the single-escalating dose study.

BODY SYSTEMS	COSTART Term	All Placebo N=20(%)	Zotarolimus 100 µg N=8(%)	Zotarolimus 300µg N=8(%)	Zotarolimus 500µg N=8(%)	Zotarolimus 700µg N=8(%)	Zotarolimus 900µg N=8(%)
Body as a whole	Headache	3 (15%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
	Pain	7 (35%)	1 (13%)	0 (0%)	5 (63%)	5 (63%)	2 (25%)
Digestive System	Diarrhea	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nervous System	Circumoral Paresthesia	0 (0%)	0 (0%)	0 (0%)	3 (38%)	0 (0%)	0 (0%)
Skin and Appendage	Injection site Reaction	8 (40%)	1 (13%)	5 (63%)	2 (25%)	1 (13%)	5 (63%)

In the multiple dose study the proportion of subjects reporting treatment-emergent adverse events was similar among subjects who received doses of zotarolimus and the most common treatment-emergent adverse events associated with zotarolimus were headache, pain, injection site reaction, dry skin, abdominal pain, diarrhea and rash. There were no deaths or other serious adverse events. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for vital signs, laboratory safety assessments and physical examinations were unremarkable for each treatment group. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles or overall drug safety. **Table 7-2** provides a summary of the analysis.

Table 7-2: Summary of Treatment-Emergent Adverse Events reported by two or more subjects in any one treatment by Body Systems and COSTART Term in the multiple dose study.

BODY SYSTEM	COSTART Term	All Placebo (N = 16) N (%)	200 µg QD (N = 16) N (%)	400 µg QD (N = 16) N (%)	800 µg QD (N = 16) N (%)
Body as a whole	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)
Digestive System	Diarrhea	1 (4)	0 (0)	1 (6)	0 (0)
Skin and Appendage	Dry Skin	0 (0)	0 (0)	2 (13)	0 (0)
	Rash	0 (0)	1 (6)	1 (6)	0 (0)

Primary adverse event experience with the **Endeavor** Stent comes from four clinical studies, the ENDEAVOR IV, the ENDEAVOR III, the ENDEAVOR II and the ENDEAVOR I trial. See **Section 8 – Clinical Studies** for more complete description of the study design and results.

The ENDEAVOR IV, III, II and I trials have evaluated the performance of the **Endeavor** Stent in patients with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. Major study characteristics are summarized in **Table 8-1**. Principal adverse events are shown in **Table7-3**.

Table 7-3: Principal Adverse Events

Description of Event	ENDEAVOR IV to 270 days		Endeavor III to 720 days		Endeavor II to 1080 days		Endeavor I to 1440 days
	Endeavor (N=773 patients)	Control (N=775 patients)	Endeavor (N=323 patients)	Control (N=113 patients)	Endeavor (N=598 patients)	Control (N=599 patients)	Endeavor (N=100 patients)
In-Hospital							
MACE	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Myocardial Infarction (Q wave or Non-Q wave)	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
Q wave MI	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.3% (2/596)	0.0% (0/100)
Non-Q wave MI	0.5% (4/773)	1.9% (15/775)	0.6% (2/323)	3.5% (4/113)	2.3% (14/597)	2.3% (14/596)	0.0% (0/100)
Target Lesion Revascularization	0.4% (3/773)	0.5% (4/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
TL-CABG	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TL-PTCA	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Revascularization non Target Lesion	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-CABG	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-PTCA	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Target Vessel Revascularization	0.4% (3/773)	0.6%(5/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Failure	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Perforation	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Stent Thrombosis (acute)	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.3% (2/597)	0.3% (2/596)	0.0% (0/100)
Cerebrovascular Accident (CVA)	0.1% (1/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Out-of-Hospital							
MACE	4.7% (35/740)	3.0% (22/734)	8.6% (27/313)	8.9% (10/112)	9.5% (55/577)	18.7% (108/579)	7.2% (7/97)
Death	0.7% (5/740)	0.8% (6/734)	1.6% (5/313)	4.5% (5/112)	3.1% (18/577)	4.5% (26/579)	4.1% (4/97)
Myocardial Infarction (Q wave or Non-Q wave)	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.7% (4/577)	1.6% (9/579)	1.0% (1/97)
Q wave MI	0.0% (0/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.7% (4/579)	0.0% (0/97)
Non-Q wave MI	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.5% (3/577)	0.9% (5/579)	1.0% (1/97)
Target Lesion Revascularization	3.8% (28/740)	2.2% (16/734)	7.0% (22/313)	4.5% (5/112)	6.8% (39/577)	14.3% (83/579)	3.1% (3/97)
TL-CABG	0.4% (3/740)	0.4% (3/734)	1.3% (4/313)	0.0% (0/112)	0.5% (3/577)	1.0% (6/579)	1.0% (1/97)
TL-PTCA	3.5% (26/740)	1.8% (13/734)	5.8% (18/313)	4.5% (5/112)	6.4% (37/577)	13.5% (78/579)	3.1% (3/97)

Target Vessel Revascularization non Target Lesion	2.0% (15/740)	2.6% (19/734)	8.3% (26/313)	6.3% (7/112)	2.9% (17/577)	4.8% (28/579)	2.1% (2/97)
TV/non-TL-CABG	0.4% (3/740)	0.1% (1/734)	1.0% (3/313)	0.0% (0/112)	0.2% (1/577)	0.3% (2/579)	1.0% (1/97)
TV/non-TL-PTCA	1.8% (13/740)	2.5% (18/734)	7.7% (24/313)	6.3% (7/112)	2.8% (16/577)	4.7% (27/579)	1.0% (1/97)
Target Vessel Revascularization	5.1% (38/740)	4.4% (32/734)	13.7% (43/313)	9.8% (11/112)	9.0% (52/577)	17.4% (101/579)	5.2% (5/97)
Target Vessel Failure	5.8% (43/740)	4.8% (35/734)	13.7% (43/313)	10.7% (12/112)	10.4% (60/577)	19.2% (111/579)	5.2% (5/97)
Stent Thrombosis (sub-acute/<30 days)	0.1% (1/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.9% (5/579)	1.0% (1/97)
Stent Thrombosis (late /≥ 30 days)	0.4% (3/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.0% (0/577)	0.0% (0/579)	0.0% (0/97)
Cerebrovascular Accident (CVA)	0.5% (4/740)	0.5% (4/734)	0.6% (2/313)	0.9% (1/112)	1.0% (6/577)	1.2% (7/579)	1.0% (1/97)

N = The maximum number of eligible patients
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization.
ENDEAVOR IV: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR III: The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
ENDEAVOR II: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR I: The primary endpoint is 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months.

In the ENDEAVOR IV trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. In the ENDEAVOR III trial all enrolled patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluation at 8-months. In the ENDEAVOR II trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. Rates of incomplete stent apposition are shown in **Table 7-4** for ENDEAVOR II, ENDEAVOR III and ENDEAVOR IV trials.

Table 7-4: Rates of Incomplete Stent Apposition.

	ENDEAVOR II Trial		ENDEAVOR III Trial		ENDEAVOR IV Trial	
	Endeavor Stent (N=169)	Control Stent (N=159)	Endeavor Stent (N=323)	Control Stent (N=113)	Endeavor Stent (N=164)	Control Stent (N=164)
Incomplete Stent Apposition Rate at Post-Procedure	24.8% (36/145)	19.6% (28/143)	12.4% (31/251)	17.7% (17/96)	12.5% (17/136)	11.8% (15/127)
Incomplete Stent Apposition Rate at 8 Month Follow-up	16.8% (21/125)	14.5% (16/110)	7.5% (17/226)	17.1% (13/76)	10.0% (12/120)	14.7% (17/116)
Resolved	7.0% (8/114)	6.7% (7/104)	5.8% (11/189)	7.4% (5/68)	3.8% (4/106)	2.1% (2/95)
Persistent	17.5% (20/114)	14.4% (15/104)	7.9% (15/189)	11.8% (8/68)	8.5% (9/106)	10.5% (10/95)
Late Acquired	0% (0/114)	0% (0/104)	0.5% (1/189)	5.9% (4/68)	0.9% (1/106)	3.2% (3/95)

7.2 Potential Adverse Events

7.2.1 Potential Adverse Events Related to Zotarolimus

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.

The adverse events that have been associated with the intravenous injection of zotarolimus in humans include:

- Anemia
- Circumoral paresthesia
- Diarrhea
- Dry Skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

7.2.2 Potential Risks Associated with Percutaneous Coronary Diagnostic and Treatment Procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks may include, but are not limited to, the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias
- Balloon rupture
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Infection or fever
- Myocardial infarction (MI)
- Peripheral ischemia / peripheral nerve injury
- Restenosis of the stented artery
- Shock / pulmonary edema
- Stent deformation, collapse, or fracture
- Stent migration
- Stent misplacement
- Stroke / transient ischemic attack
- Thrombosis (acute and subacute)
- Unstable angina

8.0 Clinical Studies

8.1 Overview of Clinical Studies

The principle safety and efficacy information for the **Endeavor** Stent is presented from the following clinical studies – the ENDEAVOR I trial , the ENDEAVOR II trial, the ENDEAVOR III trial and the ENDEAVOR IV trial. The ENDEAVOR I, II, III and IV trials have evaluated the performance of the **Endeavor** Stent in patients with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. Major study characteristics are summarized in **Table 8-1**.

The ENDEAVOR IV trial was a prospective, multi-center, single blind, two arm randomized controlled trial that compared the Endeavor Stent to a control consisting of the Taxus Stent. Eligibility was based on the careful assessments of a lesion reference vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 6 months.

The ENDEAVOR III trial was a prospective, multi-center, single blind, two arm randomized controlled trial that compared the **Endeavor** Stent to a control consisting of the Cypher Stent. Eligibility was based on the careful assessments of a lesion reference vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR II trial was a prospective, multi-center, double-blind, two arm randomized controlled trial that compared the **Endeavor** Stent to a control consisting of the DRIVER bare metal stent (cobalt based alloy). Eligibility was based on careful assessments of lesion reference

vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR I trial was the First-in-man study for the **Endeavor** Stent. ENDEAVOR I is a non-randomized, prospective, multicenter, single arm trial that followed patients clinically and angiographically. The primary emphasis of the ENDEAVOR I trial was to assess the safety of the **Endeavor** Stent; the study also has significant value because it provides the longest available follow-up information on patients, currently four years.

Table 8-1: Clinical Trial Comparisons

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Study Type	Multi-center (n=8) Prospective Non-randomized	Multi-center (n=72) Prospective Randomized	Multi-center (n=29) Prospective Randomized	Multi-center (n=80) Prospective Randomized
Number of Patients	Total : 100 (**Endeavor** Stent)	Total : 1197 (**Endeavor** Stent: 598, Control: 599)	Total : 436 (3:1 randomization with control)	Total : 1548 (**Endeavor** Stent: 773, Taxus: 775)
Lesion Criteria	Single *de novo* lesion in native coronary artery ≤ 15mm in length and ≥3.0 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥2.25 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥2.5 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≤ 27 mm in length and ≥2.5 to ≤3.5mm in diameter
Product Used	**Endeavor** Stent on the Rapid Exchange Stent Delivery System	**Endeavor** Stent on the Rapid Exchange Stent Delivery System	**Endeavor** Stent on the Over-The -Wire Stent Delivery System	**Endeavor** Stent on the Over-The -Wire Stent Delivery System
Antiplatelet Therapy	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 6 months
Follow up	30 days : Clinical 4 & 12 months : Clinical and angiographic 9 month: Clinical 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic 9 month: Clinical 6 month, 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic 9 month: Clinical 6 month, 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic/ IVUS 9 month: Clinical 6 month, 1-5 years: Telephone
Status	48 month follow-up complete. Yearly follow up to 5 years is ongoing.	36 month follow-up is complete. Yearly follow up to 5 years is ongoing.	24 month follow-up is complete. Yearly follow up to 5 years is ongoing.	9 month follow-up is complete.

8.2 ENDEAVOR IV Trial

Purpose: To demonstrate the equivalence in safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Taxus Paclitaxel-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5-3.5 mm

Conclusion: Based on acute procedural results, 8-month angiographic, and 9-month clinical follow-up the Endeavor Zotarolimus-Eluting CSS has demonstrated similar safety and efficacy compared to the Taxus control stent.

Design: This was a prospective, multi-center, randomized, two-arm, single-blind trial that enrolled 1548 patients with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to treatment by percutaneous stenting.

Follow-up was performed at 30 days, 6, 8, and 9 months, and will be performed at 12 months, then annually thereafter out to 5 years. Angiography and IVUS evaluations were performed immediately post-procedure and at 8 months post-procedure for the first 328 consecutively enrolled patients (combined from all sites). In addition, patients at all sites receiving two or more stents at the target lesion will have/had angiographic and IVUS evaluations immediately post-procedure and at 8 months post-

procedure (known as the Multi-stent subset). Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 6 months.

Demographics: The analysis population of this report consisted of 1548 patients. Baseline demographics and clinical characteristics showed a mean age of 63.5 years for patients in the Endeavor arm and 63.6 years for patients in the Taxus arm. The Endeavor group had 66.9% (517/773) male enrollment and the Taxus group had 68.5% (531/775) male enrollment. In the Endeavor arm, 28.2% (218/773) of patients had prior percutaneous coronary revascularization compared to 29.5% (229/775) of subjects in the Taxus arm. In the Endeavor group, 31.2% (241/773) of patients had a history of diabetes mellitus compared to 30.5% (236/775) of patients in the Taxus group.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by study personnel at the clinical sites. Angiographic and IVUS outcomes were assessed at designated core laboratories. Clinical events were adjudicated by an independent Clinical Events committee and the trial was monitored by an independent Data Monitoring Committee.

Results: The effectiveness and safety results for Endeavor and Taxus are presented in Table 8-3.

The incidence of the primary endpoint of TVF at 270 days for Endeavor was 6.8% (50/740) and for Taxus it was 7.4% (54/734) (p=0.685). The incidence of TLR at 270 days post-index procedure for the Endeavor arm was 4.2% (31/740); for Taxus it was 2.7% (20/734) (p=0.154).

At 270 days, the cumulative incidence of MACE for the Endeavor patients was 5.7% (42/740) compared to the Taxus patients which was 5.7% (42/734). The Kaplan-Meier estimate of freedom from MACE at 270 days for Endeavor patients was 94.4%; for Taxus patients it was 94.5%.

In Table 8-2 the outcome of the primary endpoint from the ENDEAVOR IV trial is summarized.

Table 8-2: Primary endpoint from ENDEAVOR IV

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value*
ENDEAVOR IV	Target Vessel Failure at 9 months post-procedure	Endeavor	6.8% (50/740)	0.0005
		Taxus	7.4% (54/734)	

* P-value is for the test of Non-Inferiority.

Table 8-3 summarizes the principal effectiveness and safety results of the ENDEAVOR IV trial through 270 days. Figure 8-1 provides the cumulative percent of patients who are TVF-free through 270 days.

Table 8-3: Principal Effectiveness and Safety - ITT population

Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Lesion Success	99.6% (767/770)	99.2% (766/772)	0.4%[-0.4%, 1.1%]	0.507
Device Success	97.3% (751/772)	97.9% (757/773)	-0.7%[-2.2%, 0.9%]	0.412
Procedure Success	98.7% (760/770)	96.8% (747/772)	1.9% [0.5%, 3.4%]	0.015
Device-Specific Procedure Success	96.5% (745/772)	95.6% (739/773)	0.9% [-1.0%, 2.8%]	0.433
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.62±0.43 (763)	2.61±0.44 (763)	0.01 [-0.04, 0.05]	0.703
In-Segment	2.22±0.47 (770)	2.19±0.50 (772)	0.03 [-0.02, 0.08]	0.196
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	5.50±9.61 (763)	5.01±10.49 (763)	0.48 [-0.53, 1.49]	0.348
In-Segment	20.47±9.54 (770)	20.97±11.12 (772)	-0.50 [-1.53, 0.54]	0.344
Eight-Month Follow-Up MLD (mm)				
In-Stent	1.95±0.61 (143)	2.25±0.61 (135)	-0.30 [-0.45, -0.16]	<0.001
In-Segment	1.80±0.55 (144)	1.98±0.56 (135)	-0.18 [-0.31, -0.05]	0.008
Eight-Month Follow-up %DS				
In-Stent	26.41±19.74 (143)	16.09±17.99 (135)	10.32 [5.85, 14.79]	<0.001
In-Segment	32.28±17.02 (144)	26.61±15.52 (135)	5.68 [1.83, 9.52]	0.004
Eight-Month Late Loss (mm)				
In-Stent	0.67±0.49 (142)	0.42±0.50 (135)	0.25 [0.13, 0.37]	<0.001
In-Segment	0.36±0.47 (143)	0.23±0.45 (135)	0.13 [0.02, 0.23]	0.023
Eight-Month Binary Restenosis				
In-Stent	13.3% (19/143)	6.7% (9/135)	6.6% [-0.4%, 13.6%]	0.075
In-Segment	15.3% (22/144)	10.4% (14/135)	4.9% [-2.9%, 12.7%]	0.284
Eight-Month Volume Obstruction (%)	15.72±10.40 (74)	9.88±9.24 (77)	5.84 [2.68, 9.00]	<0.001
Eight-Month Minimal Lumen Area (mm2)	4.62±1.82 (113)	5.50±2.14 (109)	-0.87 [-1.39, -0.35]	0.001
Eight-Month NIH Volume (mm3)	24.14±19.38 (74)	14.88±16.62 (77)	9.26 [3.46, 15.06]	0.002
In-Hospital MACE	0.9% (7/773)	2.6% (20/775)	-1.7% [-3.0%, -0.4%]	0.018
MACE to 30 Days	1.2% (9/770)	3.0% (23/771)	-1.8% [-3.2%, -0.4%]	0.019
MACE to 270 Days	5.7% (42/740)	5.7% (42/734)	-0.0% [-2.4%, 2.3%]	1.000
Death to 270 Days	0.7% (5/740)	0.8% (6/734)	-0.1% [-1.0%, 0.7%]	0.773
Vascular Complications to 270 Days	0.5% (4/740)	0.8% (6/734)	-0.3% [-1.1%, 0.6%]	0.546

Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Bleeding complications to 270 Days	1.6% (12/740)	2.9% (21/734)	-1.2% [-2.8%, 0.3%]	0.116
Early Stent Thrombosis to 30 Days	0.4% (3/770)	0.1% (1/771)	0.3% [-0.2%, 0.8%]	0.374
Late Stent Thrombosis to 270 days	0.4% (3/740)	0.0% (0/734)	0.4% [-0.1%, 0.9%]	0.250
Cerebrovascular Accident (CVA) to 270 Days	0.7% (5/740)	0.5% (4/734)	0.1% [-0.7%, 0.9%]	1.000
Perforation to 270 Days	0.1% (1/740)	0.4% (3/734)	-0.3% [-0.8%, 0.3%]	0.372
Target Vessel Revascularization to 30 days	0.4% (3/770)	0.9% (7/771)	-0.5% [-1.3%, 0.3%]	0.342
Target Vessel Revascularization to 270 days	5.5% (41/740)	5.0% (37/734)	0.5% [-1.8%, 2.8%]	0.727
Target Vessel Failure to 30 days	1.0% (8/770)	3.0% (23/771)	-1.9% [-3.3%, -0.5%]	0.010
Target Vessel Failure to 270 days	6.8% (50/740)	7.4% (54/734)	-0.6% [-3.2%, 2.0%]	0.685
Target Lesion Revascularization to 30 days	0.4% (3/770)	0.8% (6/771)	-0.4% [-1.1%, 0.4%]	0.507
Target Lesion Revascularization to 270 days	4.2% (31/740)	2.7% (20/734)	1.5% [-0.4%, 3.3%]	0.154

Kaplan-Meier Estimate	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	P-value†
*MACE-Free at 270 days	94.4%	94.5%	0.952
*TLR-Free at 270 days	95.8%	97.3%	0.127
*TVR-Free at 270 days	94.4%	95.0%	0.682
*TVF-Free at 270 days	93.3%	92.8%	0.626

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – TAXUS.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.

CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.

Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed

Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.

The following survival estimates are by Kaplan-Meier Methods:

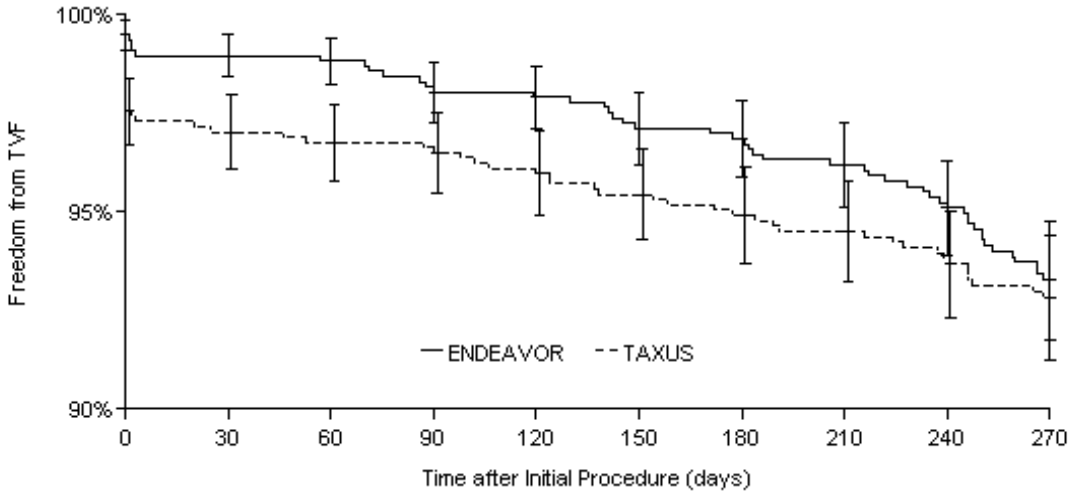
*TLR free - No target lesion revascularization

*TVR free – No target vessel revascularization

*TVF free – No cardiac death, MI or target vessel revascularization.

*MACE free– No Death, MI, emergent CABG or target lesion revascularization

Figure 8-1. Survival Free from Target Vessel Failure (at 270 days)



TVF	0	7	14	21	30	60	90	120	150	180	210	240	270
ENDEAVOR													
# Entered	773	769	760	760	760	756	750	744	743	736	728	718	703
# Censored	0	5	0	0	4	5	0	0	1	6	5	7	118
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	4	4	0	0	0	1	6	1	6	2	5	8	13
% Survived	99.5%	99.0%	99.0%	99.0%	99.0%	98.8%	98.0%	97.9%	97.1%	96.9%	96.2%	95.1%	93.3%
SE	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.6%	0.6%	0.7%	0.8%	1.0%
TAXUS													
# Entered	775	755	748	748	747	744	735	732	726	720	710	694	683
# Censored	1	5	0	0	2	7	1	2	2	6	13	5	105
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	19	2	0	1	1	2	2	4	4	4	3	6	6
% Survived	97.5%	97.3%	97.3%	97.2%	97.0%	96.8%	96.5%	96.0%	95.4%	94.9%	94.5%	93.7%	92.8%
SE	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.7%	0.7%	0.8%	0.8%	0.8%	0.9%	1.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Log-Rank	0.24	1	0.626									
	Wilcoxon	0.43	1	0.511									

8.3 ENDEAVOR III Trial

Purpose: The purpose of the ENDEAVOR III trial was to demonstrate the non-inferiority in in-segment late lumen loss at 8 months between the **Endeavor** Zotarolimus-Eluting Coronary Stent System and the Cypher Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter.

Conclusion: As demonstrated in this clinical trial, the **Endeavor** Stent was shown to have higher device success rate, a favorable safety profile (lower peri-procedural myocardial infarctions and no stent thrombosis) and comparable clinical efficacy (target lesion revascularization), despite higher restenosis and angiographic late loss. The criterion for non-inferiority of the **Endeavor** Stent to Cypher Stent was not met with regards to the 8-month in-segment late lumen loss.
Design: This was a prospective, multi-center, single-blind, parallel, two-arm, randomized, controlled trial which enrolled 436 patients. Twenty-nine (29) study sites in the United States (US) enrolled subjects in this trial. The primary endpoint for this trial was in-segment late lumen loss at 8 months post-procedure. To be eligible, patients were required to have symptomatic ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters ≥2.5 mm and ≤3.5 mm and lesion lengths of ≥14 mm and ≤27 mm that were amenable to percutaneous treatment with stenting.

Patients were randomized in a single-blind fashion (3:1 randomization) to one of two treatments: the **Endeavor** Stent or the Cypher Stent. A total of 436 patients were enrolled in the clinical trial – 323 patients were randomized to the **Endeavor** Stent and 113 were randomized to the Cypher Stent. All patients were pre-specified to receive angiographic and IVUS follow-up at 8 months. Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

Clinical follow-up through the 9 month is available on 434 patients. Angiographic follow-up was completed on 371 patients at eight months. Clinical follow-up is available through through 24 months on 425 patients.
Demographics:
Patients were well matched for baseline demographics with no statistically significant differences between treatment arms, except for gender. The **Endeavor** arm had 65.3% (211/323) male enrollment and Cypher had 81.4% (92/113) male enrollment. Of the 436 enrolled patients, baseline demographics and clinical characteristics showed a mean age of 61.4 in the **Endeavor** arm and 61.7 years in the Cypher arm. In the **Endeavor** arm, 22.6% (73/323) had prior percutaneous coronary revascularization compared to 16.8% (19/113) in Cypher arm. In the **Endeavor** Stent arm, 29.7% (96/323) of patients had a history of diabetes mellitus compared to 28.3% (32/113) of patients in the Cypher arm.

Methods:
Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent angiographic core lab assessed angiographic outcomes, and an independent intravascular ultrasound core laboratory assessed IVUS outcomes. An independent Clinical Events Committee adjudicated clinical events and an independent Data Monitoring Committee monitored the trial.

Results:
In selected patients, elective **Endeavor** Stent placement in native coronary artery *de novo* lesions resulted in similar incidence of TVF at 720 days 14.4% for the **Endeavor** Stent group and 13.4% for the Cypher Stent group. Overall Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) were 9.3% in the **Endeavor** Stent group at 720 days compared to 11.6%, in the Cypher Stent group (p = 0.465). At 720 days, the rate of stent thrombosis was 0.0% in both arms.

As summarized in **Table 8-4** the mean and standard deviation for the primary endpoint of In-Segment Late Lumen Loss at 8 months for **Endeavor** Stent arm was 0.36±0.46 (mm) and for Cypher it was 0.13± 0.33 (mm), (p < 0.001). The mean and standard deviation for the secondary endpoint of in-stent Late Lumen Loss at 8 months for **Endeavor** Stent was 0.62±0.49 (mm) and for Cypher it was 0.15± 0.34 (mm), (p < 0.001).

Table 8-4: Primary endpoint from Endeavor III trial

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
Endeavor III	In-segment Late Lumen Loss at 8 months post-procedure (mm)	Endeavor	0.36 ± 0.46	0.791*
		Cypher	0.13 ± 0.33	

* P-value is for the test of Non-Inferiority.

Table 8-5 summarizes the principal safety and effectiveness results of the ENDEAVOR III Trial through 720 days. **Figure 8-2** provides of the cumulative percent of patients who are TVF-Free through 720 days.

Table 8-5: Principal Effectiveness and Safety Results - ITT Population

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Lesion Success	100.0% (323/323)	99.1% (112/113)	0.9% [-0.8%,2.6%]	0.259
Device Success	98.8% (319/323)	94.7% (107/113)	4.1% [-0.2%,8.4%]	0.022
Procedure Success	99.4% (321/323)	95.6% (108/113)	3.8% [-0.1%,7.7%]	0.014
Device-Specific Procedure Success	98.1% (317/323)	91.2% (103/113)	7.0% [1.6%,12.4%]	0.002
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.67±0.42 (323)	2.67±0.40 (112)	0.00 [-0.09,0.09]	0.993
In-Segment	2.27±0.45 (323)	2.28±0.47 (113)	-0.01 [-0.11,0.09]	0.836
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	4.33±9.77 (323)	5.92±9.07 (112)	-1.59 [-3.66,0.48]	0.132
In-Segment	19.38±9.25 (323)	20.17±11.74 (113)	-0.78 [-2.92,1.36]	0.522
Eight-Month Follow-Up MLD (mm)				
In-Stent	2.06±0.57 (277)	2.52±0.56 (94)	-0.46 [-0.60,-0.33]	<0.001
In-Segment	1.91±0.53 (277)	2.16±0.50 (94)	-0.25 [-0.37,-0.13]	<0.001
Eight-Month Follow-up %DS				
In-Stent	24.90±17.45 (277)	11.01±15.91 (94)	13.89 [9.88,17.90]	<0.001
In-Segment	30.42±15.57 (277)	23.86±13.87 (94)	6.56 [3.01,10.12]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.49 (277)	0.15±0.34 (94)	0.47 [0.36,0.58]	<0.001
In-Segment	0.36±0.46 (277)	0.13±0.33 (94)	0.24 [0.13,0.34]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.7% (27/277)	2.1% (2/94)	7.6% [3.1%,12.2%]	0.014
In-Segment	12.3% (34/277)	4.3% (4/94)	8.0% [2.4%,13.6%]	0.029
Eight-Month Volume Obstruction (%)	15.94±10.94 (187)	2.66±3.11 (61)	13.27 [10.48,16.07]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.89±1.96 (209)	5.77±1.97 (66)	-0.88 [-1.43,-0.34]	0.002
Eight-Month NIH Volume (mm^3)	24.09±21.16 (209)	3.74±5.20 (67)	20.36 [15.21,25.50]	<0.001
In-Hospital MACE	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 30 Days	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 270 Days	7.5% (24/321)	7.1% (8/113)	0.4% [-5.1%,5.9%]	1.000
MACE to 360 Days	7.8% (25/320)	8.0% (9/112)	-0.2% [-6.1%,5.6%]	1.000
MACE to 720 Days	9.3% (29/313)	11.6% (13/112)	-2.3% [-9.1%,4.4%]	0.465
Death to 720 Days	1.6% (5/313)	4.5% (5/112)	-2.9% [-6.9%,1.2%]	0.138
Vascular Complications to 720 Days	1.9% (6/313)	5.4% (6/112)	-3.4% [-7.9%,1.0%]	0.090
Major Bleeding to 720 Days	2.2% (7/313)	6.3% (7/112)	-4.0% [-8.8%,0.8%]	0.060
Early Stent Thrombosis to 30 Days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Late Stent Thrombosis to 270 days	0.0% (0/321)	0.0% (0/113)	0.0% [--,--]	--

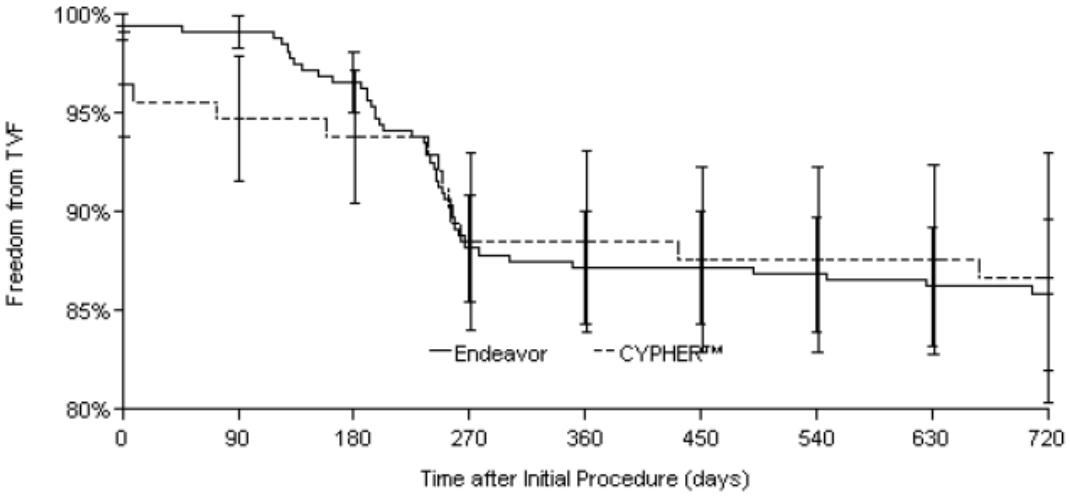
Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Late Stent Thrombosis to 360 days	0.0% (0/320)	0.0% (0/112)	0.0% [--,--]	--
Late Stent Thrombosis to 720 days	0.0% (0/313)	0.0% (0/112)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 720 Days	0.6% (2/313)	0.9% (1/112)	-0.3% [-2.2%,1.7%]	1.000
Perforation to 720 Days	0.0% (0/313)	0.9% (1/112)	-0.9% [-2.6%,0.8%]	0.264
Target Vessel Revascularization to 30 days	0.0% (0/323)	0.9% (1/113)	-0.9% [-2.6%,0.8%]	0.259
Target Vessel Revascularization to 270 days	11.2% (36/321)	8.0% (9/113)	3.3% [-2.8%,9.3%]	0.375
Target Vessel Revascularization to 360 days	12.2% (39/320)	8.0% (9/112)	4.2% [-2.0%,10.3%]	0.295
Target Vessel Revascularization to 720 days	13.7% (43/313)	9.8% (11/112)	3.9% [-2.8%,10.6%]	0.325
Target Vessel Failure to 30 days	0.6% (2/323)	4.4% (5/113)	-3.8% [-7.7%,0.1%]	0.014
Target Vessel Failure to 270 days	11.8% (38/321)	11.5% (13/113)	0.3% [-6.5%,7.2%]	1.000
Target Vessel Failure to 360 days	12.8% (41/320)	11.6% (13/112)	1.2% [-5.8%,8.2%]	0.868
Target Vessel Failure to 720 days	14.4% (45/313)	13.4% (15/112)	1.0% [-6.4%,8.4%]	0.875
Target Lesion Revascularization to 30 days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Target Lesion Revascularization to 270 days	6.2% (20/321)	3.5% (4/113)	2.7% [-1.6%,7.0%]	0.346
Target Lesion Revascularization to 360 days	6.6% (21/320)	3.6% (4/112)	3.0% [-1.4%,7.4%]	0.347
Target Lesion Revascularization to 720 days	7.0% (22/313)	4.5% (5/112)	2.6% [-2.2%,7.3%]	0.498

Kaplan-Meier Estimate	ENDEAVOR III (N= 323 Patients)	CYPHER™ (N= 113 Patients)	P-value†
*MACE-Free at 720 days	90.9%	88.5%	0.464
*TLR-Free at 720 days	93.0%	95.5%	0.336
*TVR-Free at 720 days	86.4%	90.2%	0.304
*TVF-Free at 720 days	85.8%	86.7%	0.867

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – CYPHER.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).

Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free – No Death, MI, emergent CABG or target lesion revascularization.

Figure 8-2. Survival Free from Target Vessel Failure (at 720 days)



TVF	0	90	180	270	360	450	540	630	720
Endeavor									
# Entered	323	321	318	310	281	274	268	264	262
# Censored	0	2	0	2	4	6	3	0	102
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	2	1	8	27	3	0	1	2	1
% Survived	99.4%	99.1%	96.6%	88.1%	87.2%	87.2%	86.9%	86.2%	85.8%
SE	0.4%	0.5%	1.0%	1.8%	1.9%	1.9%	1.9%	2.0%	2.6%
CYPHER™									
# Entered	113	109	107	106	100	98	97	97	95
# Censored	0	0	0	0	2	0	0	2	38
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	4	2	1	6	0	1	0	0	1
% Survived	96.5%	94.7%	93.8%	88.5%	88.5%	87.6%	87.6%	87.6%	86.7%
SE	1.7%	2.1%	2.3%	3.0%	3.0%	3.1%	3.1%	3.2%	4.2%
Tests Between Groups									
	Test	Chi-Square	Deg Frdm	P-value					
	Wilcoxon	0.01	1	0.906					
	Log-Rank	0.03	1	0.867					

8.4 ENDEAVOR II Trial

Purpose: The purpose of the ENDEAVOR II trial was to demonstrate the safety and efficacy of the **Endeavor** Stent with 10 µg/mm zotarolimus compared to the DRIVER Stent for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter.

Conclusion: Based on acute procedural results, 8-month angiographic, 9, 12, 24 and 36 month follow-up the **Endeavor** Stent has demonstrated similar safety and superior efficacy compared with the DRIVER Control Stent.

Design: This was a prospective, multi-center, double-blind, two-arm randomized controlled trial to evaluate the safety and efficacy of the **Endeavor** Stent in subjects with *de novo* lesions of the native coronary arteries. Seventy-two (72) study sites in Asia, Australia, Europe, Israel and New Zealand enrolled subjects into this trial. The primary endpoint for this trial was the target vessel

failure (TVF) rate, defined as a composite of target vessel revascularization (TVR), recurrent Q or non-Q wave myocardial infarction (MI), or cardiac death that could not be clearly attributed to a vessel other than the target vessel at 270 days post index procedure. To be eligible, patients were required to have symptomatic ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters ≥2.25 mm and ≤3.5 mm and lesion lengths of ≥14 mm and ≤27 mm that were amenable to percutaneous treatment with stenting.

Patients were randomized in a double-blind fashion (1:1 randomization) to one of two treatments: **Endeavor** Stent or Uncoated DRIVER Coronary Stent System (DRIVER). A total of 1,197 patients were enrolled in the clinical trial – 598 patients were randomized to the **Endeavor** Stent and 599 were randomized to the control. A total of 600 patients were pre-specified to receive angiographic follow-up at 8 months. Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 12 weeks.

Clinical follow-up through the 1080 days follow-up period is available on 1,156 patients. Angiographic follow-up was completed on 529 patients at eight months. Clinical follow-up is available through 1080 days.

Demographics: Patients were well matched for baseline demographics with no statistically significant differences between treatment arms. Factors evaluated included age (mean 62 years), gender (24% female), diabetes (20%), prior MI (41%), hypertension requiring treatment (66%), hyperlipidemia requiring treatment (79%), ejection fraction (mean 61%), CSS Angina Class (54% Class III or IV), IIb/IIIa inhibitor use (12%), LAD (45%), LCX (22%), RCA (33%), reference vessel diameter (mean 2.75 mm), minimum lumen diameter (mean 0.83 mm), percent diameter stenosis (70%), and lesion length (mean 14.2 mm).

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent angiographic core lab assessed angiographic outcomes in a blinded fashion, and an independent intravascular ultrasound core laboratory assessed IVUS outcomes in a blinded fashion. An independent Clinical Events Committee adjudicated clinical events and an independent Data Monitoring Committee monitored the trial.

Results: In selected patients, elective **Endeavor** Stent placement in native coronary artery *de novo* lesions resulted in reduction of the incidence of TVF at 1080 days compared to Control (12.8% vs. 21.4%, $p < 0.001$). **Table 8-6** summarizes the results of the primary endpoint of target vessel failure (TVF) at 270 days post index procedure. Overall Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) were reduced in the **Endeavor** Stent group at 1080 days compared to control (12.0% vs. 20.7%, $p < 0.001$). The rate of early stent thrombosis was lower in the **Endeavor** Stent arm when compared to the control (0.5% vs. 1.2%, $p = 0.342$).

Table 8-6: Primary endpoint from Endeavor II trial

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
Endeavor II	Target Vessel Failure at 9 months post-procedure	Endeavor Driver	7.9% (47/592) 15.1% (89/591)	< 0.001

By follow-up angiography at 8-months, there was significantly lower in-stent late loss (0.62 vs. 1.03, $p < 0.001$) and in-segment late loss (0.36 vs. 0.72, $p < 0.001$) in Endeavor stent as compared to the Driver stent. Mean in-stent percent diameter stenosis was significantly reduced (27.9% vs. 42.2%, $p < 0.001$). Additionally, in-stent and in-segment binary angiographic restenosis were significantly reduced (9.5% vs. 33.2%, $p < 0.001$ and 13.3% vs. 34.7%, p <

0.001). There was no significant increase in proximal or distal edge late loss or BAR for the **Endeavor** Stent arm.

Examination by IVUS at 8 months showed that neointimal hyperplasia (NIH) volume was significantly reduced in the **Endeavor** Stent arm (30.2 mm^3 vs. 53.5 mm^3, $p < 0.001$). There was no evidence of late stent incomplete apposition in either treatment arm at 8 months.

Table 8-7 summarizes the principal effectiveness and safety results of the ENDEAVOR II Trial through 1080 days. **Figure 8-3** provides of the cumulative percent of patients who are TVF-Free through 1080 days.

Table 8-7: Principal Effectiveness and Safety Results (to 1080 Days)

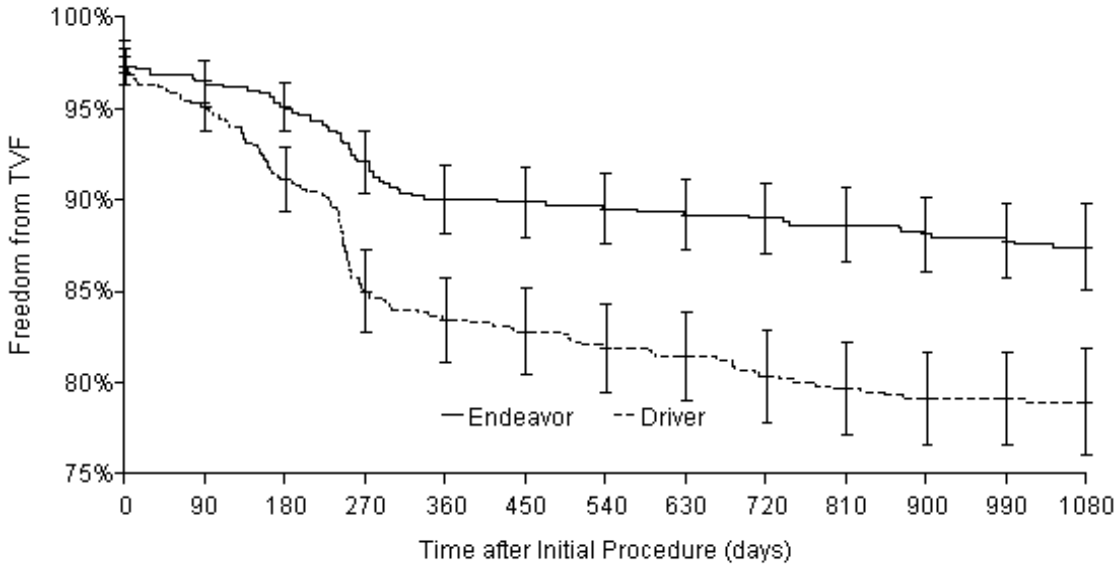
Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
Lesion Success	99.7% (587/589)	100.0% (590/590)	-0.3% [-0.8%,0.1%]	0.249
Device Success	98.8% (585/592)	99.2% (586/591)	-0.3% [-1.5%,0.8%]	0.773
Procedure Success	97.3% (573/589)	97.1% (573/590)	0.2% [-1.7%,2.0%]	1.000
Device-Specific Procedure Success	96.5% (571/592)	96.4% (570/591)	0.0% [-2.1%,2.1%]	1.000
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.59±0.43 (588)	2.61±0.44 (589)	-0.02 [-0.07,0.03]	0.436
In-Segment	2.21±0.49 (589)	2.24±0.49 (590)	-0.03 [-0.09,0.03]	0.302
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	6.04±10.43 (588)	6.23±10.03 (589)	-0.18 [-1.36,0.99]	0.757
In-Segment	20.39±10.26 (589)	20.11±9.38 (590)	0.28 [-0.84,1.41]	0.622
Eight-Month Follow-Up MLD (mm)				
In-Stent	1.99±0.56 (264)	1.62±0.70 (265)	0.37 [0.26,0.48]	<0.001
In-Segment	1.86±0.55 (264)	1.56±0.67 (265)	0.30 [0.19,0.40]	<0.001
Eight-Month Follow-up %DS				
In-Stent	27.91±17.30 (264)	42.24±21.73 (265)	-14.33 [-17.68,-10.97]	<0.001
In-Segment	32.67±16.27 (264)	44.33±20.45 (265)	-11.66 [-14.82,-8.50]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.46 (264)	1.03±0.59 (263)	-0.41 [-0.50,-0.32]	<0.001
In-Segment	0.36±0.46 (264)	0.72±0.61 (263)	-0.36 [-0.45,-0.27]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.5% (25/264)	33.2% (88/265)	-23.7% [-30.4%,-17.1%]	<0.001
In-Segment	13.3% (35/264)	34.7% (92/265)	-21.5% [-28.5%,-14.4%]	<0.001
Eight-Month Volume Obstruction (%)	17.34±10.27 (90)	29.55±17.58 (81)	-12.22 [-16.51,-7.92]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.99±1.66 (122)	3.98±1.72 (107)	1.01 [0.57,1.45]	<0.001
Eight-Month NIH Volume (mm^3)	30.15±21.66 (90)	53.51±39.80 (81)	-23.36 [-32.91,-13.81]	<0.001
In-Hospital MACE	2.5% (15/597)	2.9% (17/596)	-0.3% [-2.2%,1.5%]	0.725
MACE to 30 Days	2.9% (17/596)	3.7% (22/594)	-0.9% [-2.9%,1.2%]	0.421
MACE to 270 Days	7.3% (43/592)	14.4% (85/591)	-7.1% [-10.6%,-3.6%]	<0.001
MACE to 360 Days	8.8% (52/590)	15.6% (92/589)	-6.8% [-10.5%,-3.1%]	<0.001

Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
MACE to 720 Days	9.9% (58/587)	18.1% (106/586)	-8.2% [-12.2%,-4.3%]	<0.001
MACE to 1080 Days	12.0% (69/577)	20.7% (120/579)	-8.8% [-13.0%,-4.5%]	<0.001
Death to 1080 Days	3.3% (19/577)	4.5% (26/579)	-1.2% [-3.4%,1.0%]	0.362
Vascular Complications to 1080 Days	0.5% (3/577)	1.2% (7/579)	-0.7% [-1.8%,0.4%]	0.342
Major Bleeding to 1080 Days	1.2% (7/577)	2.4% (14/579)	-1.2% [-2.7%,0.3%]	0.185
Early Stent Thrombosis	0.5% (3/596)	1.2% (7/594)	-0.7% [-1.7%,0.4%]	0.224
Late Stent Thrombosis to 270 days	0.0% (0/592)	0.0% (0/591)	0.0% [--,--]	--
Late Stent Thrombosis to 360 days	0.0% (0/590)	0.0% (0/589)	0.0% [--,--]	--
Late Stent Thrombosis to 720 days	0.0% (0/587)	0.0% (0/586)	0.0% [--,--]	--
Late Stent Thrombosis to 1080 days	0.0% (0/577)	0.0% (0/579)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 1080 Days	1.0% (6/577)	1.2% (7/579)	-0.2% [-1.4%,1.0%]	1.000
Perforation to 1080 Days	0.5% (3/577)	0.3% (2/579)	0.2% [-0.6%,0.9%]	0.686
Target Vessel Revascularization to 30 days	1.2% (7/596)	1.2% (7/594)	-0.0% [-1.2%,1.2%]	1.000
Target Vessel Revascularization to 270 days	5.6% (33/592)	12.5% (74/591)	-6.9% [-10.2%,-3.7%]	<0.001
Target Vessel Revascularization to 360 days	7.5% (44/590)	14.1% (83/589)	-6.6% [-10.2%,-3.1%]	<0.001
Target Vessel Revascularization to 720 days	8.3% (49/587)	16.4% (96/586)	-8.0% [-11.8%,-4.3%]	<0.001
Target Vessel Revascularization to 1080 days	9.5% (55/577)	17.6% (102/579)	-8.1% [-12.0%,-4.2%]	<0.001
Target Vessel Failure to 30 days	3.2% (19/596)	3.7% (22/594)	-0.5% [-2.6%,1.6%]	0.638
Target Vessel Failure to 270 days	7.9% (47/592)	15.1% (89/591)	-7.1% [-10.7%,-3.5%]	<0.001
Target Vessel Failure to 360 days	10.0% (59/590)	16.6% (98/589)	-6.6% [-10.5%,-2.8%]	<0.001
Target Vessel Failure to 720 days	11.1% (65/587)	19.8% (116/586)	-8.7% [-12.8%,-4.6%]	<0.001
Target Vessel Failure to 1080 days	12.8% (74/577)	21.4% (124/579)	-8.6% [-12.9%,-4.3%]	<0.001
Target Lesion Revascularization to 30 days	0.8% (5/596)	1.2% (7/594)	-0.3% [-1.5%,0.8%]	0.579
Target Lesion Revascularization to 270 days	4.6% (27/592)	11.8% (70/591)	-7.3% [-10.4%,-4.2%]	<0.001
Target Lesion Revascularization to 360 days	5.9% (35/590)	13.1% (77/589)	-7.1% [-10.5%,-3.8%]	<0.001
Target Lesion Revascularization to 720 days	6.5% (38/587)	14.2% (83/586)	-7.7% [-11.1%,-4.2%]	<0.001
Target Lesion Revascularization to 1080 days	7.3% (42/577)	14.7% (85/579)	-7.4% [-11.0%,-3.8%]	<0.001

Kaplan-Meier Estimate	Endeavor (N=598 patients)	Driver (N=599 patients)	P-value†
*MACE-Free at 1080 days	88.3%	79.6%	<0.001
*TLR-Free at 1080 days	92.8%	85.4%	<0.001
*TVR-Free at 1080 days	90.6%	82.6%	<0.001
*TVF-Free at 1080 days	87.4%	78.9%	<0.001

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter.
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – DRIVER.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary end point is Target Vessel Failure at 9 months.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
* MACE free – No Death, MI, emergent CABG or target lesion revascularization.

Figure 8-3. Survival Free from Target Vessel Failure (at 1080 days)



TVF	0	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor													
# Entered	597	584	570	561	541	525	522	519	515	512	503	500	497
# Censored	0	6	1	2	4	2	1	2	2	7	0	1	108
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	13	8	8	18	12	1	2	2	1	2	3	2	2
% Survived	97.8%	96.5%	95.1%	92.1%	90.0%	89.9%	89.5%	89.2%	89.0%	88.6%	88.1%	87.8%	87.4%
SE	0.6%	0.8%	0.9%	1.1%	1.2%	1.3%	1.3%	1.3%	1.3%	1.3%	1.4%	1.4%	1.6%
Driver													
# Entered	596	580	565	540	500	485	478	473	470	460	453	450	448
# Censored	0	2	1	4	6	3	0	0	4	3	0	2	109
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	16	13	24	36	9	4	5	3	6	4	3	0	1
% Survived	97.3%	95.1%	91.1%	85.0%	83.5%	82.8%	81.9%	81.4%	80.3%	79.6%	79.1%	79.1%	78.9%
SE	0.7%	0.9%	1.2%	1.5%	1.5%	1.6%	1.6%	1.6%	1.7%	1.7%	1.7%	1.7%	2.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Wilcoxon	15.19	1	<0.001									
	Log-Rank	15.19	1	<0.001									

8.5 ENDEAVOR I Trial

Purpose: The purpose of this study was to demonstrate the safety and efficacy of the **Endeavor** Stent for the treatment of single *de novo* lesions in native coronary arteries. This study provides the longest follow-up experience available.

Conclusion: In selected patients, use of the **Endeavor** Stent provided favorable IVUS, angiographic, and clinical results through 1440 days of follow-up.

Design: This is a prospective, multi-center, non-randomized, single-arm study that enrolled 100 subjects at eight (8) study sites in Australia and New Zealand. To be eligible, a patient was required to have a *de novo* ischemic lesion (≤ 15 mm in length) of a native coronary artery with reference vessel diameter of 3.0 mm to 3.5 mm. The study allowed for use of 18 mm **Endeavor** Stents. A total of 100 patients were treated with the **Endeavor** Stent. After the procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 12 weeks. Angiographic follow up was performed at 4 and 12 months post-procedure. Clinical follow-up is available through 1440 days.

Demographics: Patients had a mean age of 59 years, there were 21% females, 16% had a history of diabetes mellitus, and 47% had a prior MI. Forty-three (43) percent of the lesions treated were in LAD, 23% were in LCX, 34% were in RCA, mean reference vessel diameter pre-procedure was 2.96 mm, mean pre-procedure minimal lumen diameter was 0.88 mm, mean pre-procedure percent diameter stenosis was 70.3%, and the mean lesion length was 10.9 mm (43% of patients had a lesion length < 10 mm and 56% of patients had a lesion length between 10 mm and 19.9 mm). No patients received IIb/IIIa inhibitors in this study.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. An independent Clinical Events Committee adjudicated clinical events and an independent Data Safety Monitoring Board monitored the trial.

Results: The primary safety endpoint of 30-day MACE was 1.0%. The cumulative MACE rate at 12, 24, 36 and 48 months was 2%, 3.0%, 6.1% and 7.2% respectively. There was minimal late lumen loss and consequential binary angiographic restenosis by 4 months, at 12-month in-stent late lumen loss was 0.58±0.44 mm and in-stent binary restenosis occurred in 4.3% of patients.

Table 8-8 summarizes the principal effectiveness and safety results of the ENDEAVOR I Trial through 1440 days.

Table 8-8: Principal Effectiveness and Safety Results

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Lesion Success	100.0% (100/100)
Device Success	100.0% (100/100)
Procedure Success	100.0% (100/100)
Device-Specific Procedure Success	100.0% (100/100)
Post- Procedure Minimal Lumen Diameter (MLD, in mm)	
In-Stent	2.84±0.35 (100)
In-Segment	2.52±0.42(100)
Post-Procedure % Diameter Stenosis (%DS)	
In-Stent	5.37±7.51 (100)
In-Segment	16.54±8.40 (100)
4-Month Follow-Up MLD (mm)	
In-Stent	2.52±0.44 (98)
In-Segment	2.29±0.46 (98)
4-Month Follow-up %DS	
In-Stent	14.40±13.10 (98)
In-Segment	22.36±12.08 (98)

Safety & Effectiveness Measures	Endeavor (N=100 patients)
4-Month Late Loss (mm)	
In-Stent	0.32±0.37 (98)
In-Segment	0.22±0.43 (98)
4-Month Binary Restenosis	
In-Stent	2.0% (2/98)
In-Segment	3.1% (3/98)
4-Month Volume Obstruction (%)	4.46±6.05 (94)
4-Month Minimal Lumen Area (mm^2)	5.96±1.66 (95)
4-Month NIH Volume (mm^3)	6.10±7.39 (94)
12-Month Follow-Up MLD (mm)	
In-Stent	2.26±0.49 (92)
In-Segment	2.08±0.47 (92)
12-Month Follow-up %DS	
In-Stent	21.75±15.35 (92)
In-Segment	28.00±13.41 (92)
12-Month Late Loss (mm)	
In-Stent	0.58±0.44 (92)
In-Segment	0.43±0.44 (92)
12-Month Binary Restenosis	
In-Stent	4.3% (4/92)
In-Segment	5.4% (5/92)
12-Month Volume Obstruction (%)	9.73±8.50 (86)
12-Month Minimal Lumen Area (mm^2)	5.69±1.74 (86)
12-Month NIH Volume (mm^3)	14.15±11.82 (86)
In-Hospital MACE	0.0% (0/100)
MACE to 30 Days	1.0% (1/100)
MACE to 270 Days	2.0% (2/100)
MACE to 360 Days	2.0% (2/98)
MACE to 720 Days	3.0% (3/99)
MACE to 1080 Days	6.1% (6/98)
MACE to 1440 Days	7.2% (7/97)
Death to 1440 Days	4.1% (4/97)
Vascular Complications to 1440 Days	3.1% (3/97)
Major Bleeding to 1440 Days	2.1% (2/97)
Early Stent Thrombosis	1.0% (1/97)
Late Stent Thrombosis to 270 days	0.0% (0/100)
Late Stent Thrombosis to 360 days	0.0% (0/98)
Late Stent Thrombosis to 720 days	0.0% (0/98)
Late Stent Thrombosis to 1080 days	0.0% (0/97)
Late Stent Thrombosis to 1440 days	0.0% (0/97)
Cerebrovascular Accident (CVA) to 1440 Days	1.0% (1/97)
Perforation to 1440 Days	0.0% (0/97)

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Target Vessel Revascularization to 30 days	1.0% (1/100)
Target Vessel Revascularization to 270 days	2.0% (2/100)
Target Vessel Revascularization to 360 days	2.0% (2/98)
Target Vessel Revascularization to 720 days	4.0% (4/99)
Target Vessel Revascularization to 1080 days	5.1% (5/98)
Target Vessel Revascularization to 1440 days	5.2% (5/97)
Target Vessel Failure to 30 days	1.0% (1/100)
Target Vessel Failure to 270 days	2.0% (2/100)
Target Vessel Failure to 360 days	2.0% (2/99)
Target Vessel Failure to 720 days	4.0% (4/99)
Target Vessel Failure to 1080 days	5.2% (5/98)
Target Vessel Failure to 1440 days	5.2% (5/97)
Target Lesion Revascularization to 30 days	1.0% (1/100)
Target Lesion Revascularization to 270 days	2.0% (2/100)
Target Lesion Revascularization to 360 days	2.0% (2/99)
Target Lesion Revascularization to 720 days	2.0% (2/99)
Target Lesion Revascularization to 1080 days	3.1% (3/98)
Target Lesion Revascularization to 1440 days	3.1% (3/97)

Kaplan-Meier Estimate	Endeavor (N=100 patients)
*MACE-Free at 1440 days	92.9%
*TLR-Free at 1440 days	96.9%
*TVR-Free at 1440 days	94.9%
*TVF-Free at 1440 days	94.9%

N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
The primary endpoint was 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
MLD = Minimal luminal diameter .
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair

Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
* MACE free– No Death, MI, emergent CABG or target lesion revascularization.

9.0 Individualization of Treatment

See also **Precautions-5.6 Use in Special Populations** and **Precautions-5.7 Lesion/Vessel Characteristics.**

The risks and benefits described above should be carefully considered for each patient before use of the **Endeavor** Zotarolimus-Eluting Coronary Stent System. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anticoagulation. Stenting is generally avoided in patients at risk of bleeding and for those with contraindicated anticoagulation therapy.

10.0 Patient Counseling Information

Physicians should consider the following in counseling the patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a zotarolimus eluting stent implant
- Discuss the risks/benefits issues for this particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term
- Discuss the risks of early discontinuation of the antiplatelet therapy

The following information is provided in the package or online for physicians to provide to their patients:

- A Patient Guide which includes information on the **Endeavor** Zotarolimus-Eluting Coronary Stent System, coronary artery disease, and the implantation procedure.
- A Patient Implant Card that is used to record information about the patient and the stent.

11.0 How Supplied

STERILE: **FOR SINGLE USE ONLY**. This product is sterilized with ethylene oxide (EO) and is nonpyrogenic. Do not use if the package is opened or damaged. Do not resterilize. Return product if package is opened or damaged to Medtronic Returned Goods. Contact your local Medtronic, Inc. Representative for return information..

CONTENTS: One (1) **Endeavor** Zotarolimus-Eluting Over-the-Wire Coronary Stent System.

- One (1) Patient Implant Card
- One (1) Reference card to the electronic Instructions for Use

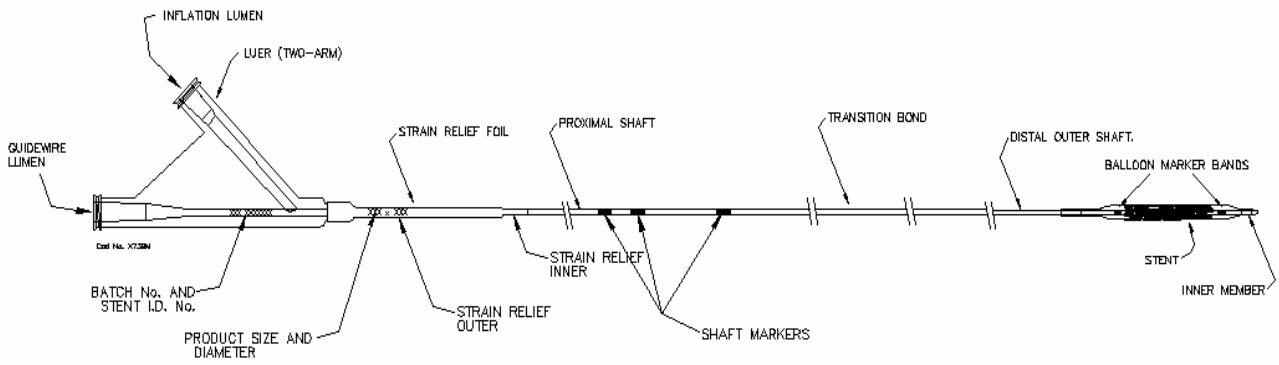
STORAGE: Store in the original container. Store at 25 ºC (77 ºF); excursions permitted to 15-30 ºC (59-86 ºF). Use by the “Use By” date noted on the package.

DISPOSAL INSTRUCTIONS:

After use, dispose of product and packaging in accordance with hospital, administrative and/ or local government policy.

12.0 Operator's Manual

Figure 12-1. Diagram of the Endeavor Zotarolimus-Eluting Coronary Stent System Over-the-Wire (OTW) Delivery System



12.1 Access to Package Holding Sterile Stent Delivery System

Tear open the outer foil pouch to reveal the inner pouch. Do not drop or hand the inner pouch into the sterile field. Remove the inner pouch from the outer foil pouch. Peel open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
Note: The outer surface of the inner pouch is not sterile.

12.2 Inspection Prior to Use

Before opening the product, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Do not use after the "Use By" date. If the sterile package is intact, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the product if any damage to the packaging is noted.

A protective sheath covers the stent mounted on the balloon. After removal of the sheath, visually inspect the stent to ensure that it has not been damaged or displaced from its original position (between proximal and distal marker bands) on the balloon.

12.3 Materials Required

Quantity	Material
N/A	Guiding catheter [≥ 5 F (1.4 mm, 0.056 inch) inner diameter]
2-3	20 cc syringe
1,000 u /500 cc	Heparinized normal saline
1	Guidewire [≤ 0.014 inch (0.36 mm) diameter]
1	Rotating hemostatic valve
N/A	Contrast medium diluted 1:1 with heparinized normal saline
1	Inflation device
1	Stopcock (3-way minimum)
1	Torque device
N/A	Appropriate anticoagulation and antiplatelet drugs

12.4 Preparation Precaution

- DO NOT use product if the protective sheath is not present or the stent is damaged/displaced.
- AVOID manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- DO NOT apply negative or positive pressure to the balloon during the delivery system preparation.

12.4.1 Guidewire Lumen Flush

Flush the stent system guidewire lumen with heparinized normal saline until the fluid exits the distal tip.

12.4.2 Delivery System Preparation

Step	Action
1.	Prepare the guide catheter and guidewire according to the manufacturer's instructions.
2.	Remove the stent delivery system from the package.
3.	Remove protective sheath covering from the stent mounted balloon.
4.	Fill a 20 cc syringe with 5 cc of contrast/heparinized normal saline mixture (1:1).
5.	Attach to delivery system and apply negative pressure for 20-30 seconds.
6.	Slowly release pressure to allow negative pressure to draw mixture into balloon lumen.
7.	Detach syringe and leave a meniscus of mixture on the hub of the balloon lumen.
8.	Prepare inflation device in standard manner and purge to remove all air from syringe and tubing.
9.	Attach inflation device to catheter directly ensuring no bubbles remain at connection.
10.	Leave on ambient pressure (neutral position). ***Note***: Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent.

12.5 Delivery Procedure

Step	Action
1.	Prepare the vascular access site according to standard practice.
2.	**Pre-dilate the lesion with a PTCA catheter.** Pre-dilatation must be performed using a balloon with the following three characteristics: • A diameter at least 0.5 mm smaller than the treatment stent. • A length equal to or shorter than the lesion length to be dilated. • A length shorter than the stent to be implanted.
3.	Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible. **Note:** If resistance is encountered, **do not force passage**. Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine**.**
4.	Ensure guiding catheter stability before advancing the **Endeavor** Coronary Stent Delivery System into the coronary artery. Carefully advance the **Endeavor** Coronary Stent Delivery System into the hub of the guiding catheter.
5.	Advance the stent delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent. If the position of the stent is not optimal, it should be carefully repositioned or removed (see **Precautions – 5.12 Stent/System Removal Precautions**). Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.
6.	Sufficiently tighten the rotating hemostatic valve. The stent is now ready to be deployed. ***Note***: Should unusual resistance be felt at any time during either lesion access or removal of the stent delivery system before stent implantation, do not force passage. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. See **Precautions – 5.12 Stent/System Removal Precautions** for specific stent delivery system removal instructions.

12.6 Deployment Procedure

Step	Action
1.	Prior to stent expansion, utilize high-resolution fluoroscopy to verify the stent has not been damaged or shifted during positioning.
2.	Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3.	Do not exceed Rated Burst Pressure. The **Endeavor** Stent should not be expanded to a diameter beyond 0.5 mm of its nominal expansion.
4.	Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

12.7 Removal Procedures

Step	Action
1.	Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 15 seconds, for full balloon deflation. Longer stents may require more time for deflation. Deflation of the balloon should be confirmed by absence of contrast within the balloon.
2.	Open the hemostatic valve to allow removal of the delivery system.
3.	Maintain position of guiding catheter and guidewire Very slowly, withdraw the balloon from the stent, maintaining negative pressure, allowing movement of the myocardium to gently dislodge the balloon from the stent.
4.	After removal of the delivery system, tighten the hemostatic valve.
5.	Repeat angiography and visually assess the vessel and the stent for proper expansion. ***Note***: Observation of the patient and angiographic evaluation of the stent site should be performed periodically within the first 30 minutes after stent placement. If stent placement is associated with the onset of thrombus or suspected thrombus in the region of the stented segment, an intracoronary infusion of a thrombolytic agent is recommended.

12.8 In-vitro Information

Table 12-1: Inflation Pressure Recommendations						
Pressure				**Stent Nominal Inner Diameter (mm)**		
atm	**kPa**	**bar**		**2.5**	**3.0**	**3.5**
6	**608**	**6.08**		2.3	2.9	3.3
7	**709**	**7.09**		2.3	2.9	3.4
8	**811**	**8.11**		2.4	3.0	3.4
9	**912**	**9.12**	Nominal	2.4	3.0	3.5
10	**1013**	**10.13**		2.5	3.1	3.5
11	**1115**	**11.15**		2.5	3.1	3.6
12	**1216**	**12.16**		2.5	3.2	3.6
13	**1317**	**13.17**		2.6	3.2	3.6
14	**1419**	**14.19**		2.6	3.2	3.7
15	**1520**	**15.20**		2.6	3.3	3.7
16	**1621**	**16.21**	RBP*	2.6	3.3	3.8
17	**1723**	**17.23**		2.7	3.3	3.8
18	**1824**	**18.24**		2.7	3.4	3.8

*Do not exceed the rated burst pressure (RBP)

12.9 Further Dilatation of Stented Segment

The stent delivery balloon may not be used for post-dilatation. Post-dilatation may be performed with appropriately sized (length and diameter) balloons to ensure that the stent is in full contact with the vessel wall. To achieve this, a balloon to artery ratio of 1.0 to 1.1:1.0 should be used to leave a residual diameter stenosis of near 0% (with a recommended maximum of no greater than 10%). Whenever possible, avoid the use of grossly oversized balloons (balloon:artery ratio > 1.2).

Precaution: Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilatation Limits
2.50 mm	3.00 mm
3.00 mm	3.50 mm
3.50 mm	4.00 mm

All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. This further expansion should be performed using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

13.0 Reuse Precaution Statement

For single use only. Do not resterilize or reuse.

Disclaimer of Warranty and Limitation of Remedy

NOTE: ALTHOUGH THE MEDTRONIC CORONARY STENT SYSTEM, HEREAFTER REFERRED TO AS “PRODUCT,” HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS, MEDTRONIC, INC., MEDTRONIC VASCULAR, INC. AND THEIR AFFILIATES (COLLECTIVELY, “MEDTRONIC”) HAVE NO CONTROL OVER CONDITIONS UNDER WHICH THIS PRODUCT IS USED. MEDTRONIC, THEREFORE, DISCLAIMS ALL WARRANTIES, BOTH EXPRESSED AND IMPLIED, WITH RESPECT TO THE PRODUCT, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANT ABILITY OR FITNESS FOR A PARTICULAR PURPOSE. MEDTRONIC SHALL NOT BE LIABLE TO ANY PERSON OR ENTITY FOR ANY MEDICAL EXPENSES OR ANY DIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT OR OTHERWISE. NO PERSON HAS ANY AUTHORITY TO BIND MEDTRONIC TO ANY REPRESENTATION OR WARRANTY WITH RESPECT TO THE PRODUCT.

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ATTACHMENT 9B Draft Endeavor Rapid Exchange (RX) Instructions For Use

Instructions for Use

ENDEAVOR® Zotarolimus-Eluting Coronary Stent System
Rapid Exchange Delivery System

Caution: Federal (USA) law restricts this product to sale by or on the order of a physician

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1.0 Endeavor Zotarolimus-Eluting Coronary Stent System

The **Endeavor** Zotarolimus-Eluting Coronary Stent System (**Endeavor** Coronary Stent System) is a device / drug combination product comprised of device components (Driver® Coronary Stent and Micro-Driver® Coronary Stent and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus contained in a polymer coating).

The characteristics of the **Endeavor** Coronary Stent System are described in **Table 1-1**.

Table 1–1: Device Component Description

Component	Endeavor Zotarolimus-Eluting Rapid Exchange (RX) Delivery System	
Available Stent Diameters (mm):	2.5	3.0, 3.5
Available Stent Lengths (mm):	8† 12, 14, 18, 24, 30	9†, 12, 15, 18, 24, 30
Stent Material :	A cobalt based alloy (MP35N) – the Driver & Micro-Driver Stents	
Drug Component:	A spray coating of polymer carrier loaded with zotarolimus is applied to the stent at a drug loading of 10 µg/mm stent length. The maximum nominal drug content on the longest stent (30 mm) is 300 µg.	
Delivery System Usable Length:	135 cm	
Delivery System Luer Adapter Ports:	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤0.014” (0.36 mm).	
Stent Delivery Balloon:	A semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. There are proximal and distal pillows formed on either side of the stent which aid in holding the stent in position. Two radiopaque balloon markers are located on the distal section of the inner member and are positioned to mark the working length of the balloon.	
Balloon Inflation Pressure:	Nominal Pressure: 9 atm (912 kPa, 9.12 bar) Rated Burst Pressure: 16 atm (1621 kPa, 16.21 bar)	
Guide Catheter Compatibility:	0.056” minimum (5F)	
Distal Section OD:	Distal = 2.7F	
	Proximal = 3.0F	
Proximal OD:	2.2F	

† The 8 mm and 9 mm stent lengths are used for bailout procedures or insufficient lesion coverage.

1.1 Device Component Description

The device component consists of the **Driver** or **Micro-Driver** Balloon-Expandable Coronary Stent pre-mounted onto a stent delivery system (SDS). The range of stent diameters is made possible by varying the element lengths and number of crowns on the stent. The 2.5 mm diameter cobalt-based alloy stent (**Micro-Driver**) has 1.2 mm length elements and seven crowns; the 3.0 and 3.5 mm diameter cobalt-based stents (**Driver**) have 1.0 mm length elements and ten crowns. The stent is crimped on various size delivery catheter balloons, which are sized from 2.5 to 3.5 mm.

1.2 Drug Component Description

The drug component of the **Endeavor** Coronary Stent System consists of zotarolimus (the active ingredient) and Phosphorylcholine (PC) polymer (the inactive ingredient).

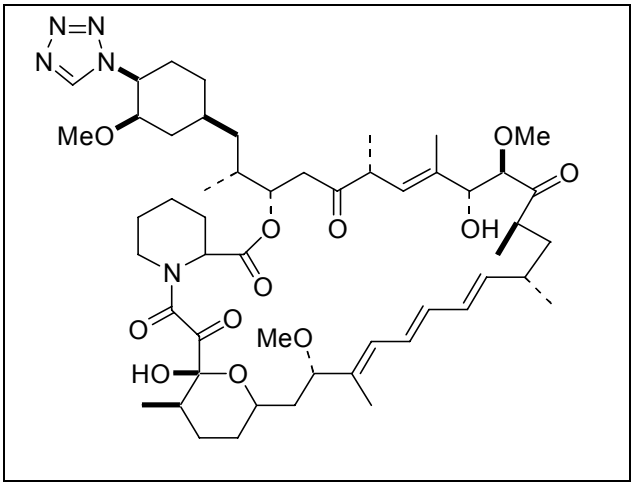
1.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the Endeavor Stent is zotarolimus. It is a tetrazole-containing macrocyclic immunosuppressant.

The chemical name of zotarolimus is: [3S-[3R*[S*(1R*,3S*,4R*)],6S*, 7E,9S*,10S*,12S*,14R*,15E,17E,19E, 21R* ,23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27, 32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown below:

Figure 1-1: Zotarolimus Chemical Structure



Zotarolimus has extremely low water solubility and is a lipophilic compound but is freely soluble in Propylene glycol, Acetone, Toluene, Acetonitrile, Ethanol, Benzyl alcohol and DMSO. The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

Zotarolimus does not have any ionizable group(s) in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

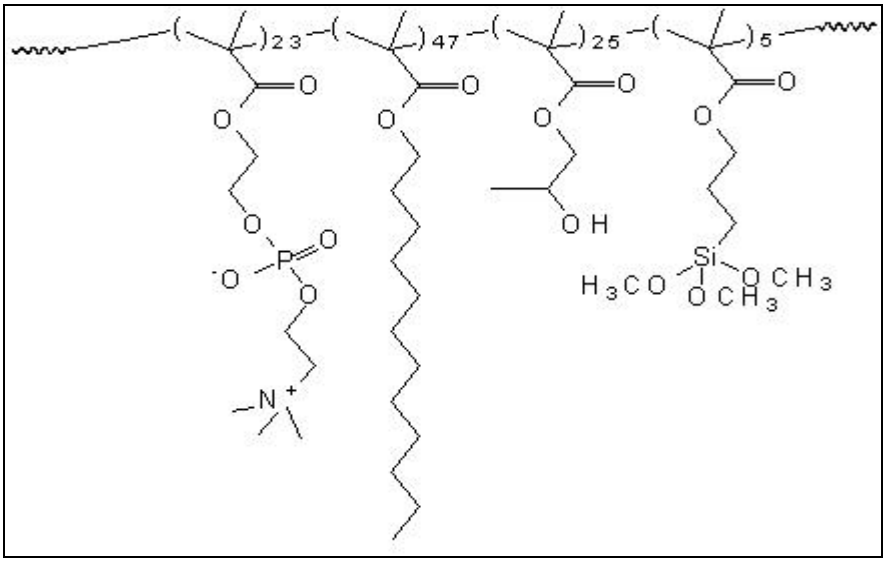
1.2.2 Polymer Component Description

The only inactive ingredient in the **Endeavor** Stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for zotarolimus. The PC polymer consists of 2-Methacryloyloxyethyl phosphorylcholine that is synthesized and then used in the preparation of crosslinked polymer membranes with lauryl methacrylate, hydroxypropyl methacrylate and trimethoxysilylpropyl methacrylate (crosslinker) co-monomers. The PC polymer contains a biocompatible component which mimics the body's own chemistry, a hydrophobic component for adhesion and stability, and a crosslinking component for robustness.

The molecular weight of PC polymer was estimated using viscometry and resulted in values of Mv ranging from 160,000 to 270,000. These figures were supported by light scattering values of Mw (g/mol) ranging from 100,000 to 200,000.

PC polymer in a solvent carrier (ethanol) is applied to the Driver stent to form the base layer coat of the Endeavor stent. The polymer is also mixed with the drug zotarolimus and then applied to the base layer-coated stents. Finally, a drug-free overspray of PC polymer is applied after the stent has been coated with the drug/polymer formulation and it has been crimped onto the balloon. The drug/polymer coating is applied to the entire surface (i.e. luminal and abluminal) of the stent. The structural formula of the polymer is shown below:

Figure 1-2. PC Polymer Structure*



* PC Technology™ is licensed under patents or patent applications owned by Biocompatibles

1.2.3 Product Matrix and Zotarolimus Content

Table 1–2: Endeavor Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number RX	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
EN25008UX	2.50	8*	84
EN30009UX	3.00	9	90
EN35009UX	3.50	9	90
EN25012UX	2.50	12	120
EN30012UX	3.00	12	120
EN35012UX	3.50	12	120
EN25014UX	2.50	14*	144
EN30015UX	3.00	15	150
EN35015UX	3.50	15	150
EN25018UX	2.50	18	180
EN30018UX	3.00	18	180
EN35018UX	3.50	18	180
EN25024UX	2.50	24	240
EN30024UX	3.00	24	240
EN35024UX	3.50	24	240
EN25030UX	2.50	30	300
EN30030UX	3.00	30	300
EN35030UX	3.50	30	300

* Note the 8 mm and 14 mm stent lengths have a total nominal drug content of 84 µg and 144 µg respectively since the actual stent length for the 8 mm stent is 8.4 mm and the actual stent length for the 14 mm stent is 14.4 mm

2.0 Indications

The **Endeavor** Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5mm to ≤ 3.5mm.

3.0 Contraindications

Use of the **Endeavor** Zotarolimus-Eluting Coronary Stent System is contraindicated for use in:

- Patients with a known hypersensitivity to zotarolimus or structurally-related compounds.
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Patients with a known hypersensitivity to phosphorylcholine polymer or its individual components (see details in **Section 1.2.2 – Polymer Component Description** for details).

Coronary artery stenting is contraindicated for use in:

- Patients in whom anti-platelet and/or anticoagulation therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

4.0 Warnings

- Please ensure that the inner package has not been opened or damaged as this indicates the sterile barrier has been breached.
- The use of this product carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.

5.0 Precautions

5.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Risks and benefits of the stent should be assessed for patients with history of severe reaction to contrast agents.
- Do not expose or wipe the product with organic solvents, such as alcohol, or detergents.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In the ENDEAVOR I, ENDEAVOR II, and ENDEAVOR III studies, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 12 weeks post-procedure. In ENDEAVOR IV, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 6 months post-procedure in order to ensure proper blinding to the randomized comparator, the Taxus stent. Aspirin was administered pre-procedure and continued indefinitely. Based on empirical data from the Endeavor randomized clinical trials (ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV), approximately 82% of the patients remained on dual antiplatelet therapy at 6 months. See **Section 8, Clinical Studies,** for more specific information.
- It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a drug eluting stent and its associated recommended antiplatelet therapy is the appropriate treatment of choice. Following PCI, recommendations of a surgical or dental procedure and the risks and benefits of the procedure should be

weighed against the possible risks associated with early discontinuation of antiplatelet therapy.

5.3 Use of Multiple Stents

The long-term effects of zotarolimus are currently unknown. In clinical trials of the **Endeavor** Stent, patients were treated with no more than 48 mm of total **Endeavor** Stent, except in situations involving bailout stenting. The extent of the patient's exposure to the drug and polymer coating is directly related to the number of stents and stent length implanted.

When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. Data obtained from in vitro corrosion tests using F562 CoCr alloy stent (Medtronic **Driver** Coronary Stent) in combination with a 316L stainless steel alloy stent (Medtronic **S7** Coronary Stent) do not suggest an increased risk of in vivo corrosion. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.

Potential interactions of the **Endeavor** Stent with other drug-eluting or coated stents have not been evaluated.

5.4 Brachytherapy

The safety and effectiveness of the **Endeavor** Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of the use of brachytherapy to treat in-stent restenosis in an Endeavor Stent has not been established. Both vascular brachytherapy and the **Endeavor** Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with **Endeavor** Stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

- There are no adequate and well-controlled studies in pregnant women or in men intending to father children.
- The **Endeavor** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

5.6.2 Lactation

It is not known whether zotarolimus is excreted in human milk. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

5.6.3 Gender

Clinical studies of the **Endeavor** Stent did not find any significant differences in safety and effectiveness for male and female patients.

5.6.4 Ethnicity

Clinical studies of the **Endeavor** Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity.

5.6.5 Pediatric Use

The safety and effectiveness of the **Endeavor** Stent in pediatric patients below the age of 18 years have not been established.

5.6.6 Geriatric Use

Clinical studies of the **Endeavor** Stent did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.7 Lesion/Vessel Characteristics

The safety and effectiveness of the **Endeavor** Stent have not yet been established in the following patient populations:

- Patients with unresolved vessel thrombus at the target lesion site
- Patients with reference vessel diameters <2.5 mm or >3.5 mm.
- Patients with lesions located in saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor flow distal to the identified lesions.
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.
- Patients for longer than 48 months of follow-up.
- Patients with severe calcification in the lesion.

5.8 Drug Interactions

While no specific clinical data are available, drugs, like sirolimus, that act through the same binding protein (FKBP) may interfere with the efficacy of zotarolimus. Zotarolimus is metabolized by CYP3A4, a human cytochrome P450 enzyme. Strong inhibitors of CYP3A4 (e.g., ketoconazole) might cause increased zotarolimus exposure to levels associated with systemic effects, especially if multiple stents are deployed. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

5.9 Magnetic Resonance Imaging (MRI)

Non-clinical testing on single and overlapped stents has demonstrated that the Endeavor Zotarolimus-eluting coronary stent is MR Conditional. It can be scanned safely under the following conditions:

Single Stenting (Stent Length 30mm)	Overlapped Stenting (Total Length 55mm)
Static magnetic field of 3 - Tesla	Static magnetic field of 3 - Tesla
Spatial gradient field of 525 Gauss/cm	Spatial gradient field of 720 Gauss/cm
Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of scanning	Maximum whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning
In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of MR scanning in a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.	In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.
The Endeavor stent should not move or migrate when exposed to MR scanning immediately post-implantation.	
The image artifact extends approximately 9 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR system with a send-receive RF body coil.	The image artifact extends approximately 10 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR system with a send-receive RF body coil.

5.10 Stent Handling Precautions

- For single use only. The **Endeavor** Coronary Stent System is provided sterile. Do not resterilize or reuse this product. Note the "Use By" date on the product label. (See Reuse Precaution Statement, Section 13.0). Do not use if package or product has been opened or damaged.
- The foil pouch is not a sterile barrier. The pouch contained within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is not sterile.**
- Do not remove the contents of foil pouch until immediately prior to the use of device.
- Do not remove the stent from the delivery balloon – removal may damage the stent and polymer coating and/or lead to stent embolization. The **Endeavor** Coronary Stent System is intended to perform as a system. The stent is not designed to be crimped onto another delivery device.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the rotating hemostatic valve and guiding catheter hub.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may cause coating damage, contamination or dislodgement of the stent from the delivery system balloon.
- The **Endeavor** Stent must not be exposed to any direct handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug elution.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

- The **Endeavor** Coronary Stent Delivery System should not be used in conjunction with any other stents or for post-dilatation.
- In the event the **Endeavor** Stent is not deployed contact your local Medtronic, Inc. representative for return information.

5.11 Stent Placement Precautions

- The vessel should be pre-dilated with an appropriately sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 12.5 – Delivery Procedure**.
- Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in **Section 12.0 – Operator's Manual**.
- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Device Component Description** in **Table 1-1**).
- Do not induce negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- In smaller or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection.
- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel (see **Precautions – 5.12 Stent/System Removal Precautions**).
- Placement of the stent has the potential to compromise side branch patency.
- Do not attempt to pull an unexpanded stent back through the guiding catheter as dislodgement of the stent from the balloon may occur. Remove as a single unit per instructions in **Precautions – 5.12 Stent/System Removal Precautions**.
- Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure that the stent is in full contact with the arterial wall upon deflation of the balloon.
- Stent retrieval methods (e.g., use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.
- Administration of appropriate anticoagulant, antiplatelet and coronary vasodilator therapy is critical to successful stent implantation.

5.12 Stent/System Removal Precautions

If removal of a stent system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the stent delivery system, and cautiously withdraw the stent delivery system into the guide catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guide catheter, the Stent Delivery System and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.

When removing the Stent Delivery System and guiding catheter as a single unit:

- Do not retract the Stent Delivery System into the guiding catheter. Maintain guidewire placement across the lesion and carefully pull back the Stent Delivery System until the proximal balloon marker of the Stent Delivery System is aligned with the distal tip of the guiding catheter.
- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten, allowing safe withdrawal of the Stent Delivery System into the guiding catheter

and the subsequent removal of the Stent Delivery System and the guiding catheter from the arterial sheath.

Failure to follow these steps and/or applying excessive force to the Stent Delivery System can potentially result in loss or damage to the stent and/or Stent Delivery System components such as the balloon.

5.13 Post-Procedure

- Care should be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Post-dilatation: All efforts should be made to assure that the stent is not under dilated. If the deployed stent is not fully apposed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2 mm) than the stent. The post-dilatation can be done using a low-profile, high pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. **Do not use the stent delivery balloon for post-dilatation.**
- Non-clinical testing on single and overlapped stents has demonstrated that the **Endeavor** Zotarolimus-eluting coronary stent is MR Conditional (see **Precautions – 5.9 Magnetic Resonance Imaging (MRI)**). MR imaging quality may be compromised if the area of interest is in the same area of the position of the stent.
- Antiplatelet therapy should be administered post-procedure (see **Precautions – 5.2 Pre- and Post-Procedure Antiplatelet Regimen**). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.

6.0 Drug Information

6.1 Mechanisms of Action

The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control.

6.2 Pharmacokinetics of the Endeavor Stent

The pharmacokinetics of zotarolimus delivered from the **Endeavor** Coronary Stent System have been determined in patients with coronary artery disease after stent implantation in the ENDEAVOR US Pharmacokinetic trial. The dose of zotarolimus was calculated from the total implanted stent length; the parameters determined from these patients are provided in **Table 6-1**.

Table 6-1: Zotarolimus Pharmacokinetics in Patients after Implantation of Endeavor-Zotarolimus Eluting Coronary Stents

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	1.584	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
$AUC_{0\text{-last}}$	(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
$AUC_{0\text{-inf}}$	(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
$t_{½}$‡	(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
Cmax Maximum blood concentration
Tmax Time to Cmax
$AUC_{0\text{-last}}$ Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration
$AUC_{0\text{-inf}}$ AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).
t½ Harmonic mean half-life
CL/F Mean apparent clearance

a. Primary dose groups
‡ Harmonic mean ± pseudo-standard deviation
† No SD was reported when N ≤ 2
§ Mean only
# N = 6

The results in **Table 6-1** show that pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 2), 180, 240 and 300 µg, following the implantation of **Endeavor** Zotarolimus-Eluting Stents as illustrated by dose proportional increases in maximum blood concentration (C_{max}), area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration ($AUC_{0\text{-last}}$) and AUC from time 0 to infinity($AUC_{0\text{-inf}}$). Mean apparent clearance (CL/F) and harmonic mean half-life ($t_{1/2}$) for the primary dose groups ranged from 2.8 to 3.5 L/h and 57.5 to 59.7 h, respectively. The mean time to reach peak systemic concentration (T_{max}) ranged from 1.2 to 1.5 h after stent implantation.

6.3 Pharmacokinetics following Intravenous Administration of Zotarolimus

Zotarolimus pharmacokinetic activity has been determined following intravenous administration in healthy subjects. **Table 6-2** provides a summary of the pharmacokinetic analysis.

Table 6-2: Pharmacokinetic Parameters (Mean ± standard deviation) in Patients Following Intravenous Administration of Zotarolimus

PK Parameters	Units	**200µg QD** (N = 15)		**400µg QD** (N= 16)		**800µg QD** (N=16)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max}	(ng/mL)	11.41± 1.38¥	11.93 ± 1.25	21.99 ± 3.79	23.31± 3.15	37.72 ± 7.00	41.79 ± 6.68
T_{max}	(h)	1.05 ± 0.04¥	1.03 ± 0.04	1.00 ± 0.14	1.05 ± 0.04	1.03 ± 0.04	1.03 ± 0.05
$AUC_{0\text{-}24}$	(ng•h/mL)	34.19 ± 4.39¥	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
$t_{1/2}$$	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL [b]	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

¥ N = 16; $ Harmonic mean ± pseudo-standard deviation
[b] Clearance data is calculated using compartmental methods. All other data presented in Table 6-2 is calculated using non-compartmental methods.

When administered intravenously for 14 consecutive days, zotarolimus showed dose proportionality. Renal excretion is not a major route of elimination for zotarolimus as approximately 0.1% of the dose was excreted as unchanged drug in the urine per day. In multiple doses of 200, 400 and 800 µg, zotarolimus was generally well tolerated by the subjects. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study.

6.4 Metabolism

Zotarolimus undergoes oxidative metabolism in the liver to form the desmethyl and hydroxylated metabolites of the parent drug. Further metabolism can lead to the formation of hydroxyl-demethyl and dihydroxyl-demethyl metabolites. Enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities, however the IC_{50} values (3 µM and above) are many fold higher than the systemic concentrations expected following implantation of a drug-eluting stent. The anticipated zotarolimus blood levels in stented patients are expected to be less than 0.004 µM, suggesting that clinically significant drug-drug interactions are unlikely.

6.5 Mutagenesis, Carcinogenicity and Reproductive Toxicology

6.5.1 Mutagenesis

Zotarolimus was not genotoxic in a standard battery of tests.

6.5.2 Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of zotarolimus.

6.5.3 Reproductive Toxicology

No effect on fertility or early embryonic development in female rats following the administration of zotarolimus was observed at intravenous dosages up to 100 µg/kg/day (approximately 5 times the maximum blood level and about 11 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus). Administration at a dosage of 300 µg/kg/day (approximately 10 times the maximum blood level and about 28 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus) resulted in embryotoxicity and embryolethality.

For male rats, there was no effect on fertility rate at intravenous dosages up to 300 µg/kg/day (approximately 13 times the maximum blood level and about 50 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus) administered for 28 days prior to mating. No effects on testicular toxicity were observed as a result of chronic exposure when administered for approximately 70 days at dosages of 10 µg/kg/day (approximately 1.3 times the maximum blood level and about 10 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus). Testicular changes observed at higher doses were reversible after 10 weeks.

6.6 Pregnancy

There are no adequate and well-controlled studies in pregnant women with zotarolimus.

Administration of zotarolimus to pregnant female rats in a developmental toxicity study at an intravenous dosage of 60 µg/kg/day (approximately 4 times the maximum blood level and about 5 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus) resulted in embryolethality. Fetal ossification delays were also observed at this dosage, but no major fetal malformations or minor fetal anomalies were observed in this study.

No embryo-fetal effects were observed in pregnant rabbits administered zotarolimus in a developmental toxicity study at intravenous dosages up to 100 µg/kg/day (approximately 19 times the maximum blood level and about 22 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus).

6.7 Lactation

It is not known whether zotarolimus is excreted in human milk. The potential adverse reactions in nursing infants from zotarolimus have not been determined.

7.0 Adverse Events

7.1 Observed Adverse Events

The incidence of adverse events attributed to the drug zotarolimus was determined in intravenous escalating and multiple dose studies. In the single-escalating dose study the proportion of subjects reporting treatment-emergent adverse events was slightly lower among subjects who received doses of zotarolimus than those who received placebo for zotarolimus. The most common treatment-emergent adverse events associated with zotarolimus were injection site reaction, pain, and circumoral paresthesia. There were no serious adverse events reported in this study. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles. There were no apparent differences among the doses with regard to safety. **Table 7-1** provides a summary of the analysis.

Table 7-1: Summary of Treatment-Emergent Adverse Events reported by two or more subjects in any one treatment by Body Systems and COSTART Term in the single-escalating dose study.

BODY SYSTEMS	COSTART Term	All Placebo N=20(%)	Zotarolimus 100 µg N=8(%)	Zotarolimus 300µg N=8(%)	Zotarolimus 500µg N=8(%)	Zotarolimus 700µg N=8(%)	Zotarolimus 900µg N=8(%)
Body as a whole	Headache	3 (15%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
	Pain	7 (35%)	1 (13%)	0 (0%)	5 (63%)	5 (63%)	2 (25%)
Digestive System	Diarrhea	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nervous System	Circumoral Paresthesia	0 (0%)	0 (0%)	0 (0%)	3 (38%)	0 (0%)	0 (0%)
Skin and Appendage	Injection site Reaction	8 (40%)	1 (13%)	5 (63%)	2 (25%)	1 (13%)	5 (63%)

In the multiple dose study the proportion of subjects reporting treatment-emergent adverse events was similar among subjects who received doses of zotarolimus and the most common treatment-emergent adverse events associated with zotarolimus were headache, pain, injection site reaction, dry skin, abdominal pain, diarrhea and rash. There were no deaths or other serious adverse events. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for vital signs, laboratory safety assessments and physical examinations were unremarkable for each treatment group. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles or overall drug safety. **Table 7-2** provides a summary of the analysis.

Table 7-2: **Summary of Treatment-Emergent Adverse Events reported by two or more subjects in any one treatment by Body Systems and COSTART Term in the multiple dose study.**

BODY SYSTEM	COSTART Term	All Placebo (N = 16) N (%)	200 µg QD (N = 16) N (%)	400 µg QD (N = 16) N (%)	800 µg QD (N = 16) N (%)
Body as a whole	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)
Digestive System	Diarrhea	1 (4)	0 (0)	1 (6)	0 (0)
Skin and Appendage	Dry Skin	0 (0)	0 (0)	2 (13)	0 (0)
	Rash	0 (0)	1 (6)	1 (6)	0 (0)

Primary adverse event experience with the Endeavor Stent comes from four clinical studies, the Endeavor IV, the ENDEAVOR III, the ENDEAVOR II and the ENDEAVOR I trial. See **Section 8 – Clinical Studies** for more complete description of the trial design and results.

The ENDEAVOR IV, III, II and I trials have evaluated the performance of the **Endeavor** Stent in patients with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. Major study characteristics are summarized in **Table 8-1**. Principal adverse events are shown in **Table 7-3**.

Table 7-3: Principal Adverse Events

Description of Event	ENDEAVOR IV to 270 days		Endeavor III to 720 days		Endeavor II to 1080 days		Endeavor I to 1440 days
	Endeavor (N=773 patients)	Control (N=775 patients)	Endeavor (N=323 patients)	Control (N=113 patients)	Endeavor (N=598 patients)	Control (N=599 patients)	Endeavor (N=100 patients)
In-Hospital							
MACE	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Myocardial Infarction (Q wave or Non-Q wave)	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
Q wave MI	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.3% (2/596)	0.0% (0/100)
Non-Q wave MI	0.5% (4/773)	1.9% (15/775)	0.6% (2/323)	3.5% (4/113)	2.3% (14/597)	2.3% (14/596)	0.0% (0/100)
Target Lesion Revascularization	0.4% (3/773)	0.5% (4/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
TL-CABG	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TL-PTCA	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Revascularization non Target Lesion	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-CABG	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-PTCA	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Target Vessel Revascularization	0.4% (3/773)	0.6%(5/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Failure	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Perforation	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Stent Thrombosis (acute)	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.3% (2/597)	0.3% (2/596)	0.0% (0/100)
Cerebrovascular Accident (CVA)	0.1% (1/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Out-of-Hospital							
MACE	4.7% (35/740)	3.0% (22/734)	8.6% (27/313)	8.9% (10/112)	9.5% (55/577)	18.7% (108/579)	7.2% (7/97)
Death	0.7% (5/740)	0.8% (6/734)	1.6% (5/313)	4.5% (5/112)	3.1% (18/577)	4.5% (26/579)	4.1% (4/97)
Myocardial Infarction (Q wave or Non-Q wave)	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.7% (4/577)	1.6% (9/579)	1.0% (1/97)
Q wave MI	0.0% (0/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.7% (4/579)	0.0% (0/97)
Non-Q wave MI	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.5% (3/577)	0.9% (5/579)	1.0% (1/97)
Target Lesion Revascularization	3.8% (28/740)	2.2% (16/734)	7.0% (22/313)	4.5% (5/112)	6.8% (39/577)	14.3% (83/579)	3.1% (3/97)
TL-CABG	0.4% (3/740)	0.4% (3/734)	1.3% (4/313)	0.0% (0/112)	0.5% (3/577)	1.0% (6/579)	1.0% (1/97)
TL-PTCA	3.5%	1.8%	5.8%	4.5% (5/112)	6.4% (37/577)	13.5%	3.1% (3/97)

	(26/740)	(13/734)	(18/313)			(78/579)	
Target Vessel Revascularization non Target Lesion	2.0% (15/740)	2.6% (19/734)	8.3% (26/313)	6.3% (7/112)	2.9% (17/577)	4.8% (28/579)	2.1% (2/97)
TV/non-TL-CABG	0.4% (3/740)	0.1% (1/734)	1.0% (3/313)	0.0% (0/112)	0.2% (1/577)	0.3% (2/579)	1.0% (1/97)
TV/non-TL-PTCA	1.8% (13/740)	2.5% (18/734)	7.7% (24/313)	6.3% (7/112)	2.8% (16/577)	4.7% (27/579)	1.0% (1/97)
Target Vessel Revascularization	5.1% (38/740)	4.4% (32/734)	13.7% (43/313)	9.8% (11/112)	9.0% (52/577)	17.4% (101/579)	5.2% (5/97)
Target Vessel Failure	5.8% (43/740)	4.8% (35/734)	13.7% (43/313)	10.7% (12/112)	10.4% (60/577)	19.2% (111/579)	5.2% (5/97)
Stent Thrombosis (sub-acute/<30 days)	0.1% (1/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.9% (5/579)	1.0% (1/97)
Stent Thrombosis (late /≥ 30 days)	0.4% (3/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.0% (0/577)	0.0% (0/579)	0.0% (0/97)
Cerebrovascular Accident (CVA)	0.5% (4/740)	0.5% (4/734)	0.6% (2/313)	0.9% (1/112)	1.0% (6/577)	1.2% (7/579)	1.0% (1/97)

N = The maximum number of eligible patients
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization.
ENDEAVOR IV: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR III: The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
ENDEAVOR II: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR I: The primary endpoint is 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months.

In the ENDEAVOR IV trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. In the ENDEAVOR III trial all enrolled patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluation at 8-months. In the ENDEAVOR II trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. Rates of incomplete stent apposition are shown in **Table 7-4** for ENDEAVOR II, ENDEAVOR III and ENDEAVOR IV trials.

Table 7-4: Rates of Incomplete Stent Apposition.

	ENDEAVOR II Trial		ENDEAVOR III Trial		ENDEAVOR IV Trial	
	Endeavor Stent (N=169)	Control Stent (N=159)	Endeavor Stent (N=323)	Control Stent (N=113)	Endeavor Stent (N=164)	Control Stent (N=164)
Incomplete Stent Apposition Rate at Post-Procedure	24.8% (36/145)	19.6% (28/143)	12.4% (31/251)	17.7% (17/96)	12.5% (17/136)	11.8% (15/127)
Incomplete Stent Apposition Rate at 8 Month Follow-up	16.8% (21/125)	14.5% (16/110)	7.5% (17/226)	17.1% (13/76)	10.0% (12/120)	14.7% (17/116)
Resolved	7.0% (8/114)	6.7% (7/104)	5.8% (11/189)	7.4% (5/68)	3.8% (4/106)	2.1% (2/95)
Persistent	17.5% (20/114)	14.4% (15/104)	7.9% (15/189)	11.8% (8/68)	8.5% (9/106)	10.5% (10/95)
Late Acquired	0% (0/114)	0% (0/104)	0.5% (1/189)	5.9% (4/68)	0.9% (1/106)	3.2% (3/95)

7.2 Potential Adverse Events

7.2.1 Potential Adverse Events Related to Zotarolimus

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.

The adverse events that have been associated with the intravenous injection of zotarolimus in humans include:

- Anemia
- Circumoral paresthesia
- Diarrhea
- Dry Skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

7.2.2 Potential Risks Associated with Percutaneous Coronary Diagnostic and Treatment Procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks may include, but are not limited to, the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias
- Balloon rupture
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Infection or fever
- Myocardial infarction (MI)
- Peripheral ischemia / peripheral nerve injury
- Restenosis of the stented artery
- Shock / pulmonary edema
- Stent deformation, collapse, or fracture
- Stent migration
- Stent misplacement
- Stroke / transient ischemic attack
- Thrombosis (acute and subacute)
- Unstable angina

8.0 Clinical Studies

8.1 Overview of Clinical Studies

The principle safety and efficacy information for the **Endeavor** Stent is presented from the following clinical studies – the ENDEAVOR I trial, the ENDEAVOR II trial, the ENDEAVOR III trial and the ENDEAVOR IV trial. The ENDEAVOR I, II, III and IV trials have evaluated the performance of the **Endeavor** Stent in patients with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. Major study characteristics are summarized in **Table 8-1**.

The ENDEAVOR IV trial was a prospective, multi-center, single blind, two arm randomized controlled trial that compared the **Endeavor** Stent to the Taxus Stent. Eligibility was based on the careful assessments of a lesion reference vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 6 months.

The ENDEAVOR III trial was a prospective, multi-center, single-blind, two arm randomized controlled trial that compared the **Endeavor** Stent to a control consisting of the Cypher stent. Eligibility was based on the careful assessments of a lesion reference vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR II trial was a prospective, multi-center, double-blind, two arm randomized controlled trial that compared the **Endeavor** Stent to a control consisting of the DRIVER bare metal stent (cobalt based alloy). Eligibility was based on careful assessments of lesion reference vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary

angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR I trial was the First-in-man study for the **Endeavor** Stent. ENDEAVOR I was a non-randomized, prospective, multicenter, single-arm trial that followed patients clinically and angiographically. The primary emphasis of the ENDEAVOR I trial was to assess the safety of the **Endeavor** Stent; the study also has significant value because it provides the longest available follow-up information on patients, currently four years.

Table 8-1: Clinical Trial Comparisons

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Study Type	Multi-center (n=8) Prospective Non-randomized	Multi-center (n=72) Prospective Randomized	Multi-center (n=29) Prospective Randomized	Multi-center (n=80) Prospective Randomized
Number of Patients	Total : 100 (**Endeavor** Stent)	Total : 1197 (**Endeavor** Stent: 598, Control: 599)	Total : 436 (3:1 randomization with control)	Total : 1548 (**Endeavor** Stent: 773, Taxus: 775)
Lesion Criteria	Single *de novo* lesion in native coronary artery ≤ 15mm in length and ≥3.0 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥2.25 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥2.5 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≤ 27 mm in length and ≥2.5 to ≤3.5mm in diameter
Product Used	**Endeavor** Stent on the Rapid Exchange Stent Delivery System	**Endeavor** Stent on the Rapid Exchange Stent Delivery System	**Endeavor** Stent on the Over-The -Wire Stent Delivery System	**Endeavor** Stent on the Over-The -Wire Stent Delivery System
Antiplatelet Therapy	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 6 months
Follow up	30 days : Clinical 4 & 12 months : Clinical and angiographic 9 month: Clinical 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic 9 month: Clinical 6 month, 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic 9 month: Clinical 6 month, 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic/ IVUS 9 month: Clinical 6 month, 1-5 years: Telephone
Status	48 month follow-up complete. Yearly follow up to 5 years is ongoing.	36 month follow-up is complete. Yearly follow up to 5 years is ongoing.	24 month follow-up is complete. Yearly follow up to 5 years is ongoing.	9 month follow-up is complete.

8.2 ENDEAVOR IV Trial

Purpose: To demonstrate the equivalence in safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Taxus Paclitaxel-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5-3.5 mm

Conclusion: Based on acute procedural results, 8-month angiographic, and 9-month clinical follow-up the Endeavor Zotarolimus-Eluting CSS has demonstrated similar safety and efficacy compared to the Taxus control stent.

Design: This was a prospective, multi-center, randomized, two-arm, single-blind trial that enrolled 1548 patients with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to treatment by percutaneous stenting.

Follow-up was performed at 30 days, 6, 8, and 9 months, and will be performed at 12 months, then annually thereafter out to 5 years. Angiography and IVUS evaluations were performed immediately post-procedure and at 8 months post-procedure for the first 328 consecutively enrolled patients (combined from all sites). In addition, patients at all sites receiving two or more stents at the target lesion had angiographic and IVUS evaluations immediately post-procedure and at 8 months post-procedure (known as the Multi-stent subset). Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 6 months.

Demographics: The analysis population of this trial consisted of 1548 patients. Baseline demographics and clinical characteristics showed a mean age of 63.5 years for patients in the Endeavor arm and 63.6 years for patients in the Taxus arm. The Endeavor group had 66.9% (517/773) male enrollment and the Taxus group had 68.5% (531/775) male enrollment. In the Endeavor arm, 28.2% (218/773) of patients had prior percutaneous coronary revascularization compared to 29.5% (229/775) of subjects in the Taxus arm. In the Endeavor group, 31.2% (241/773) of patients had a history of diabetes mellitus compared to 30.5% (236/775) of patients in the Taxus group.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by study personnel at the clinical sites. Angiographic and IVUS outcomes were assessed at designated core laboratories. Clinical events were adjudicated by an independent Clinical Events Committee and the trial was monitored by an independent Data Monitoring Committee.

Results: The effectiveness and safety results for Endeavor and Taxus are presented in **Table 8-3.**

The incidence of the primary endpoint of TVF at 270 days for Endeavor was 6.8% (50/740) and for Taxus it was 7.4% (54/734) (p=0.685). The incidence of TLR at 270 days post-index procedure for the Endeavor arm was 4.2% (31/740); for Taxus it was 2.7% (20/734) (p=0.154).

At 270 days, the cumulative incidence of MACE for the Endeavor patients was 5.7% (42/740) compared to the Taxus patients which was 5.7% (42/734). The Kaplan-Meier estimate of freedom from MACE at 270 days for Endeavor patients was 94.4%; for Taxus patients it was 94.5%.

In **Table 8-2** the outcome of the primary endpoint from the ENDEAVOR IV trial is summarized.

Table 8-2: Primary endpoint from ENDEAVOR IV

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
ENDEAVOR IV	Target Vessel Failure at 9 months post-procedure	Endeavor	6.8% (50/740)	0.0005
		Taxus	7.4% (54/734)	

* P-value is for the test of Non-Inferiority.

Table 8-3 summarizes the principal effectiveness and safety results of the ENDEAVOR IV trial through 270 days. **Figure 8-1** provides the cumulative percent of patients who are TVF-free through 270 days.

Table 8-3: Principal Effectiveness and Safety Results- ITT population

Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Lesion Success	99.6% (767/770)	99.2% (766/772)	0.4%[-0.4%, 1.1%]	0.507
Device Success	97.3% (751/772)	97.9% (757/773)	-0.7%[-2.2%, 0.9%]	0.412
Procedure Success	98.7% (760/770)	96.8% (747/772)	1.9% [0.5%, 3.4%]	0.015
Device-Specific Procedure Success	96.5% (745/772)	95.6% (739/773)	0.9% [-1.0%, 2.8%]	0.433
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.62±0.43 (763)	2.61±0.44 (763)	0.01 [-0.04, 0.05]	0.703
In-Segment	2.22±0.47 (770)	2.19±0.50 (772)	0.03 [-0.02, 0.08]	0.196
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	5.50±9.61 (763)	5.01±10.49 (763)	0.48 [-0.53, 1.49]	0.348
In-Segment	20.47±9.54 (770)	20.97±11.12 (772)	-0.50 [-1.53, 0.54]	0.344
Eight-Month Follow-Up MLD (mm)				
In-Stent	1.95±0.61 (143)	2.25±0.61 (135)	-0.30 [-0.45, -0.16]	<0.001
In-Segment	1.80±0.55 (144)	1.98±0.56 (135)	-0.18 [-0.31, -0.05]	0.008
Eight-Month Follow-up %DS				
In-Stent	26.41±19.74 (143)	16.09±17.99 (135)	10.32 [5.85, 14.79]	<.001
In-Segment	32.28±17.02 (144)	26.61±15.52 (135)	5.68 [1.83, 9.52]	0.004
Eight-Month Late Loss (mm)				
In-Stent	0.67±0.49 (142)	0.42±0.50 (135)	0.25 [0.13, 0.37]	<0.001
In-Segment	0.36±0.47 (143)	0.23±0.45 (135)	0.13 [0.02, 0.23]	0.023
Eight-Month Binary Restenosis				
In-Stent	13.3% (19/143)	6.7% (9/135)	6.6% [-0.4%, 13.6%]	0.075
In-Segment	15.3% (22/144)	10.4% (14/135)	4.9% [-2.9%, 12.7%]	0.284
Eight-Month Volume Obstruction (%)	15.72±10.40 (74)	9.88±9.24 (77)	5.84 [2.68, 9.00]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.62±1.82 (113)	5.50±2.14 (109)	-0.87 [-1.39, -0.35]	0.001
Eight-Month NIH Volume (mm^3)	24.14±19.38 (74)	14.88±16.62 (77)	9.26 [3.46, 15.06]	0.002
In-Hospital MACE	0.9% (7/773)	2.6% (20/775)	-1.7% [-3.0%, -0.4%]	0.018
MACE to 30 Days	1.2% (9/770)	3.0% (23/771)	-1.8% [-3.2%, -0.4%]	0.019
MACE to 270 Days	5.7% (42/740)	5.7% (42/734)	-0.0% [-2.4%, 2.3%]	1.000
Death to 270 Days	0.7% (5/740)	0.8% (6/734)	-0.1% [-1.0%, 0.7%]	0.773
Vascular Complications to 270 Days	0.5% (4/740)	0.8% (6/734)	-0.3% [-1.1%, 0.6%]	0.546

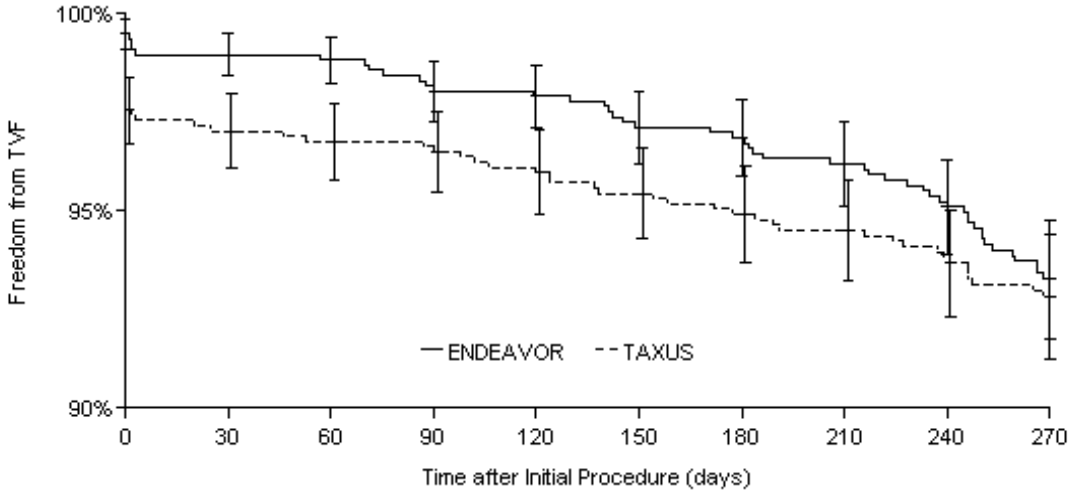
Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Bleeding complications to 270 Days	1.6% (12/740)	2.9% (21/734)	-1.2% [-2.8%, 0.3%]	0.116
Early Stent Thrombosis to 30 Days	0.4% (3/770)	0.1% (1/771)	0.3% [-0.2%, 0.8%]	0.374
Late Stent Thrombosis to 270 days	0.4% (3/740)	0.0% (0/734)	0.4% [-0.1%, 0.9%]	0.250
Cerebrovascular Accident (CVA) to 270 Days	0.7% (5/740)	0.5% (4/734)	0.1% [-0.7%, 0.9%]	1.000
Perforation to 270 Days	0.1% (1/740)	0.4% (3/734)	-0.3% [-0.8%, 0.3%]	0.372
Target Vessel Revascularization to 30 days	0.4% (3/770)	0.9% (7/771)	-0.5% [-1.3%, 0.3%]	0.342
Target Vessel Revascularization to 270 days	5.5% (41/740)	5.0% (37/734)	0.5% [-1.8%, 2.8%]	0.727
Target Vessel Failure to 30 days	1.0% (8/770)	3.0% (23/771)	-1.9% [-3.3%, -0.5%]	0.010
Target Vessel Failure to 270 days	6.8% (50/740)	7.4% (54/734)	-0.6% [-3.2%, 2.0%]	0.685
Target Lesion Revascularization to 30 days	0.4% (3/770)	0.8% (6/771)	-0.4% [-1.1%, 0.4%]	0.507
Target Lesion Revascularization to 270 days	4.2% (31/740)	2.7% (20/734)	1.5% [-0.4%, 3.3%]	0.154

Kaplan-Meier Estimate	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	P-value†
*MACE-Free at 270 days	94.4%	94.5%	0.952
*TLR-Free at 270 days	95.8%	97.3%	0.127
*TVR-Free at 270 days	94.4%	95.0%	0.682
*TVF-Free at 270 days	93.3%	92.8%	0.626

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – TAXUS.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.

CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free– No Death, MI, emergent CABG or target lesion revascularization

Figure 8-1. Survival Free from Target Vessel Failure (at 270 days)



TVF	0	7	14	21	30	60	90	120	150	180	210	240	270
ENDEAVOR													
# Entered	773	769	760	760	760	756	750	744	743	736	728	718	703
# Censored	0	5	0	0	4	5	0	0	1	6	5	7	118
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	4	4	0	0	0	1	6	1	6	2	5	8	13
% Survived	99.5%	99.0%	99.0%	99.0%	99.0%	98.8%	98.0%	97.9%	97.1%	96.9%	96.2%	95.1%	93.3%
SE	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.6%	0.6%	0.7%	0.8%	1.0%
TAXUS													
# Entered	775	755	748	748	747	744	735	732	726	720	710	694	683
# Censored	1	5	0	0	2	7	1	2	2	6	13	5	105
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	19	2	0	1	1	2	2	4	4	4	3	6	6
% Survived	97.5%	97.3%	97.3%	97.2%	97.0%	96.8%	96.5%	96.0%	95.4%	94.9%	94.5%	93.7%	92.8%
SE	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.7%	0.7%	0.8%	0.8%	0.8%	0.9%	1.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Log-Rank	0.24	1	0.626									
	Wilcoxon	0.43	1	0.511									

8.3 ENDEAVOR III Trial

Purpose: The purpose of the ENDEAVOR III trial was to demonstrate the non-inferiority in in-segment late lumen loss at 8 months between the **Endeavor** Zotarolimus-Eluting Coronary Stent System and the Cypher Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter.

Conclusion: As demonstrated in this clinical trial, the **Endeavor** Stent was shown to have a higher device success rate, a favorable safety profile (lower peri-procedural myocardial infarctions and no stent thrombosis) and comparable clinical efficacy (target lesion revascularization), despite higher restenosis and angiographic late loss. The criterion for non-inferiority of the **Endeavor** Stent to Cypher Stent was not met with regards to the 8-month in-segment late lumen loss.

Design: This was a prospective, multi-center, single-blind, parallel, two-arm, randomized, controlled trial which enrolled 436 patients. Twenty-nine (29) study sites in the United States (US) enrolled subjects in this trial. The primary endpoint for this trial was in-segment late lumen loss at 8 months post-procedure. To be eligible, patients were required to have symptomatic ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters ≥2.5 mm and ≤3.5 mm and lesion lengths of ≥14 mm and ≤27 mm that were amenable to percutaneous treatment with stenting.

Patients were randomized in a single-blind fashion (3:1 randomization) to one of two treatments: the **Endeavor** Stent or the Cypher Stent. A total of 436 patients were enrolled in the clinical trial – 323 patients were randomized to the **Endeavor** Stent and 113 were randomized to the Cypher Stent. All patients were pre-specified to receive angiographic and IVUS follow-up at 8 months. Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

Clinical follow-up through the 9 month is available on 434 patients. Angiographic follow-up was completed on 371 patients at eight months. Clinical follow-up is available through 24 months on 425 patients.

Demographics:
Patients were well matched for baseline demographics with no statistically significant differences between treatment arms, except for gender. The **Endeavor** arm had 65.3% (211/323) male enrollment and Cypher had 81.4% (92/113) male enrollment. Of the 436 enrolled patients, baseline demographics and clinical characteristics showed a mean age of 61.4 in the **Endeavor** arm and 61.7 years in the Cypher arm. In the **Endeavor** arm, 22.6% (73/323) had prior percutaneous coronary revascularization compared to 16.8% (19/113) in Cypher arm. In the **Endeavor** Stent arm, 29.7% (96/323) of patients had a history of diabetes mellitus compared to 28.3% (32/113) of patients in the Cypher arm.

Methods:
Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent angiographic core lab assessed angiographic outcomes, and an independent intravascular ultrasound core laboratory assessed IVUS outcomes. An independent Clinical Events Committee adjudicated clinical events and an independent Data Monitoring Committee monitored the trial.

Results:
In selected patients, elective **Endeavor** Stent placement in native coronary artery *de novo* lesions resulted in similar incidence of TVF at 720 days 14.4% for the **Endeavor** Stent group and 13.4% for the Cypher Stent group. Overall Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) were 9.3% in the **Endeavor** Stent group at 720 days compared to 11.6%, in the Cypher Stent group (p = 0.465). At 720 days, the rate of stent thrombosis was 0.0% in both arms.

As summarized in **Table 8-4** the mean and standard deviation for the primary endpoint of In-Segment Late Lumen Loss at 8 months for **Endeavor** Stent arm was 0.36±0.46 (mm) and for Cypher it was 0.13± 0.33 (mm).. The mean and standard deviation for the secondary endpoint of In-Stent Late Lumen Loss at 8 months for **Endeavor** Stent was 0.62±0.49 (mm) and for Cypher it was 0.15± 0.34 (mm), (p < 0.001).

Table 8-4: Primary endpoint from Endeavor III trial

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
Endeavor III	In-segment Late Lumen Loss at 8 months post-procedure (mm)	Endeavor	0.36 ± 0.46	0.791*
		Cypher	0.13 ± 0.33	

* P-value is for the test of Non-Inferiority.

Table 8-5 summarizes the principal safety and effectiveness results of the ENDEAVOR III Trial through 720 days. **Figure 8-2** provides of the cumulative percent of patients who are TVF-Free through 720 days.

Table 8-5: Principal Effectiveness and Safety Results - ITT Population

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Lesion Success	100.0% (323/323)	99.1% (112/113)	0.9% [-0.8%,2.6%]	0.259
Device Success	98.8% (319/323)	94.7% (107/113)	4.1% [-0.2%,8.4%]	0.022
Procedure Success	99.4% (321/323)	95.6% (108/113)	3.8% [-0.1%,7.7%]	0.014
Device-Specific Procedure Success	98.1% (317/323)	91.2% (103/113)	7.0% [1.6%,12.4%]	0.002
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.67±0.42 (323)	2.67±0.40 (112)	0.00 [-0.09,0.09]	0.993
In-Segment	2.27±0.45 (323)	2.28±0.47 (113)	-0.01 [-0.11,0.09]	0.836
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	4.33±9.77 (323)	5.92±9.07 (112)	-1.59 [-3.66,0.48]	0.132
In-Segment	19.38±9.25 (323)	20.17±11.74 (113)	-0.78 [-2.92,1.36]	0.522
Eight-Month Follow-Up MLD (mm)				
In-Stent	2.06±0.57 (277)	2.52±0.56 (94)	-0.46 [-0.60,-0.33]	<0.001
In-Segment	1.91±0.53 (277)	2.16±0.50 (94)	-0.25 [-0.37,-0.13]	<0.001
Eight-Month Follow-up %DS				
In-Stent	24.90±17.45 (277)	11.01±15.91 (94)	13.89 [9.88,17.90]	<0.001
In-Segment	30.42±15.57 (277)	23.86±13.87 (94)	6.56 [3.01,10.12]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.49 (277)	0.15±0.34 (94)	0.47 [0.36,0.58]	<0.001
In-Segment	0.36±0.46 (277)	0.13±0.33 (94)	0.24 [0.13,0.34]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.7% (27/277)	2.1% (2/94)	7.6% [3.1%,12.2%]	0.014
In-Segment	12.3% (34/277)	4.3% (4/94)	8.0% [2.4%,13.6%]	0.029
Eight-Month Volume Obstruction (%)	15.94±10.94 (187)	2.66±3.11 (61)	13.27 [10.48,16.07]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.89±1.96 (209)	5.77±1.97 (66)	-0.88 [-1.43,-0.34]	0.002
Eight-Month NIH Volume (mm^3)	24.09±21.16 (209)	3.74±5.20 (67)	20.36 [15.21,25.50]	<0.001
In-Hospital MACE	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 30 Days	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 270 Days	7.5% (24/321)	7.1% (8/113)	0.4% [-5.1%,5.9%]	1.000
MACE to 360 Days	7.8% (25/320)	8.0% (9/112)	-0.2% [-6.1%,5.6%]	1.000
MACE to 720 Days	9.3% (29/313)	11.6% (13/112)	-2.3% [-9.1%,4.4%]	0.465
Death to 720 Days	1.6% (5/313)	4.5% (5/112)	-2.9% [-6.9%,1.2%]	0.138
Vascular Complications to 720 Days	1.9% (6/313)	5.4% (6/112)	-3.4% [-7.9%,1.0%]	0.090
Major Bleeding to 720 Days	2.2% (7/313)	6.3% (7/112)	-4.0% [-8.8%,0.8%]	0.060
Early Stent Thrombosis to 30 Days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Late Stent Thrombosis to 270 days	0.0% (0/321)	0.0% (0/113)	0.0% [--,--]	--
Late Stent Thrombosis to 360 days	0.0% (0/320)	0.0% (0/112)	0.0% [--,--]	--

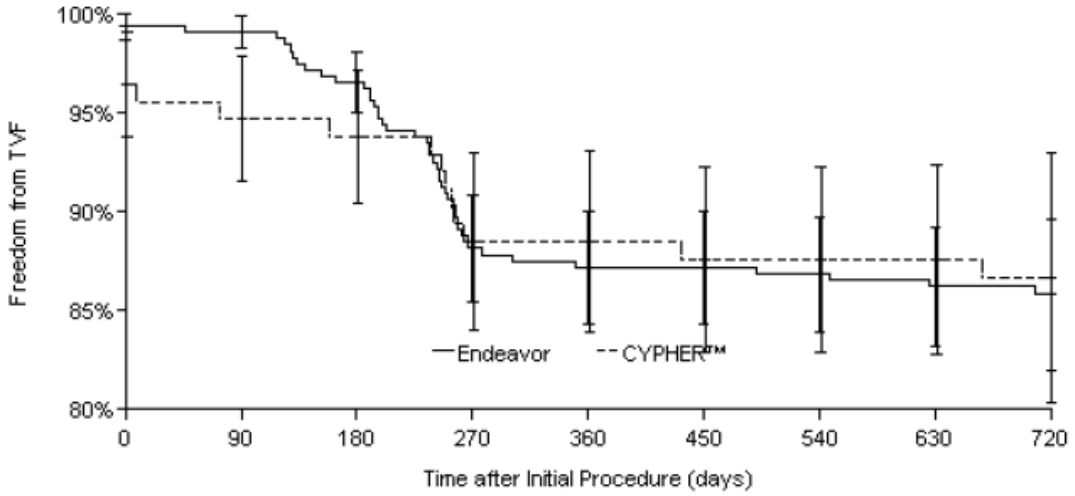
Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Late Stent Thrombosis to 720 days	0.0% (0/313)	0.0% (0/112)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 720 Days	0.6% (2/313)	0.9% (1/112)	-0.3% [-2.2%,1.7%]	1.000
Perforation to 720 Days	0.0% (0/313)	0.9% (1/112)	-0.9% [-2.6%,0.8%]	0.264
Target Vessel Revascularization to 30 days	0.0% (0/323)	0.9% (1/113)	-0.9% [-2.6%,0.8%]	0.259
Target Vessel Revascularization to 270 days	11.2% (36/321)	8.0% (9/113)	3.3% [-2.8%,9.3%]	0.375
Target Vessel Revascularization to 360 days	12.2% (39/320)	8.0% (9/112)	4.2% [-2.0%,10.3%]	0.295
Target Vessel Revascularization to 720 days	13.7% (43/313)	9.8% (11/112)	3.9% [-2.8%,10.6%]	0.325
Target Vessel Failure to 30 days	0.6% (2/323)	4.4% (5/113)	-3.8% [-7.7%,0.1%]	0.014
Target Vessel Failure to 270 days	11.8% (38/321)	11.5% (13/113)	0.3% [-6.5%,7.2%]	1.000
Target Vessel Failure to 360 days	12.8% (41/320)	11.6% (13/112)	1.2% [-5.8%,8.2%]	0.868
Target Vessel Failure to 720 days	14.4% (45/313)	13.4% (15/112)	1.0% [-6.4%,8.4%]	0.875
Target Lesion Revascularization to 30 days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Target Lesion Revascularization to 270 days	6.2% (20/321)	3.5% (4/113)	2.7% [-1.6%,7.0%]	0.346
Target Lesion Revascularization to 360 days	6.6% (21/320)	3.6% (4/112)	3.0% [-1.4%,7.4%]	0.347
Target Lesion Revascularization to 720 days	7.0% (22/313)	4.5% (5/112)	2.6% [-2.2%,7.3%]	0.498

Kaplan-Meier Estimate	ENDEAVOR III (N= 323 Patients)	CYPHER™ (N= 113 Patients)	P-value†
*MACE-Free at 720 days	90.9%	88.5%	0.464
*TLR-Free at 720 days	93.0%	95.5%	0.336
*TVR-Free at 720 days	86.4%	90.2%	0.304
*TVF-Free at 720 days	85.8%	86.7%	0.867

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – CYPHER.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).

Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free– No Death, MI, emergent CABG or target lesion revascularization

Figure 8-2. Survival Free from Target Vessel Failure (at 720 days)



TVF	0	90	180	270	360	450	540	630	720
Endeavor									
# Entered	323	321	318	310	281	274	268	264	262
# Censored	0	2	0	2	4	6	3	0	102
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	2	1	8	27	3	0	1	2	1
% Survived	99.4%	99.1%	96.6%	88.1%	87.2%	87.2%	86.9%	86.2%	85.8%
SE	0.4%	0.5%	1.0%	1.8%	1.9%	1.9%	1.9%	2.0%	2.6%
CYPHER™									
# Entered	113	109	107	106	100	98	97	97	95
# Censored	0	0	0	0	2	0	0	2	38
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	4	2	1	6	0	1	0	0	1
% Survived	96.5%	94.7%	93.8%	88.5%	88.5%	87.6%	87.6%	87.6%	86.7%
SE	1.7%	2.1%	2.3%	3.0%	3.0%	3.1%	3.1%	3.2%	4.2%
Tests Between Groups									
	Test	Chi-Square	Deg Frdm	P-value					
	Wilcoxon	0.01	1	0.906					
	Log-Rank	0.03	1	0.867					

8.4 ENDEAVOR II Trial

Purpose: The purpose of the ENDEAVOR II trial was to demonstrate the safety and efficacy of the **Endeavor** Stent with 10 µg/mm zotarolimus compared to the DRIVER Stent for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter.

Conclusion: Based on acute procedural results, 8-month angiographic, 9, 12, 24 and 36 month clinical follow-up the **Endeavor** Stent has demonstrated similar safety and superior efficacy compared with the DRIVER control stent.

Design: This was a prospective, multi-center, double-blind, two-arm randomized controlled trial to evaluate the safety and efficacy of the **Endeavor** Stent in subjects with *de novo* lesions of the native coronary arteries. Seventy-two (72) study sites in Asia, Australia, Europe, Israel and New Zealand enrolled subjects into this trial. The primary endpoint for this trial was the target vessel

failure (TVF) rate, defined as a composite of target vessel revascularization (TVR), recurrent Q or non-Q wave myocardial infarction (MI), or cardiac death that could not be clearly attributed to a vessel other than the target vessel at 270 days post index procedure. To be eligible, patients were required to have symptomatic ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters ≥2.25 mm and ≤3.5 mm and lesion lengths of ≥14 mm and ≤27 mm that were amenable to percutaneous treatment with stenting.

Patients were randomized in a double-blind fashion (1:1 randomization) to one of two treatments: **Endeavor** Stent or Uncoated DRIVER Coronary Stent System (DRIVER). A total of 1,197 patients were enrolled in the clinical trial – 598 patients were randomized to the **Endeavor** Stent and 599 were randomized to the control. A total of 600 patients were pre-specified to receive angiographic follow-up at 8 months. Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 12 weeks.

Clinical follow-up through the 1080 days follow-up period is available on 1,156 patients. Angiographic follow-up was completed on 529 patients at eight months. Clinical follow-up is available through 1080 days.

Demographics: Patients were well matched for baseline demographics with no statistically significant differences between treatment arms. Factors evaluated included age (mean 62 years), gender (24% female), diabetes (20%), prior MI (41%), hypertension requiring treatment (66%), hyperlipidemia requiring treatment (79%), ejection fraction (mean 61%), CSS Angina Class (54% Class III or IV), IIb/IIIa inhibitor use (12%), LAD (45%), LCX (22%), RCA (33%), reference vessel diameter (mean 2.75 mm), minimum lumen diameter (mean 0.83 mm), percent diameter stenosis (70%), and lesion length (mean 14.2 mm).

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent angiographic core lab assessed angiographic outcomes in a blinded fashion, and an independent intravascular ultrasound core laboratory assessed IVUS outcomes in a blinded fashion. An independent Clinical Events Committee adjudicated clinical events and an independent Data Monitoring Committee monitored the trial.

Results: In selected patients, elective **Endeavor** Stent placement in native coronary artery *de novo* lesions resulted in reduction of the incidence of TVF at 1080 days compared to Control (12.8% vs. 21.4%, p < 0.001). **Table 8-6** summarizes the results of the primary endpoint of target vessel failure (TVF) at 270 days post index procedure. Overall Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) were reduced in the **Endeavor** Stent group at 1080 days compared to control (12.0% vs. 20.7%, p < 0.001). The rate of early stent thrombosis was lower in the **Endeavor** Stent arm when compared to the control (0.5% vs. 1.2%, p = 0.342).

Table 8-6: Primary endpoint from Endeavor II trial

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
Endeavor II	Target Vessel Failure at 9 months post-procedure	Endeavor Driver	7.9% (47/592) 15.1% (89/591)	< 0.001

By follow-up angiography at 8-months, there was significantly lower in-stent late loss (0.62 vs. 1.03, p < 0.001) and in-segment late loss (0.36 vs. 0.72, p < 0.001) in Endeavor stent as compared to the Driver stent. Mean in-stent percent diameter stenosis was significantly reduced (27.9% vs. 42.2%, p < 0.001). Additionally, in-stent and in-segment binary angiographic restenosis were significantly reduced (9.5% vs. 33.2%, p < 0.001 and 13.3% vs. 34.7%, p <

0.001). There was no significant increase in proximal or distal edge late loss or BAR for the **Endeavor** Stent arm.

Examination by IVUS at 8 months showed that neointimal hyperplasia (NIH) volume was significantly reduced in the **Endeavor** Stent arm (30.2 mm^3 vs. 53.5 mm^3, $p < 0.001$). There was no evidence of late stent incomplete apposition in either treatment arm at 8 months.

Table 8-7 summarizes the principal effectiveness and safety results of the ENDEAVOR II Trial through 1080 days. **Figure 8-3** provides of the cumulative percent of patients who are TVF-Free through 1080 days.

Table 8-7: Principal Effectiveness and Safety Results (to 1080 Days)

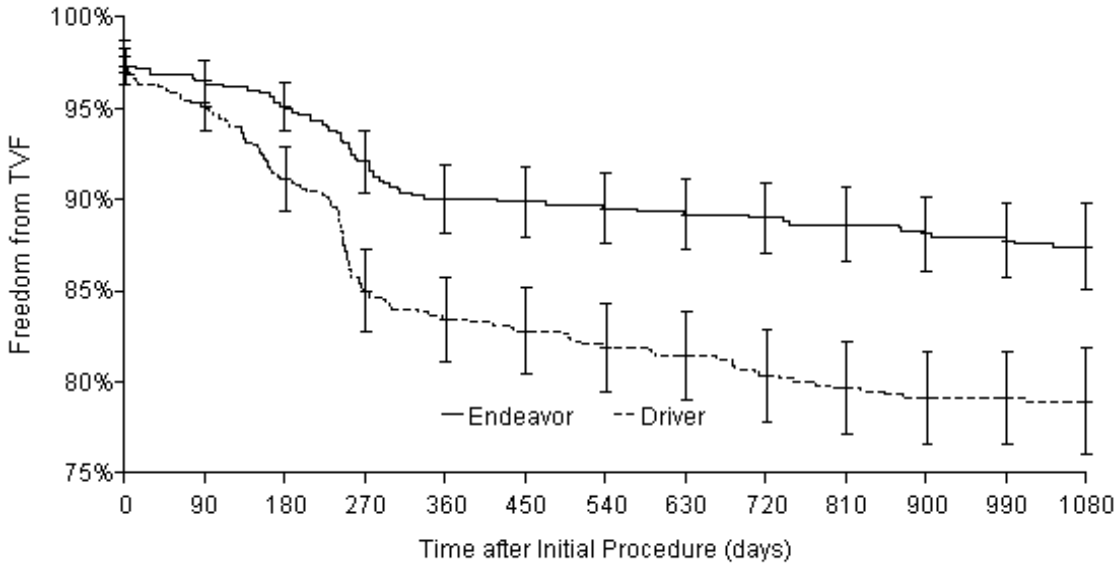
Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
Lesion Success	99.7% (587/589)	100.0% (590/590)	-0.3% [-0.8%,0.1%]	0.249
Device Success	98.8% (585/592)	99.2% (586/591)	-0.3% [-1.5%,0.8%]	0.773
Procedure Success	97.3% (573/589)	97.1% (573/590)	0.2% [-1.7%,2.0%]	1.000
Device-Specific Procedure Success	96.5% (571/592)	96.4% (570/591)	0.0% [-2.1%,2.1%]	1.000
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.59±0.43 (588)	2.61±0.44 (589)	-0.02 [-0.07,0.03]	0.436
In-Segment	2.21±0.49 (589)	2.24±0.49 (590)	-0.03 [-0.09,0.03]	0.302
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	6.04±10.43 (588)	6.23±10.03 (589)	-0.18 [-1.36,0.99]	0.757
In-Segment	20.39±10.26 (589)	20.11±9.38 (590)	0.28 [-0.84,1.41]	0.622
Eight-Month Follow-Up MLD (mm)				
In-Stent	1.99±0.56 (264)	1.62±0.70 (265)	0.37 [0.26,0.48]	<0.001
In-Segment	1.86±0.55 (264)	1.56±0.67 (265)	0.30 [0.19,0.40]	<0.001
Eight-Month Follow-up %DS				
In-Stent	27.91±17.30 (264)	42.24±21.73 (265)	-14.33 [-17.68,-10.97]	<0.001
In-Segment	32.67±16.27 (264)	44.33±20.45 (265)	-11.66 [-14.82,-8.50]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.46 (264)	1.03±0.59 (263)	-0.41 [-0.50,-0.32]	<0.001
In-Segment	0.36±0.46 (264)	0.72±0.61 (263)	-0.36 [-0.45,-0.27]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.5% (25/264)	33.2% (88/265)	-23.7% [-30.4%,-17.1%]	<0.001
In-Segment	13.3% (35/264)	34.7% (92/265)	-21.5% [-28.5%,-14.4%]	<0.001
Eight-Month Volume Obstruction (%)	17.34±10.27 (90)	29.55±17.58 (81)	-12.22 [-16.51,-7.92]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.99±1.66 (122)	3.98±1.72 (107)	1.01 [0.57,1.45]	<0.001
Eight-Month NIH Volume (mm^3)	30.15±21.66 (90)	53.51±39.80 (81)	-23.36 [-32.91,-13.81]	<0.001
In-Hospital MACE	2.5% (15/597)	2.9% (17/596)	-0.3% [-2.2%,1.5%]	0.725
MACE to 30 Days	2.9% (17/596)	3.7% (22/594)	-0.9% [-2.9%,1.2%]	0.421
MACE to 270 Days	7.3% (43/592)	14.4% (85/591)	-7.1% [-10.6%,-3.6%]	<0.001
MACE to 360 Days	8.8% (52/590)	15.6% (92/589)	-6.8% [-10.5%,-3.1%]	<0.001
MACE to 720 Days	9.9% (58/587)	18.1% (106/586)	-8.2% [-12.2%,-4.3%]	<0.001

Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
MACE to 1080 Days	12.0% (69/577)	20.7% (120/579)	-8.8% [-13.0%,-4.5%]	<0.001
Death to 1080 Days	3.3% (19/577)	4.5% (26/579)	-1.2% [-3.4%,1.0%]	0.362
Vascular Complications to 1080 Days	0.5% (3/577)	1.2% (7/579)	-0.7% [-1.8%,0.4%]	0.342
Major Bleeding to 1080 Days	1.2% (7/577)	2.4% (14/579)	-1.2% [-2.7%,0.3%]	0.185
Early Stent Thrombosis	0.5% (3/596)	1.2% (7/594)	-0.7% [-1.7%,0.4%]	0.224
Late Stent Thrombosis to 270 days	0.0% (0/592)	0.0% (0/591)	0.0% [--,--]	--
Late Stent Thrombosis to 360 days	0.0% (0/590)	0.0% (0/589)	0.0% [--,--]	--
Late Stent Thrombosis to 720 days	0.0% (0/587)	0.0% (0/586)	0.0% [--,--]	--
Late Stent Thrombosis to 1080 days	0.0% (0/577)	0.0% (0/579)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 1080 Days	1.0% (6/577)	1.2% (7/579)	-0.2% [-1.4%,1.0%]	1.000
Perforation to 1080 Days	0.5% (3/577)	0.3% (2/579)	0.2% [-0.6%,0.9%]	0.686
Target Vessel Revascularization to 30 days	1.2% (7/596)	1.2% (7/594)	-0.0% [-1.2%,1.2%]	1.000
Target Vessel Revascularization to 270 days	5.6% (33/592)	12.5% (74/591)	-6.9% [-10.2%,-3.7%]	<0.001
Target Vessel Revascularization to 360 days	7.5% (44/590)	14.1% (83/589)	-6.6% [-10.2%,-3.1%]	<0.001
Target Vessel Revascularization to 720 days	8.3% (49/587)	16.4% (96/586)	-8.0% [-11.8%,-4.3%]	<0.001
Target Vessel Revascularization to 1080 days	9.5% (55/577)	17.6% (102/579)	-8.1% [-12.0%,-4.2%]	<0.001
Target Vessel Failure to 30 days	3.2% (19/596)	3.7% (22/594)	-0.5% [-2.6%,1.6%]	0.638
Target Vessel Failure to 270 days	7.9% (47/592)	15.1% (89/591)	-7.1% [-10.7%,-3.5%]	<0.001
Target Vessel Failure to 360 days	10.0% (59/590)	16.6% (98/589)	-6.6% [-10.5%,-2.8%]	<0.001
Target Vessel Failure to 720 days	11.1% (65/587)	19.8% (116/586)	-8.7% [-12.8%,-4.6%]	<0.001
Target Vessel Failure to 1080 days	12.8% (74/577)	21.4% (124/579)	-8.6% [-12.9%,-4.3%]	<0.001
Target Lesion Revascularization to 30 days	0.8% (5/596)	1.2% (7/594)	-0.3% [-1.5%,0.8%]	0.579
Target Lesion Revascularization to 270 days	4.6% (27/592)	11.8% (70/591)	-7.3% [-10.4%,-4.2%]	<0.001
Target Lesion Revascularization to 360 days	5.9% (35/590)	13.1% (77/589)	-7.1% [-10.5%,-3.8%]	<0.001
Target Lesion Revascularization to 720 days	6.5% (38/587)	14.2% (83/586)	-7.7% [-11.1%,-4.2%]	<0.001
Target Lesion Revascularization to 1080 days	7.3% (42/577)	14.7% (85/579)	-7.4% [-11.0%,-3.8%]	<0.001

Kaplan-Meier Estimate	Endeavor (N=598 patients)	Driver (N=599 patients)	P-value†
*MACE-Free at 1080 days	88.3%	79.6%	<0.001
*TLR-Free at 1080 days	92.8%	85.4%	<0.001
*TVR-Free at 1080 days	90.6%	82.6%	<0.001
*TVF-Free at 1080 days	87.4%	78.9%	<0.001

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter.
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – DRIVER.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary end point is Target Vessel Failure at 9 months.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
* MACE free– No Death, MI, emergent CABG or target lesion revascularization.

Figure 8-3. Survival Free from Target Vessel Failure (at 1080 days)



TVF	0	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor													
# Entered	597	584	570	561	541	525	522	519	515	512	503	500	497
# Censored	0	6	1	2	4	2	1	2	2	7	0	1	108
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	13	8	8	18	12	1	2	2	1	2	3	2	2
% Survived	97.8%	96.5%	95.1%	92.1%	90.0%	89.9%	89.5%	89.2%	89.0%	88.6%	88.1%	87.8%	87.4%
SE	0.6%	0.8%	0.9%	1.1%	1.2%	1.3%	1.3%	1.3%	1.3%	1.3%	1.4%	1.4%	1.6%
Driver													
# Entered	596	580	565	540	500	485	478	473	470	460	453	450	448
# Censored	0	2	1	4	6	3	0	0	4	3	0	2	109
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	16	13	24	36	9	4	5	3	6	4	3	0	1
% Survived	97.3%	95.1%	91.1%	85.0%	83.5%	82.8%	81.9%	81.4%	80.3%	79.6%	79.1%	79.1%	78.9%
SE	0.7%	0.9%	1.2%	1.5%	1.5%	1.6%	1.6%	1.6%	1.7%	1.7%	1.7%	1.7%	2.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Wilcoxon	15.19	1	<0.001									
	Log-Rank	15.19	1	<0.001									

8.5 ENDEAVOR I Trial

Purpose: The purpose of this study was to demonstrate the safety and efficacy of the **Endeavor** Stent for the treatment of single *de novo* lesions in native coronary arteries. This study provides the longest follow-up experience available.

Conclusion: In selected patients, use of the **Endeavor** Stent provided favorable IVUS, angiographic, and clinical results through 1440 days of follow-up.

Design: This is a prospective, multi-center, non-randomized, single-arm study that enrolled 100 subjects at eight (8) study sites in Australia and New Zealand. To be eligible, a patient was required to have a *de novo* ischemic lesion (≤ 15 mm in length) of a native coronary artery with reference vessel diameter of 3.0 mm to 3.5 mm. The study allowed for use of 18 mm **Endeavor** Stents. A total of 100 patients were treated with the **Endeavor** Stent. After the procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 12 weeks. Angiographic follow up was performed at 4 and 12 months post-procedure. Clinical follow-up is available through 1440 days.

Demographics: Patients had a mean age of 59 years, there were 21% females, 16% had a history of diabetes mellitus, and 47% had a prior MI. Forty-three (43) percent of the lesions treated were in LAD, 23% were in LCX, 34% were in RCA, mean reference vessel diameter pre-procedure was 2.96 mm, mean pre-procedure minimal lumen diameter was 0.88 mm, mean pre-procedure percent diameter stenosis was 70.3%, and the mean lesion length was 10.9 mm (43% of patients had a lesion length < 10 mm and 56% of patients had a lesion length between 10 mm and 19.9 mm). No patients received IIb/IIIa inhibitors in this study.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. An independent Clinical Events Committee adjudicated clinical events and an independent Data Safety Monitoring Board monitored the trial.

Results: The primary safety endpoint of 30-day MACE was 1.0%. The cumulative MACE rate at 12, 24, 36 and 48 months was 2%, 3.0%, 6.1% and 7.2% respectively. There was minimal late lumen loss and consequential binary angiographic restenosis by 4 months, at 12-month in-stent late lumen loss was 0.58±0.44 mm and in-stent binary restenosis occurred in 4.3% of patients.

Table 8-8 summarizes the principal effectiveness and safety results of the ENDEAVOR I Trial through 1440 days.

Table 8-8: Principal Effectiveness and Safety Results

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Lesion Success	100.0% (100/100)
Device Success	100.0% (100/100)
Procedure Success	100.0% (100/100)
Device-Specific Procedure Success	100.0% (100/100)
Post- Procedure Minimal Lumen Diameter (MLD, in mm)	
In-Stent	2.84±0.35 (100)
In-Segment	2.52±0.42(100)
Post-Procedure % Diameter Stenosis (%DS)	
In-Stent	5.37±7.51 (100)
In-Segment	16.54±8.40 (100)
4-Month Follow-Up MLD (mm)	
In-Stent	2.52±0.44 (98)
In-Segment	2.29±0.46 (98)
4-Month Follow-up %DS	
In-Stent	14.40±13.10 (98)
In-Segment	22.36±12.08 (98)

Safety & Effectiveness Measures	Endeavor (N=100 patients)
4-Month Late Loss (mm)	
In-Stent	0.32±0.37 (98)
In-Segment	0.22±0.43 (98)
4-Month Binary Restenosis	
In-Stent	2.0% (2/98)
In-Segment	3.1% (3/98)
4-Month Volume Obstruction (%)	4.46±6.05 (94)
4-Month Minimal Lumen Area (mm^2)	5.96±1.66 (95)
4-Month NIH Volume (mm^3)	6.10±7.39 (94)
12-Month Follow-Up MLD (mm)	
In-Stent	2.26±0.49 (92)
In-Segment	2.08±0.47 (92)
12-Month Follow-up %DS	
In-Stent	21.75±15.35 (92)
In-Segment	28.00±13.41 (92)
12-Month Late Loss (mm)	
In-Stent	0.58±0.44 (92)
In-Segment	0.43±0.44 (92)
12-Month Binary Restenosis	
In-Stent	4.3% (4/92)
In-Segment	5.4% (5/92)
12-Month Volume Obstruction (%)	9.73±8.50 (86)
12-Month Minimal Lumen Area (mm^2)	5.69±1.74 (86)
12-Month NIH Volume (mm^3)	14.15±11.82 (86)
In-Hospital MACE	0.0% (0/100)
MACE to 30 Days	1.0% (1/100)
MACE to 270 Days	2.0% (2/100)
MACE to 360 Days	2.0% (2/98)
MACE to 720 Days	3.0% (3/99)
MACE to 1080 Days	6.1% (6/98)
MACE to 1440 Days	7.2% (7/97)
Death to 1440 Days	4.1% (4/97)
Vascular Complications to 1440 Days	3.1% (3/97)
Major Bleeding to 1440 Days	2.1% (2/97)
Early Stent Thrombosis	1.0% (1/97)
Late Stent Thrombosis to 270 days	0.0% (0/100)
Late Stent Thrombosis to 360 days	0.0% (0/98)
Late Stent Thrombosis to 720 days	0.0% (0/98)
Late Stent Thrombosis to 1080 days	0.0% (0/97)
Late Stent Thrombosis to 1440 days	0.0% (0/97)
Cerebrovascular Accident (CVA) to 1440 Days	1.0% (1/97)
Perforation to 1440 Days	0.0% (0/97)

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Target Vessel Revascularization to 30 days	1.0% (1/100)
Target Vessel Revascularization to 270 days	2.0% (2/100)
Target Vessel Revascularization to 360 days	2.0% (2/98)
Target Vessel Revascularization to 720 days	4.0% (4/99)
Target Vessel Revascularization to 1080 days	5.1% (5/98)
Target Vessel Revascularization to 1440 days	5.2% (5/97)
Target Vessel Failure to 30 days	1.0% (1/100)
Target Vessel Failure to 270 days	2.0% (2/100)
Target Vessel Failure to 360 days	2.0% (2/99)
Target Vessel Failure to 720 days	4.0% (4/99)
Target Vessel Failure to 1080 days	5.1% (5/98)
Target Vessel Failure to 1440 days	5.2% (5/97)
Target Lesion Revascularization to 30 days	1.0% (1/100)
Target Lesion Revascularization to 270 days	2.0% (2/100)
Target Lesion Revascularization to 360 days	2.0% (2/99)
Target Lesion Revascularization to 720 days	2.0% (2/99)
Target Lesion Revascularization to 1080 days	3.1% (3/98)
Target Lesion Revascularization to 1440 days	3.1% (3/97)

Kaplan-Meier Estimate	Endeavor (N=100 patients)
*MACE-Free at 1440 days	92.9%
*TLR-Free at 1440 days	96.9%
*TVR-Free at 1440 days	94.9%
*TVF-Free at 1440 days	94.9%

N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
The primary endpoint was 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
MLD = Minimal luminal diameter .
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair

Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
* MACE free– No Death, MI, emergent CABG or target lesion revascularization.

9.0 Individualization of Treatment

See also **Precautions-5.6 Use in Special Populations** and **Precautions-5.7 Lesion/Vessel Characteristics.**

The risks and benefits described above should be carefully considered for each patient before use of the **Endeavor** Zotarolimus-Eluting Coronary Stent System. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anticoagulation. Stenting is generally avoided in patients at risk of bleeding and for those with contraindicated anticoagulation therapy.

10.0 Patient Counseling Information

Physicians should consider the following in counseling the patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a zotarolimus eluting stent implant
- Discuss the risks/benefits issues for this particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term
- Discuss the risks of early discontinuation of the antiplatelet therapy

The following information is provided in the package or online for physicians to provide to their patients:

- A Patient Guide which includes information on the **Endeavor** Zotarolimus-Eluting Coronary Stent System, coronary artery disease, and the implantation procedure.
- A Patient Implant Card that is used to record information about the patient and the stent.

11.0 How Supplied

STERILE: **FOR SINGLE USE ONLY**. This product is sterilized with ethylene oxide (EO) and is nonpyrogenic. Do not use if the package is opened or damaged. Do not resterilize. Return product if package is opened or damaged to Medtronic Returned Goods. Contact your local Medtronic, Inc. Representative for return information.

CONTENTS: One (1) **Endeavor** Zotarolimus-Eluting Rapid Exchange Coronary Stent System.

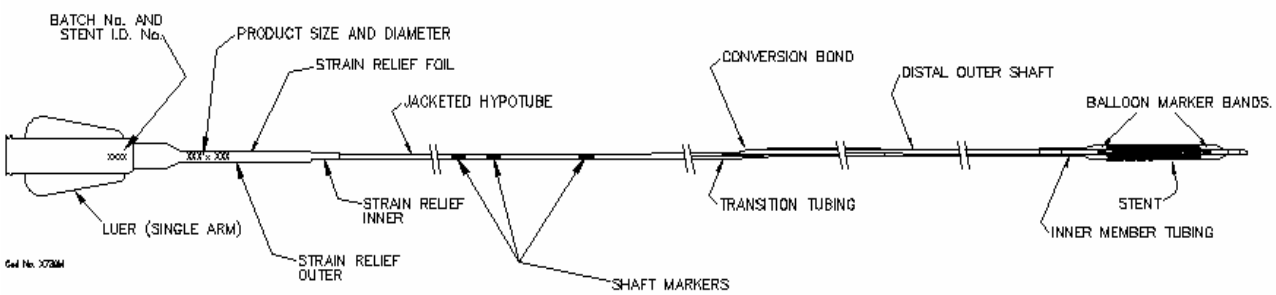
- One (1) Patient Implant Card
- One (1) Reference card to the electronic Instructions for Use

STORAGE: Store in the original container. Store at 25 ºC (77 ºF); excursions permitted to 15-30 ºC (59-86 ºF). Use by the “Use By” date noted on the package.

DISPOSAL INSTRUCTIONS:
After use, dispose of product and packaging in accordance with hospital, administrative and/ or local government policy.

12.0 Operator's Manual

Figure 12-1. Diagram of the Endeavor Zotarolimus-Eluting Coronary Stent System Rapid Exchange (RX) Delivery System



12.1 Access to Package Holding Sterile Stent Delivery System

Tear open the outer foil pouch to reveal the inner pouch. Do not drop or hand the inner pouch into the sterile field. Remove the inner pouch from the outer foil pouch. Peel open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
Note: The outer surface of the inner pouch is not sterile.

12.2 Inspection Prior to Use

Before opening the product, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Do not use after the "Use By" date. If the sterile package is intact, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the product if any damage to the packaging is noted.

A protective sheath covers the stent mounted on the balloon. After removal of the sheath, visually inspect the stent to ensure that it has not been damaged or displaced from its original position (between proximal and distal marker bands) on the balloon.

12.3 Materials Required

Quantity	Material
N/A	Guiding catheter [≥ 5 F (1.4 mm, 0.056 inch) inner diameter]
2-3	20 cc syringe
1,000 u /500 cc	Heparinized normal saline
1	Guidewire [≤ 0.014 inch (0.36 mm) diameter]
1	Rotating hemostatic valve
N/A	Contrast medium diluted 1:1 with heparinized normal saline
1	Inflation device
1	Stopcock (3-way minimum)
1	Torque device
N/A	Appropriate anticoagulation and antiplatelet drugs

12.4 Preparation Precaution

- DO NOT use product if the protective sheath is not present or the stent is damaged/displaced.
- AVOID manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- DO NOT apply negative or positive pressure to the balloon during the delivery system preparation.

12.4.1 Guidewire Lumen Flush

Flush the stent system guidewire lumen with heparinized normal saline until the fluid exits the distal tip.

12.4.2 Delivery System Preparation

Step	Action
1.	Prepare the guide catheter and guidewire according to the manufacturer's instructions.
2.	Remove the stent delivery system from the package.
3.	Remove protective sheath covering from the stent mounted balloon.
4.	Fill a 20 cc syringe with 5 cc of contrast/heparinized normal saline mixture (1:1).
5.	Attach to delivery system and apply negative pressure for 20-30 seconds.
6.	Slowly release pressure to allow negative pressure to draw mixture into balloon lumen.
7.	Detach syringe and leave a meniscus of mixture on the hub of the balloon lumen.
8.	Prepare inflation device in standard manner and purge to remove all air from syringe and tubing.
9.	Attach inflation device to catheter directly ensuring no bubbles remain at connection.
10.	Leave on ambient pressure (neutral position). ***Note***: Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent.

12.5 Delivery Procedure

Step	Action
1.	Prepare the vascular access site according to standard practice.
2.	**Pre-dilate the lesion with a PTCA catheter.** Pre-dilatation must be performed using a balloon with the following three characteristics: • A diameter at least 0.5 mm smaller than the treatment stent. • A length equal to or shorter than the lesion length to be dilated. • A length shorter than the stent to be implanted.
3.	Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible. **Note:** If resistance is encountered, **do not force passage**. Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine**.**
4.	Ensure guiding catheter stability before advancing the **Endeavor** Coronary Stent Delivery System into the coronary artery. Carefully advance the **Endeavor** Coronary Stent Delivery System into the hub of the guiding catheter.
5.	Advance the stent delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent. If the position of the stent is not optimal, it should be carefully repositioned or removed (see **Precautions – 5.12 Stent/System Removal Precautions**). Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.
6.	Sufficiently tighten the rotating hemostatic valve. The stent is now ready to be deployed. ***Note***: Should unusual resistance be felt at any time during either lesion access or removal of the stent delivery system before stent implantation, do not force passage. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. See **Precautions – 5.12 Stent/System Removal Precautions** for specific stent delivery system removal instructions.

12.6 Deployment Procedure

Step	Action
1.	Prior to stent expansion, utilize high-resolution fluoroscopy to verify the stent has not been damaged or shifted during positioning.
2.	Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3.	Do not exceed Rated Burst Pressure. The **Endeavor** Stent should not be expanded to a diameter beyond 0.5 mm of its nominal expansion.
4.	Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

12.7 Removal Procedures

Step	Action
1.	Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 15 seconds, for full balloon deflation. Longer stents may require more time for deflation. Deflation of the balloon should be confirmed by absence of contrast within the balloon.
2.	Open the hemostatic valve to allow removal of the delivery system.
3.	Maintain position of guiding catheter and guidewire. Very slowly, withdraw the balloon from the stent, maintaining negative pressure, allowing movement of the myocardium to gently dislodge the balloon from the stent.
4.	After removal of the delivery system, tighten the hemostatic valve.
5.	Repeat angiography and visually assess the vessel and the stent for proper expansion. ***Note***: Observation of the patient and angiographic evaluation of the stent site should be performed periodically within the first 30 minutes after stent placement. If stent placement is associated with the onset of thrombus or suspected thrombus in the region of the stented segment, an intracoronary infusion of a thrombolytic agent is recommended.

12.8 In-vitro Information

Table 12-1: Inflation Pressure Recommendations						
Pressure				Stent Nominal Inner Diameter (mm)		
atm	**kPa**	**bar**		**2.5**	**3.0**	**3.5**
6	**608**	**6.08**		2.3	2.9	3.3
7	**709**	**7.09**		2.3	2.9	3.4
8	**811**	**8.11**		2.4	3.0	3.4
9	**912**	**9.12**	Nominal	2.4	3.0	3.5
10	**1013**	**10.13**		2.5	3.1	3.5
11	**1115**	**11.15**		2.5	3.1	3.6
12	**1216**	**12.16**		2.5	3.2	3.6
13	**1317**	**13.17**		2.6	3.2	3.6
14	**1419**	**14.19**		2.6	3.2	3.7
15	**1520**	**15.20**		2.6	3.3	3.7
16	**1621**	**16.21**	RBP*	2.6	3.3	3.8
17	**1723**	**17.23**		2.7	3.3	3.8
18	**1824**	**18.24**		2.7	3.4	3.8

*Do not exceed the rated burst pressure (RBP)

12.9 Further Dilatation of Stented Segment

The stent delivery balloon may not be used for post-dilatation. Post-dilatation may be performed with appropriately sized (length and diameter) balloons to ensure that the stent is in full contact with the vessel wall. To achieve this, a balloon to artery ratio of 1.0 to 1.1:1.0 should be used to leave a residual diameter stenosis of near 0% (with a recommended maximum of no greater than 10%). Whenever possible, avoid the use of grossly oversized balloons (balloon:artery ratio > 1.2).

Precaution: Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilatation Limits
2.50 mm	3.00 mm
3.00 mm	3.50 mm
3.50 mm	4.00 mm

All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. This further expansion should be performed using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

13.0 Reuse Precaution Statment

For single use only. Do not resterilize or reuse.

14.0 Disclaimer of Warranty and Limitation of Remedy

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ATTACHMENT 9C Draft Endeavor Multi-Exchange II (MX2) Instructions For Use

Instructions for Use

ENDEAVOR® Zotarolimus-Eluting Coronary Stent System
Multi Exchange II (MX^2) Delivery System

Caution: Federal (USA) law restricts this product to sale by or on the order of a physician

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1.0 Endeavor Zotarolimus-Eluting Coronary Stent System

The **Endeavor** Zotarolimus-Eluting Coronary Stent System (**Endeavor** Coronary Stent System) is a device / drug combination product comprised of device components (Driver® Coronary Stent and Micro-Driver® Coronary Stent and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus contained in a polymer coating).

The characteristics of the **Endeavor** Coronary Stent System are described in **Table 1-1**.

Table 1–1: Device Component Description

Component	Endeavor Zotarolimus-Eluting Multi Exchange II (MX^2) Delivery System	
Available Stent Diameters (mm):	2.5	3.0, 3.5
Available Stent Lengths (mm):	8† 12, 14, 18, 24, 30	9†, 12, 15, 18, 24, 30
Stent Material :	A cobalt based alloy (MP35N) – the Driver & Micro-Driver Stents	
Drug Component:	A spray coating of polymer carrier loaded with zotarolimus is applied to the stent at a drug loading of 10 µg/mm stent length. The maximum nominal drug content on the longest stent (30 mm) is 300 µg.	
Delivery System Usable Length:	138 cm	
Delivery System Luer Adapter Ports:	Single access port to inflation lumen. Guidewire exits through a Z-component located on the proximal shaft. Designed for guidewire ≤0.014” (0.36mm).	
Stent Delivery Balloon:	A semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. There are proximal and distal pillows formed on either side of the stent which aid in holding the stent in position. Two radiopaque balloon markers are located on the distal section of the inner member and are positioned to mark the working length of the balloon.	
Balloon Inflation Pressure:	Nominal Pressure: 9 atm (912 kPa, 9.12 bar) Rated Burst Pressure: 16 atm (1621 kPa, 16.21 bar)	
Guide Catheter Compatibility:	0.064” minimum (6F)	
Distal Section OD:	Distal = 2.7F	
	Middle = 3.0F	
	Proximal = 3.8F	
Proximal OD:	2.3F x 4.2F (Oval)	

† The 8 mm and 9 mm stent lengths are used for bailout procedures or insufficient lesion coverage.

1.1 Device Component Description

The device component consists of the **Driver** or **Micro-Driver** Balloon-Expandable Coronary Stent pre-mounted onto an **Endeavor** Stent delivery system (SDS). The range of stent diameters is made possible by varying the element lengths and number of crowns on the stent. The 2.5 mm diameter cobalt-based alloy stent (**Micro-Driver**) has 1.2 mm length elements and seven crowns; the 3.0 and 3.5 mm diameter cobalt-based stents (**Driver**) have 1.0 mm length elements and ten crowns. The stent is crimped on various size delivery catheter balloons, which are sized from 2.5 to 3.5 mm.

1.2 Drug Component Description

The drug component of the **Endeavor** Coronary Stent System consists of zotarolimus (the active ingredient) and Phosphorylcholine (PC) polymer (the inactive ingredient).

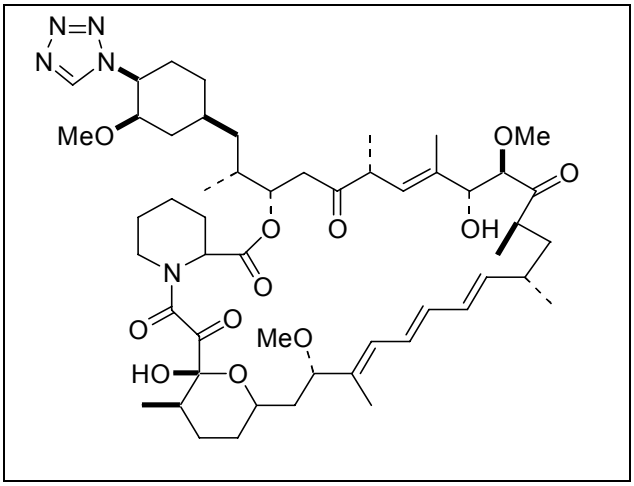
1.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the **Endeavor** Stent is zotarolimus. It is a tetrazole-containing macrocyclic immunosuppressant.

The chemical name of zotarolimus is: [3S-[3R*[S*(1R*,3S*,4R*)],6S*, 7E,9S*,10S*,12S*,14R*,15E,17E,19E, 21R* ,23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27, 32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown below:

Figure 1-1: Zotarolimus Chemical Structure



Zotarolimus has extremely low water solubility and is a lipophilic compound but is freely soluble in Propylene glycol, Acetone, Toluene, Acetonitrile, Ethanol, Benzyl alcohol and DMSO. The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

Zotarolimus does not have any ionizable group(s) in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

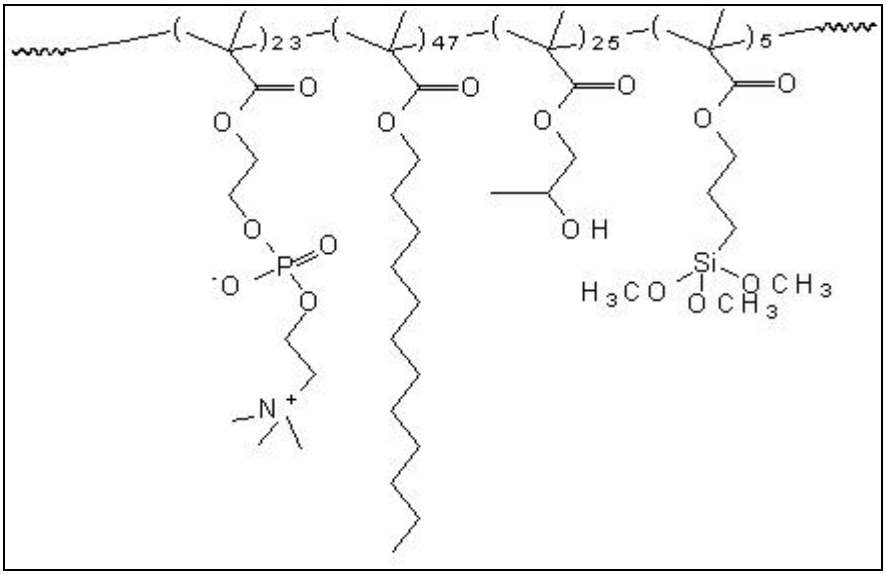
1.2.2 Polymer Component Description

The only inactive ingredient in the **Endeavor** Stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for zotarolimus. The PC polymer consists of 2-Methacryloyloxyethyl phosphorylcholine that is synthesized and then used in the preparation of crosslinked polymer membranes with lauryl methacrylate, hydroxypropyl methacrylate and trimethoxysilylpropyl methacrylate (crosslinker) co-monomers. The PC polymer contains a biocompatible component which mimics the body's own chemistry, a hydrophobic component for adhesion and stability, and a crosslinking component for robustness.

The molecular weight of PC polymer was estimated using viscometry and resulted in values of Mv ranging from 160,000 to 270,000. These figures were supported by light scattering values of Mw (g/mol) ranging from 100,000 to 200,000.

PC polymer in a solvent carrier (ethanol) is applied to the Driver Stent to form the base layer coat of the Endeavor stent. The polymer is also mixed with the drug zotarolimus and then applied to the base layer-coated stents. Finally, a drug-free overspray of PC polymer is applied after the stent has been coated with the drug/polymer formulation and it has been crimped onto the balloon. The drug/polymer coating is applied to the entire surface (i.e. luminal and abluminal) of the stent. The structural formula of the polymer is shown below:

Figure 1-2. PC Polymer Structure*



* PC Technology™ is licensed under patents or patent applications owned by Biocompatibles

1.2.3 Product Matrix and Zotarolimus Content

Table 1–2: Endeavor Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number MX[2]	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
EN25008MX	2.50	8*	84
EN30009MX	3.00	9	90
EN35009MX	3.50	9	90
EN25012MX	2.50	12	120
EN30012MX	3.00	12	120
EN35012MX	3.50	12	120
EN25014MX	2.50	14*	144
EN30015MX	3.00	15	150
EN35015MX	3.50	15	150
EN25018MX	2.50	18	180
EN30018MX	3.00	18	180
EN35018MX	3.50	18	180
EN25024MX	2.50	24	240
EN30024MX	3.00	24	240
EN35024MX	3.50	24	240
EN25030MX	2.50	30	300
EN30030MX	3.00	30	300
EN35030MX	3.50	30	300

* Note the 8 mm and 14 mm stent lengths have a total nominal drug content of 84 µg and 144 µg respectively since the actual stent length for the 8 mm stent is 8.4 mm and the actual stent length for the 14 mm stent is 14.4 mm.

2.0 Indications

The **Endeavor** Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to discrete *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5mm to ≤ 3.5mm.

3.0 Contraindications

Use of the **Endeavor** Zotarolimus-Eluting Coronary Stent System is contraindicated for use in:

- Patients with a known hypersensitivity to zotarolimus or structurally-related compounds..
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Patients with a known hypersensitivity to phosphorylcholine polymer or its individual components (see details in **Section 1.2.2 – Polymer Component Description** for details).

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

4.0 Warnings

- Please ensure that the inner package has not been opened or damaged as this indicates the sterile barrier has been breached.
- The use of this product carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.
- During guidewire exchange, the wire should be manipulated while under high quality fluoroscopic observation. Failure to do so may result in the wire moving into the vessel resulting in damage to the vessel wall.

5.0 Precautions

5.1 General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long term outcome following repeat dilatation of endothelialized stents is not well characterized.
- Risks and benefits of the stent should be assessed for patients with history of severe reaction to contrast agents.
- Do not expose or wipe the product with organic solvents, such as alcohol, or detergents,

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In the ENDEAVOR I, ENDEAVOR II, and ENDEAVOR III studies, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 12 weeks post-procedure. In ENDEAVOR IV, clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 6 months post-procedure in order to ensure proper blinding to the randomized comparator, the Taxus stent. Aspirin was administered pre-procedure and continued indefinitely. Based on empirical data from the Endeavor randomized clinical trials (ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV), approximately 82% of the patients remained on dual antiplatelet therapy at 6 months. See **Section 8, Clinical Studies,** for more specific information.
- It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a drug eluting stent and its associated recommended

antiplatelet therapy is the appropriate treatment of choice. Following PCI, recommendations of a surgical or dental procedure and the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy.

5.3 Use of Multiple Stents

The long-term effects of zotarolimus are currently unknown. In clinical trials of the **Endeavor** Stent, patients were treated with no more than 48 mm of total **Endeavor** Stent, except in situations involving bailout stenting. The extent of the patient's exposure to the drug and polymer coating is directly related to the number of stents and stent length implanted.

When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. Data obtained from in vitro corrosion tests using F562 CoCr alloy stent (Medtronic **Driver** Coronary Stent) in combination with a 316L stainless steel alloy stent (Medtronic **S7** Coronary Stent) do not suggest an increased risk of in vivo corrosion. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.

Potential interactions of the **Endeavor** Stent with other drug-eluting or coated stents have not been evaluated.

5.4 Brachytherapy

The safety and effectiveness of the **Endeavor** Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of the use of brachytherapy to treat in-stent restenosis in an **Endeavor** Stent has not been established. Both vascular brachytherapy and the **Endeavor** Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with **Endeavor** Stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

- There are no adequate and well-controlled studies in pregnant women or men intending to father children.
- The **Endeavor** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

5.6.2 Lactation

It is not known whether zotarolimus is excreted in human milk. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

5.6.3 Gender

Clinical studies of the **Endeavor** Stent did not find any significant differences in safety and effectiveness for male and female patients.

5.6.4 Ethnicity

Clinical studies of the **Endeavor** Stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity.

5.6.5 Pediatric Use

The safety and effectiveness of the **Endeavor** Stent in pediatric patients below the age of 18 years have not been established.

5.6.6 Geriatric Use

Clinical studies of the **Endeavor** Stent did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.7 Lesion/Vessel Characteristics

The safety and effectiveness of the **Endeavor** Stent have not yet been established in the following patient populations:

- Patients with unresolved vessel thrombus at the target lesion site
- Patients with reference vessel diameters <2.5 mm or >3.5 mm.
- Patients with lesions located in saphenous vein grafts, in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor flow distal to the identified lesions.
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.
- Patients for longer than 48 months of follow-up.
- Patients with severe calcification in the lesion.

5.8 Drug Interactions

While no specific clinical data are available, drugs, like sirolimus, that act through the same binding protein (FKBP) may interfere with the efficacy of zotarolimus. Zotarolimus is metabolized by CYP3A4, a human cytochrome P450 enzyme. Strong inhibitors of CYP3A4 (e.g., ketoconazole) might cause increased zotarolimus exposure to levels associated with systemic effects, especially if multiple stents are deployed. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

5.9 Magnetic Resonance Imaging (MRI)

Non-clinical testing on single and overlapped stents has demonstrated that the Endeavor Zotarolimus-eluting coronary stent is MR Conditional. It can be scanned safely under the following conditions:

Single Stenting (Stent Length 30mm)	**Overlapped Stenting (Total Length 55mm)**
Static magnetic field of 3 - Tesla	Static magnetic field of 3 - Tesla
Spatial gradient field of 525 Gauss/cm	Spatial gradient field of 720 Gauss/cm
Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of scanning	Maximum whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning

In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of MR scanning in a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.	In non-clinical testing, the Endeavor Zotarolimus-eluting coronary stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.
The Endeavor stent should not move or migrate when exposed to MR scanning immediately post-implantation.	
The image artifact extends approximately 9 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Signa, General Electric Medical Systems (software version 9.0) MR system with a send-receive RF body coil.	The image artifact extends approximately 10 mm from the device/lumen centerline when scanned in nonclinical testing using a 3 Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR system with a send-receive RF body coil.

5.10 Stent Handling Precautions

- For single use only. The **Endeavor** Coronary Stent System is provided sterile. Do not resterilize or reuse this product. Note the "Use By" date on the product label. (See Reuse Precaution Statement, Section 13.0). Do not use if package or product has been opened or damaged.
- The foil pouch is not a sterile barrier. The pouch contained within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is not sterile.**
- Do not remove the contents of foil pouch until immediately prior to the use of device.
- Do not remove the stent from the delivery balloon – removal may damage the stent and polymer coating and/or lead to stent embolization. The **Endeavor** Coronary Stent System is intended to perform as a system. The stent is not designed to be crimped onto another delivery device.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the rotating hemostatic valve and guiding catheter hub.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may cause coating damage, contamination or dislodgement of the stent from the delivery system balloon.
- The **Endeavor** Stent must not be exposed to any direct handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug elution.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.
- The **Endeavor** Coronary Stent Delivery System should not be used in conjunction with any other stents or for post-dilatation.
- In the event the **Endeavor** Stent is not deployed contact your local Medtronic, Inc. representative for return information.

5.11 Stent Placement Precautions

- The vessel should be pre-dilated with an appropriately sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 12.5 – Delivery Procedure**.
- Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in **Section 12.0 – Operator's Manual**.

- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Device Component Description** in **Table 1-1**).
- Do not induce negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- In smaller or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection.
- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel (see **Precautions – 5.12 Stent/System Removal Precautions**).
- Placement of the stent has the potential to compromise side branch patency.
- Do not attempt to pull an unexpanded stent back through the guiding catheter as dislodgement of the stent from the balloon may occur. Remove as a single unit per instructions in **Precautions – 5.12 Stent/System Removal Precautions**.
- Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure that the stent is in full contact with the arterial wall upon deflation of the balloon.
- Stent retrieval methods (e.g., use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.
- Administration of appropriate anticoagulant, antiplatelet and coronary vasodilator therapy is critical to successful stent implantation.

5.12 Stent/System Removal Precautions

If removal of a stent system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the stent delivery system, and cautiously withdraw the stent delivery system into the guide catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guide catheter, the Stent Delivery System and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.

When removing the Stent Delivery System and guiding catheter as a single unit:

- Do not retract the Stent Delivery System into the guiding catheter. Maintain guidewire placement across the lesion and carefully pull back the Stent Delivery System until the proximal balloon marker of the Stent Delivery System is aligned with the distal tip of the guiding catheter.
- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten, allowing safe withdrawal of the Stent Delivery System into the guiding catheter and the subsequent removal of the Stent Delivery System and the guiding catheter from the arterial sheath.

  Failure to follow these steps and/or applying excessive force to the Stent Delivery System can potentially result in loss or damage to the stent and/or Stent Delivery System components such as the balloon.

5.13 Post-Procedure

- Care should be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Post-dilatation: All efforts should be made to assure that the stent is not under dilated. If the deployed stent is not fully apposed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2 mm) than the stent. The post-dilatation can be done using a low-profile, high pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. **Do not use the stent delivery balloon for post-dilatation.**
- Non-clinical testing on single and overlapped stents has demonstrated that the **Endeavor** Zotarolimus-eluting coronary stent is MR Conditional (see **Precautions – 5.9 Magnetic Resonance Imaging (MRI)**). MR imaging quality may be compromised if the area of interest is in the same area of the position of the stent.
- Antiplatelet therapy should be administered post-procedure (see **Precautions – 5.2 Pre- and Post-Procedure Antiplatelet Regimen**). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.

6.0 Drug Information

6.1 Mechanisms of Action

The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control.

6.2 Pharmacokinetics of the Endeavor Stent

The pharmacokinetics of zotarolimus delivered from the **Endeavor** Coronary Stent System has been determined in patients with coronary artery disease after implantation in the ENDEAVOR US Pharmacokinetic trial. The dose of zotarolimus was calculated from the total implanted stent length; the parameters determined from these patients are provided in **Table 6-1**.

Table 6-1: Zotarolimus Pharmacokinetics in Patients after Implantation of Endeavor-Zotarolimus Eluting Coronary Stents

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	1.584	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
$AUC_{0\text{-last}}$	(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
$AUC_{0\text{-inf}}$	(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
B	(1/h)	0.010	0.013	0.012 ± 0.003	0.012 ± 0.002	0.010	0.012 ± 0.003	0.010	0.012
$t_{½}$‡	(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
Cmax Maximum blood concentration
Tmax Time to Cmax
$AUC_{0\text{-last}}$ Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration
$AUC_{0\text{-inf}}$ AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).
t½ Harmonic mean half-life
CL/F Mean apparent clearance

a. Primary dose groups
‡ Harmonic mean ± pseudo-standard deviation
† No SD was reported when N ≤ 2
§ Mean only
# N = 6

The results in **Table 6-1** show that pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 2), 180, 240 and 300 µg, following the implantation of **Endeavor** Zotarolimus-Eluting Stents as illustrated by dose proportional increases in C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$. Mean apparent clearance and harmonic mean half-life for the primary dose groups ranged from 2.8 to 3.5 L/h and 57.5 to 59.7 h, respectively. The mean time to reach peak systemic concentration (T_{max}) ranged from 1.2 to 1.5 h after stent implantation.

6.3 Pharmacokinetics following Intravenous Administration of Zotarolimus

Zotarolimus pharmacokinetic activity has been determined following intravenous administration in healthy subjects. **Table 6-2** provides a summary of the pharmacokinetic analysis.

Table 6-2: Pharmacokinetic Parameters (Mean ± standard deviation) in Patients Following Intravenous Administration of Zotarolimus

PK Parameters	Units	**200µg QD** (N = 15)		**400µg QD** (N= 16)		**800µg QD** (N=16)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max}	(ng/mL)	11.41± 1.38[¥]	11.93 ± 1.25	21.99 ± 3.79	23.31± 3.15	37.72 ± 7.00	41.79 ± 6.68
T_{max}	(h)	1.05 ± 0.04[¥]	1.03 ± 0.04	1.00 ± 0.14	1.05 ± 0.04	1.03 ± 0.04	1.03 ± 0.05
$AUC_{0\text{-}24}$	(ng•h/mL)	34.19 ± 4.39[¥]	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
$t_{1/2}$[$]	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL [b]	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

[¥] N = 16; $ Harmonic mean ± pseudo-standard deviation

[b] Clearance data is calculated using compartmental methods. All other data presented in Table 6-2 is calculated using non-compartmental methods.

When administered intravenously for 14 consecutive days, zotarolimus showed dose proportionality. Renal excretion is not a major route of elimination for zotarolimus as approximately 0.1% of the dose was excreted as unchanged drug in the urine per day. In multiple doses of 200, 400 and 800 µg, zotarolimus was generally well tolerated by the subjects. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study.

6.4 Metabolism

Zotarolimus undergoes oxidative metabolism in the liver to form the desmethyl and hydroxylated metabolites of the parent drug. Further metabolism can lead to the formation of hydroxyl-demethyl and dihydroxyl-demethyl metabolites. Enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities, however the IC_{50} values (3 µM and above) are many fold higher than the systemic concentrations expected following implantation of a drug-eluting stent. The anticipated zotarolimus blood levels in stented patients are expected to be less than 0.004 µM, suggesting that clinically significant drug-drug interactions are unlikely.

6.5 Mutagenesis, Carcinogenicity and Reproductive Toxicology

6.5.1 Mutagenesis

Zotarolimus was not genotoxic in a standard battery of tests.

6.5.2 Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of zotarolimus.

6.5.3 Reproductive Toxicology

No effect on fertility or early embryonic development in female rats following the administration of zotarolimus was observed at intravenous dosages up to 100 µg/kg/day (approximately 5

times the maximum blood level and about 11 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus). Administration at a dosage of 300 µg/kg/day (approximately 10 times the maximum blood level and about 28 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus) resulted in embryotoxicity and embryolethality.

For male rats, there was no effect on fertility rate at intravenous dosages up to 300 µg/kg/day (approximately 13 times the maximum blood level and about 50 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus) administered for 28 days prior to mating. No effects on testicular toxicity were observed as a result of chronic exposure when administered for approximately 70 days at dosages of 10 µg/kg/day (approximately 1.3 times the maximum blood level and about 10 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus). Testicular changes observed at higher doses were reversible after 10 weeks.

6.6 Pregnancy

There are no adequate and well-controlled studies in pregnant women with zotarolimus.

Administration of zotarolimus to pregnant female rats in a developmental toxicity study at an intravenous dosage of 60 µg/kg/day (approximately 4 times the maximum blood level and about 5 times the cumulative blood exposure provided by **Endeavor** Stents eluting 480 µg zotarolimus) resulted in embryolethality. Fetal ossification delays were also observed at this dosage, but no major fetal malformations or minor fetal anomalies were observed in this study.

No embryo-fetal effects were observed in pregnant rabbits administered zotarolimus in a developmental toxicity study at intravenous dosages up to 100 µg/kg/day (approximately 19 times the maximum blood level and about 22 times the cumulative blood exposure provided by **Endeavor** Stents coated with 480 µg zotarolimus).

6.7 Lactation

It is not known whether zotarolimus is excreted in human milk. The potential adverse reactions in nursing infants from zotarolimus have not been determined.

7.0 Adverse Events

7.1 Observed Adverse Events

The incidence of adverse events attributed to the drug zotarolimus was determined in intravenous escalating and multiple dose studies. In the single-escalating dose study the proportion of subjects reporting treatment-emergent adverse events was slightly lower among subjects who received doses of zotarolimus than those who received placebo for zotarolimus. The most common treatment-emergent adverse events associated with zotarolimus were injection site reaction, pain, and circumoral paresthesia. There were no serious adverse events reported in this study. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles. There were no apparent differences among the doses with regard to safety. **Table 7-1** provides a summary of the analysis.

Table 7-1: Summary of Treatment-Emergent Adverse Events reported by two or more subjects in any one treatment by Body Systems and COSTART Term in the single-escalating dose study

BODY SYSTEMS	COSTART Term	All Placebo N=20(%)	Zotarolimus 100 µg N=8(%)	Zotarolimus 300µg N=8(%)	Zotarolimus 500µg N=8(%)	Zotarolimus 700µg N=8(%)	Zotarolimus 900µg N=8(%)
Body as a whole	Headache	3 (15%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
	Pain	7 (35%)	1 (13%)	0 (0%)	5 (63%)	5 (63%)	2 (25%)
Digestive System	Diarrhea	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nervous System	Circumoral Paresthesia	0 (0%)	0 (0%)	0 (0%)	3 (38%)	0 (0%)	0 (0%)
Skin and Appendage	Injection site Reaction	8 (40%)	1 (13%)	5 (63%)	2 (25%)	1 (13%)	5 (63%)

In the multiple dose study the proportion of subjects reporting treatment-emergent adverse events was similar among subjects who received doses of zotarolimus and the most common treatment-emergent adverse events associated with zotarolimus were headache, pain, injection site reaction, dry skin, abdominal pain, diarrhea and rash. There were no deaths or other serious adverse events. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for vital signs, laboratory safety assessments and physical examinations were unremarkable for each treatment group. No clinically significant physical examination results, vital signs or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles or overall drug safety. **Table 7-2** provides a summary of the analysis.

Table 7-2: Summary of Treatment-Emergent Adverse Events reported by two or more subjects in any one treatment by Body Systems and COSTART Term in the multiple dose study

BODY SYSTEM	COSTART Term	All Placebo (N = 16) N (%)	200 µg QD (N = 16) N (%)	400 µg QD (N = 16) N (%)	800 µg QD (N = 16) N (%)
Body as a whole	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)
Digestive System	Diarrhea	1 (4)	0 (0)	1 (6)	0 (0)
Skin and Appendage	Dry Skin	0 (0)	0 (0)	2 (13)	0 (0)
	Rash	0 (0)	1 (6)	1 (6)	0 (0)

Primary adverse event experience comes from four clinical studies, the ENDEAVOR IV, the ENDEAVOR III, the ENDEAVOR II and the ENDEAVOR I trial. See **Section 8 – Clinical Studies** for more complete description of the study design and results.

The ENDEAVOR IV, III, II and I trials have evaluated the performance of the **Endeavor** Stent in patients with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. Major study characteristics are summarized in **Table 8-1**. Principal adverse events are shown in **Table 7-3**.

Table 7-3: Principal Adverse Events

Description of Event	ENDEAVOR IV to 270 days		Endeavor III to 720 days		Endeavor II to 1080 days		Endeavor I to 1440 days
	Endeavor (N=773 patients)	Control (N=775 patients)	Endeavor (N=323 patients)	Control (N=113 patients)	Endeavor (N=598 patients)	Control (N=599 patients)	Endeavor (N=100 patients)
In-Hospital							
MACE	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Myocardial Infarction (Q wave or Non-Q wave)	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
Q wave MI	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.3% (2/596)	0.0% (0/100)
Non-Q wave MI	0.5% (4/773)	1.9% (15/775)	0.6% (2/323)	3.5% (4/113)	2.3% (14/597)	2.3% (14/596)	0.0% (0/100)
Target Lesion Revascularization	0.4% (3/773)	0.5% (4/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
TL-CABG	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TL-PTCA	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Revascularization non Target Lesion	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-CABG	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
TV/non-TL-PTCA	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Target Vessel Revascularization	0.4% (3/773)	0.6%(5/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Target Vessel Failure	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Perforation	0.1% (1/773)	0.4% (3/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Stent Thrombosis (acute)	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.3% (2/597)	0.3% (2/596)	0.0% (0/100)
Cerebrovascular Accident (CVA)	0.1% (1/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Out-of-Hospital							
MACE	4.7% (35/740)	3.0% (22/734)	8.6% (27/313)	8.9% (10/112)	9.5% (55/577)	18.7% (108/579)	7.2% (7/97)
Death	0.7% (5/740)	0.8% (6/734)	1.6% (5/313)	4.5% (5/112)	3.1% (18/577)	4.5% (26/579)	4.1% (4/97)
Myocardial Infarction (Q wave or Non-Q wave)	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.7% (4/577)	1.6% (9/579)	1.0% (1/97)
Q wave MI	0.0% (0/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.7% (4/579)	0.0% (0/97)
Non-Q wave MI	0.7% (5/740)	0.3% (2/734)	0.0% (0/313)	0.0% (0/112)	0.5% (3/577)	0.9% (5/579)	1.0% (1/97)
Target Lesion Revascularization	3.8% (28/740)	2.2% (16/734)	7.0% (22/313)	4.5% (5/112)	6.8% (39/577)	14.3% (83/579)	3.1% (3/97)
TL-CABG	0.4% (3/740)	0.4% (3/734)	1.3% (4/313)	0.0% (0/112)	0.5% (3/577)	1.0% (6/579)	1.0% (1/97)

TL-PTCA	3.5% (26/740)	1.8% (13/734)	5.8% (18/313)	4.5% (5/112)	6.4% (37/577)	13.5% (78/579)	3.1% (3/97)
Target Vessel Revascularization non Target Lesion	2.0% (15/740)	2.6% (19/734)	8.3% (26/313)	6.3% (7/112)	2.9% (17/577)	4.8% (28/579)	2.1% (2/97)
TV/non-TL-CABG	0.4% (3/740)	0.1% (1/734)	1.0% (3/313)	0.0% (0/112)	0.2% (1/577)	0.3% (2/579)	1.0% (1/97)
TV/non-TL-PTCA	1.8% (13/740)	2.5% (18/734)	7.7% (24/313)	6.3% (7/112)	2.8% (16/577)	4.7% (27/579)	1.0% (1/97)
Target Vessel Revascularization	5.1% (38/740)	4.4% (32/734)	13.7% (43/313)	9.8% (11/112)	9.0% (52/577)	17.4% (101/579)	5.2% (5/97)
Target Vessel Failure	5.8% (43/740)	4.8% (35/734)	13.7% (43/313)	10.7% (12/112)	10.4% (60/577)	19.2% (111/579)	5.2% (5/97)
Stent Thrombosis (sub-acute/<30 days)	0.1% (1/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.2% (1/577)	0.9% (5/579)	1.0% (1/97)
Stent Thrombosis (late /≥ 30 days)	0.4% (3/740)	0.0% (0/734)	0.0% (0/313)	0.0% (0/112)	0.0% (0/577)	0.0% (0/579)	0.0% (0/97)
Cerebrovascular Accident (CVA)	0.5% (4/740)	0.5% (4/734)	0.6% (2/313)	0.9% (1/112)	1.0% (6/577)	1.2% (7/579)	1.0% (1/97)

N = The maximum number of eligible patients
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization.
ENDEAVOR IV: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR III: The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
ENDEAVOR II: The primary endpoint is Target Vessel Failure at 9 months.
ENDEAVOR I: The primary endpoint is 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months.

In the ENDEAVOR IV trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. In the ENDEAVOR III trial all enrolled patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluation at 8-months. In the ENDEAVOR II trial a subset of patients underwent intravascular ultrasound (IVUS) immediately after the index procedure and at the scheduled angiographic evaluations at 8 months. Rates of incomplete stent apposition are shown in **Table 7-4** for ENDEAVOR II, ENDEAVOR III and ENDEAVOR IV trials.
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Table 7-4: Rates of Incomplete Stent Apposition.

	ENDEAVOR II Trial		ENDEAVOR III Trial		ENDEAVOR IV Trial	
	Endeavor Stent (N=169)	Control Stent (N=159)	Endeavor Stent (N=323)	Control Stent (N=113)	Endeavor Stent (N=164)	Control Stent (N=164)
Incomplete Stent Apposition Rate at Post-Procedure	24.8% (36/145)	19.6% (28/143)	12.4% (31/251)	17.7% (17/96)	12.5% (17/136)	11.8% (15/127)
Incomplete Stent Apposition Rate at 8 Month Follow-up	16.8% (21/125)	14.5% (16/110)	7.5% (17/226)	17.1% (13/76)	10.0% (12/120)	14.7% (17/116)
Resolved	7.0% (8/114)	6.7% (7/104)	5.8% (11/189)	7.4% (5/68)	3.8% (4/106)	2.1% (2/95)
Persistent	17.5% (20/114)	14.4% (15/104)	7.9% (15/189)	11.8% (8/68)	8.5% (9/106)	10.5% (10/95)
Late Acquired	0% (0/114)	0% (0/104)	0.5% (1/189)	5.9% (4/68)	0.9% (1/106)	3.2% (3/95)

7.2 Potential Adverse Events

7.2.1 Potential Adverse Events Related to Zotarolimus

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.

The adverse events that have been associated with the intravenous injection of zotarolimus in humans include:

- Anemia
- Circumoral paresthesia
- Diarrhea
- Dry Skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

7.2.2 Potential Risks Associated with Percutaneous Coronary Diagnostic and Treatment Procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks may include, but are not limited to, the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias
- Balloon rupture
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Infection or fever
- Myocardial infarction (MI)
- Peripheral ischemia / peripheral nerve injury
- Restenosis of the stented artery
- Shock / pulmonary edema
- Stent deformation, collapse, or fracture
- Stent migration
- Stent misplacement
- Stroke / transient ischemic attack
- Thrombosis (acute and subacute)
- Unstable angina

8.0 Clinical Studies

8.1 Overview of Clinical Studies

The principle safety and efficacy information for the **Endeavor** Stent is presented from the following clinical studies – the ENDEAVOR I trial, the ENDEAVOR II trial, the ENDEAVOR III trial and the ENDEAVOR IV trial. The ENDEAVOR I, II, III and IV trials have evaluated the performance of the **Endeavor** Stent in patients with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. Major study characteristics are summarized in **Table 8-1**.

The ENDEAVOR IV trial was a prospective, multi-center, single blind, two arm randomized controlled trial that compared the **Endeavor** Stent to a control consisting of the Taxus Stent. Eligibility was based on the careful assessments of a lesion reference vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 6 months.

The ENDEAVOR III trial was a prospective, multi-center, single blind, two arm randomized controlled trial that compared the **Endeavor** Stent to a control consisting of the Cypher Stent. Eligibility was based on the careful assessments of a lesion reference vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR II trial was a prospective, multi-center, double-blind, two arm randomized controlled trial that compared the **Endeavor** Stent to a control consisting of the DRIVER bare metal stent (cobalt based alloy). Eligibility was based on careful assessments of lesion reference

vessel diameter and lesion length utilizing careful visual estimate, on-line quantitative coronary angiography, or intravascular ultrasound. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR I trial was the First-in-man study for the **Endeavor** Stent. ENDEAVOR I is a non-randomized, prospective, multicenter, single arm trial that followed patients clinically and angiographically. The primary emphasis of the ENDEAVOR I trial was to assess the safety of the **Endeavor** Stent; the study also has significant value because it provides the longest available follow-up information on patients, currently four years.

Table 8-1: Clinical Trial Comparisons

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Study Type	Multi-center (n=8) Prospective Non-randomized	Multi-center (n=72) Prospective Randomized	Multi-center (n=29) Prospective Randomized	Multi-center (n=80) Prospective Randomized
Number of Patients	Total : 100 (**Endeavor** Stent)	Total : 1197 (**Endeavor** Stent: 598, Control: 599)	Total : 436 (3:1 randomization with control)	Total : 1548 (**Endeavor** Stent: 773, Taxus: 775)
Lesion Criteria	Single *de novo* lesion in native coronary artery ≤ 15mm in length and ≥3.0 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥2.25 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥2.5 to ≤3.5mm in diameter	Single *de novo* lesion in native coronary artery ≤ 27 mm in length and ≥2.5 to ≤3.5mm in diameter
Product Used	**Endeavor** Stent on the Rapid Exchange Stent Delivery System	**Endeavor** Stent on the Rapid Exchange Stent Delivery System	**Endeavor** Stent on the Over-The -Wire Stent Delivery System	**Endeavor** Stent on the Over-The -Wire Stent Delivery System
Antiplatelet Therapy	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 12 weeks.	Aspirin indefinitely and Clopidogrel or ticlopidine for 6 months
Follow up	30 days : Clinical 4 & 12 months : Clinical and angiographic 9 month: Clinical 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic 9 month: Clinical 6 month, 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic 9 month: Clinical 6 month, 1-5 years: Telephone	30 days : Clinical 8 months : Clinical and angiographic/ IVUS 9 month: Clinical 6 month, 1-5 years: Telephone
Status	48 month follow-up complete. Yearly follow up to 5 years is ongoing.	36 month follow-up is complete. Yearly follow up to 5 years is ongoing.	24 month follow-up is complete. Yearly follow up to 5 years is ongoing.	9 month follow-up is complete.

8.2 ENDEAVOR IV Trial

Purpose: To demonstrate the equivalence in safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Taxus Paclitaxel-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5-3.5 mm

Conclusion: Based on acute procedural results, 8-month angiographic, and 9-month clinical follow-up the Endeavor Zotarolimus-Eluting CSS has demonstrated similar safety and efficacy compared to the Taxus control stent.

Design: This was a prospective, multi-center, randomized, two-arm, single-blind trial that enrolled 1548 patients with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to treatment by percutaneous stenting.

Follow-up was performed at 30 days, 6, 8, and 9 months, and will be performed at 12 months, then annually thereafter out to 5 years. Angiography and IVUS evaluations were performed immediately post-procedure and at 8 months post-procedure for the first 328 consecutively enrolled patients (combined from all sites). In addition, patients at all sites receiving two or more stents at the target lesion will have/had angiographic and IVUS evaluations immediately post-procedure and at 8 months post-procedure (known as the Multi-stent subset). Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 6 months.

Demographics: The analysis population of this report consisted of 1548 patients. Baseline demographics and clinical characteristics showed a mean age of 63.5 years for patients in the Endeavor arm and 63.6 years for patients in the Taxus arm. The Endeavor group had 66.9% (517/773) male enrollment and the Taxus group had 68.5% (531/775) male enrollment. In the Endeavor arm, 28.2% (218/773) of patients had prior percutaneous coronary revascularization compared to 29.5% (229/775) of subjects in the Taxus arm. In the Endeavor group, 31.2% (241/773) of patients had a history of diabetes mellitus compared to 30.5% (236/775) of patients in the Taxus group.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by study personnel at the clinical sites. Angiographic and IVUS outcomes were assessed at designated core laboratories. Clinical events were adjudicated by an independent Clinical Events committee and the trial was monitored by an independent Data Monitoring Committee.

Results: The effectiveness and safety results for Endeavor and Taxus are presented in **Table 8-3**.

The incidence of the primary endpoint of TVF at 270 days for Endeavor was 6.8% (50/740) and for Taxus it was 7.4% (54/734) (p=0.685). The incidence of TLR at 270 days post-index procedure for the Endeavor arm was 4.2% (31/740); for Taxus it was 2.7% (20/734) (p=0.154).

At 270 days, the cumulative incidence of MACE for the Endeavor patients was 5.7% (42/740) compared to the Taxus patients which was 5.7% (42/734). The Kaplan-Meier estimate of freedom from MACE at 270 days for Endeavor patients was 94.4%; for Taxus patients it was 94.5%.

In **Table 8-2** the outcome of the primary endpoint from the ENDEAVOR IV trial is summarized.

Table 8-2: Primary endpoint from ENDEAVOR IV

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
ENDEAVOR IV	Target Vessel Failure at 9 months post-procedure	Endeavor	6.8% (50/740)	0.0005
		Taxus	7.4% (54/734)	

* P-value is for the test of Non-Inferiority.

Table 8-3 summarizes the principal effectiveness and safety results of the ENDEAVOR IV trial through 270 days. Figure 8-1 provides the cumulative percent of patients who are TVF-free through 270 days.

Table 8-3: Principal Effectiveness and Safety Results - ITT population

Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Lesion Success	99.6% (767/770)	99.2% (766/772)	0.4%[-0.4%, 1.1%]	0.507
Device Success	97.3% (751/772)	97.9% (757/773)	-0.7%[-2.2%, 0.9%]	0.412
Procedure Success	98.7% (760/770)	96.8% (747/772)	1.9% [0.5%, 3.4%]	0.015
Device-Specific Procedure Success	96.5% (745/772)	95.6% (739/773)	0.9% [-1.0%, 2.8%]	0.433
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.62±0.43 (763)	2.61±0.44 (763)	0.01 [-0.04, 0.05]	0.703
In-Segment	2.22±0.47 (770)	2.19±0.50 (772)	0.03 [-0.02, 0.08]	0.196
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	5.50±9.61 (763)	5.01±10.49 (763)	0.48 [-0.53, 1.49]	0.348
In-Segment	20.47±9.54 (770)	20.97±11.12 (772)	-0.50 [-1.53, 0.54]	0.344
Eight-Month Follow-Up MLD (mm)				
In-Stent	1.95±0.61 (143)	2.25±0.61 (135)	-0.30 [-0.45, -0.16]	<0.001
In-Segment	1.80±0.55 (144)	1.98±0.56 (135)	-0.18 [-0.31, -0.05]	0.008
Eight-Month Follow-up %DS				
In-Stent	26.41±19.74 (143)	16.09±17.99 (135)	10.32 [5.85, 14.79]	<0.001
In-Segment	32.28±17.02 (144)	26.61±15.52 (135)	5.68 [1.83, 9.52]	0.004
Eight-Month Late Loss (mm)				
In-Stent	0.67±0.49 (142)	0.42±0.50 (135)	0.25 [0.13, 0.37]	<0.001
In-Segment	0.36±0.47 (143)	0.23±0.45 (135)	0.13 [0.02, 0.23]	0.023
Eight-Month Binary Restenosis				
In-Stent	13.3% (19/143)	6.7% (9/135)	6.6% [-0.4%, 13.6%]	0.075
In-Segment	15.3% (22/144)	10.4% (14/135)	4.9% [-2.9%, 12.7%]	0.284
Eight-Month Volume Obstruction (%)	15.72±10.40 (74)	9.88±9.24 (77)	5.84 [2.68, 9.00]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.62±1.82 (113)	5.50±2.14 (109)	-0.87 [-1.39, -0.35]	0.001
Eight-Month NIH Volume (mm^3)	24.14±19.38 (74)	14.88±16.62 (77)	9.26 [3.46, 15.06]	0.002
In-Hospital MACE	0.9% (7/773)	2.6% (20/775)	-1.7% [-3.0%, -0.4%]	0.018
MACE to 30 Days	1.2% (9/770)	3.0% (23/771)	-1.8% [-3.2%, -0.4%]	0.019
MACE to 270 Days	5.7% (42/740)	5.7% (42/734)	-0.0% [-2.4%, 2.3%]	1.000

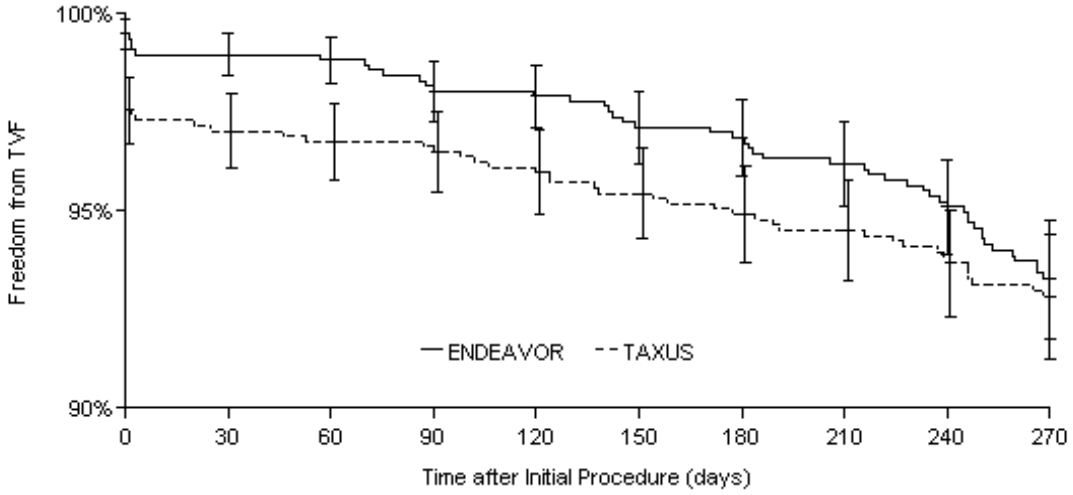
Safety & Effectiveness Measures	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	Difference [95% CI]	P-value†
Death to 270 Days	0.7% (5/740)	0.8% (6/734)	-0.1% [-1.0%, 0.7%]	0.773
Vascular Complications to 270 Days	0.5% (4/740)	0.8% (6/734)	-0.3% [-1.1%, 0.6%]	0.546
Bleeding Complications to 270 Days	1.6% (12/740)	2.9% (21/734)	-1.2% [-2.8%, 0.3%]	0.116
Early Stent Thrombosis to 30 Days	0.4% (3/770)	0.1% (1/771)	0.3% [-0.2%, 0.8%]	0.374
Late Stent Thrombosis to 270 days	0.4% (3/740)	0.0% (0/734)	0.4% [-0.1%, 0.9%]	0.250
Cerebrovascular Accident (CVA) to 270 Days	0.7% (5/740)	0.5% (4/734)	0.1% [-0.7%, 0.9%]	1.000
Perforation to 270 Days	0.1% (1/740)	0.4% (3/734)	-0.3% [-0.8%, 0.3%]	0.372
Target Vessel Revascularization to 30 days	0.4% (3/770)	0.9% (7/771)	-0.5% [-1.3%, 0.3%]	0.342
Target Vessel Revascularization to 270 days	5.5% (41/740)	5.0% (37/734)	0.5% [-1.8%, 2.8%]	0.727
Target Vessel Failure to 30 days	1.0% (8/770)	3.0% (23/771)	-1.9% [-3.3%, -0.5%]	0.010
Target Vessel Failure to 270 days	6.8% (50/740)	7.4% (54/734)	-0.6% [-3.2%, 2.0%]	0.685
Target Lesion Revascularization to 30 days	0.4% (3/770)	0.8% (6/771)	-0.4% [-1.1%, 0.4%]	0.507
Target Lesion Revascularization to 270 days	4.2% (31/740)	2.7% (20/734)	1.5% [-0.4%, 3.3%]	0.154

Kaplan-Meier Estimate	ENDEAVOR (N= 773 Patients)	TAXUS (N= 775 Patients)	P-value†
*MACE-Free at 270 days	94.4%	94.5%	0.952
*TLR-Free at 270 days	95.8%	97.3%	0.127
*TVR-Free at 270 days	94.4%	95.0%	0.682
*TVF-Free at 270 days	93.3%	92.8%	0.626

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – TAXUS.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free– No Death, MI, emergent CABG or target lesion revascularization

Figure 8-1. Survival Free from Target Vessel Failure (at 270 days)



TVF	0	7	14	21	30	60	90	120	150	180	210	240	270
ENDEAVOR													
# Entered	773	769	760	760	760	756	750	744	743	736	728	718	703
# Censored	0	5	0	0	4	5	0	0	1	6	5	7	118
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	4	4	0	0	0	1	6	1	6	2	5	8	13
% Survived	99.5%	99.0%	99.0%	99.0%	99.0%	98.8%	98.0%	97.9%	97.1%	96.9%	96.2%	95.1%	93.3%
SE	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.6%	0.6%	0.7%	0.8%	1.0%
TAXUS													
# Entered	775	755	748	748	747	744	735	732	726	720	710	694	683
# Censored	1	5	0	0	2	7	1	2	2	6	13	5	105
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	19	2	0	1	1	2	2	4	4	4	3	6	6
% Survived	97.5%	97.3%	97.3%	97.2%	97.0%	96.8%	96.5%	96.0%	95.4%	94.9%	94.5%	93.7%	92.8%
SE	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.7%	0.7%	0.8%	0.8%	0.8%	0.9%	1.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Log-Rank	0.24	1	0.626									
	Wilcoxon	0.43	1	0.511									

8.3 ENDEAVOR III Trial

Purpose: The purpose of the ENDEAVOR III trial was to demonstrate the non-inferiority in in-segment late lumen loss at 8 months between the **Endeavor** Zotaroliums-Eluting Coronary Stent System and the Cypher Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter.

Conclusion: As demonstrated in this clinical trial, the **Endeavor** Stent was shown to have higher device success rate, a favorable safety profile (lower peri-procedural myocardial infarctions and no stent thrombosis) and comparable clinical efficacy (target lesion revascularization), despite higher restenosis and angiographic late loss. The criterion for non-inferiority of the **Endeavor** Stent to Cypher Stent was not met with regards to the 8-month in-segment late lumen loss.

Design: This was a prospective, multi-center, single-blind, parallel, two-arm, randomized, controlled trial which enrolled 436 patients. Twenty-nine (29) study sites in the United States (US) enrolled subjects in this trial. The primary endpoint for this trial was in-segment late lumen loss at 8 months post-procedure. To be eligible, patients were required to have symptomatic ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters ≥2.5 mm and ≤3.5 mm and lesion lengths of ≥14 mm and ≤27 mm that were amenable to percutaneous treatment with stenting.

Patients were randomized in a single-blind fashion (3:1 randomization) to one of two treatments: the **Endeavor** Stent or the Cypher Stent. A total of 436 patients were enrolled in the clinical trial – 323 patients were randomized to the **Endeavor** Stent and 113 were randomized to the Cypher Stent. All patients were pre-specified to receive angiographic and IVUS follow-up at 8 months. Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

Clinical follow-up through the 9 month is available on 434 patients. Angiographic follow-up was completed on 371 patients at eight months. Clinical follow-up is available through 24 months on 425 patients.

Demographics:
Patients were well matched for baseline demographics with no statistically significant differences between treatment arms, except for gender. The **Endeavor** arm had 65.3% (211/323) male enrollment and Cypher had 81.4% (92/113) male enrollment. Of the 436 enrolled patients, baseline demographics and clinical characteristics showed a mean age of 61.4 in the **Endeavor** arm and 61.7 years in the Cypher arm. In the **Endeavor** arm, 22.6% (73/323) had prior percutaneous coronary revascularization compared to 16.8% (19/113) in Cypher arm. In the **Endeavor** Stent arm, 29.7% (96/323) of patients had a history of diabetes mellitus compared to 28.3% (32/113) of patients in the Cypher arm.

Methods:
Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent angiographic core lab assessed angiographic outcomes, and an independent intravascular ultrasound core laboratory assessed IVUS outcomes. An independent Clinical Events Committee adjudicated clinical events and an independent Data Monitoring Committee monitored the trial.

Results:
In selected patients, elective **Endeavor** Stent placement in native coronary artery *de novo* lesions resulted in similar incidence of TVF at 720 days 14.4% for the **Endeavor** Stent group and 13.4% for the Cypher Stent group. Overall Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) were 9.3% in the **Endeavor** Stent group at 720 days compared to 11.6%, in the Cypher Stent group (p = 0.465). At 720 days, the rate of stent thrombosis was 0.0% in both arms.

As summarized in **Table 8-4** the mean and standard deviation for the primary endpoint of In-Segment Late Lumen Loss at 8 months for **Endeavor** Stent arm was 0.36±0.46 (mm) and for Cypher it was 0.13± 0.33 (mm), (p < 0.001).

Table 8-4: Primary endpoint from Endeavor III trial

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
Endeavor III	In-segment Late Lumen Loss at 8 months post-procedure (mm)	Endeavor	0.36 ± 0.46	0.791*
		Cypher	0.13 ± 0.33	

* P-value is for the test of Non-Inferiority.

Table 8-5 summarizes the principal safety and effectiveness results of the ENDEAVOR III Trial through 720 days. **Figure 8-2** provides of the cumulative percent of patients who are TVF-Free through 720 days.

Table 8-5: Principal Effectiveness and Safety Results - ITT Population

Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Lesion Success	100.0% (323/323)	99.1% (112/113)	0.9% [-0.8%,2.6%]	0.259
Device Success	98.8% (319/323)	94.7% (107/113)	4.1% [-0.2%,8.4%]	0.022
Procedure Success	99.4% (321/323)	95.6% (108/113)	3.8% [-0.1%,7.7%]	0.014
Device-Specific Procedure Success	98.1% (317/323)	91.2% (103/113)	7.0% [1.6%,12.4%]	0.002
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.67±0.42 (323)	2.67±0.40 (112)	0.00 [-0.09,0.09]	0.993
In-Segment	2.27±0.45 (323)	2.28±0.47 (113)	-0.01 [-0.11,0.09]	0.836
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	4.33±9.77 (323)	5.92±9.07 (112)	-1.59 [-3.66,0.48]	0.132
In-Segment	19.38±9.25 (323)	20.17±11.74 (113)	-0.78 [-2.92,1.36]	0.522
Eight-Month Follow-Up MLD (mm)				
In-Stent	2.06±0.57 (277)	2.52±0.56 (94)	-0.46 [-0.60,-0.33]	<0.001
In-Segment	1.91±0.53 (277)	2.16±0.50 (94)	-0.25 [-0.37,-0.13]	<0.001
Eight-Month Follow-up %DS				
In-Stent	24.90±17.45 (277)	11.01±15.91 (94)	13.89 [9.88,17.90]	<0.001
In-Segment	30.42±15.57 (277)	23.86±13.87 (94)	6.56 [3.01,10.12]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.49 (277)	0.15±0.34 (94)	0.47 [0.36,0.58]	<0.001
In-Segment	0.36±0.46 (277)	0.13±0.33 (94)	0.24 [0.13,0.34]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.7% (27/277)	2.1% (2/94)	7.6% [3.1%,12.2%]	0.014
In-Segment	12.3% (34/277)	4.3% (4/94)	8.0% [2.4%,13.6%]	0.029
Eight-Month Volume Obstruction (%)	15.94±10.94 (187)	2.66±3.11 (61)	13.27 [10.48,16.07]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.89±1.96 (209)	5.77±1.97 (66)	-0.88 [-1.43,-0.34]	0.002
Eight-Month NIH Volume (mm^3)	24.09±21.16 (209)	3.74±5.20 (67)	20.36 [15.21,25.50]	<0.001
In-Hospital MACE	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 30 Days	0.6% (2/323)	3.5% (4/113)	-2.9% [-6.4%,0.6%]	0.042
MACE to 270 Days	7.5% (24/321)	7.1% (8/113)	0.4% [-5.1%,5.9%]	1.000
MACE to 360 Days	7.8% (25/320)	8.0% (9/112)	-0.2% [-6.1%,5.6%]	1.000
MACE to 720 Days	9.3% (29/313)	11.6% (13/112)	-2.3% [-9.1%,4.4%]	0.465
Death to 720 Days	1.6% (5/313)	4.5% (5/112)	-2.9% [-6.9%,1.2%]	0.138
Vascular Complications to 720 Days	1.9% (6/313)	5.4% (6/112)	-3.4% [-7.9%,1.0%]	0.090
Major Bleeding to 720 Days	2.2% (7/313)	6.3% (7/112)	-4.0% [-8.8%,0.8%]	0.060
Early Stent Thrombosis to 30 Days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Late Stent Thrombosis to 270 days	0.0% (0/321)	0.0% (0/113)	0.0% [--,--]	--

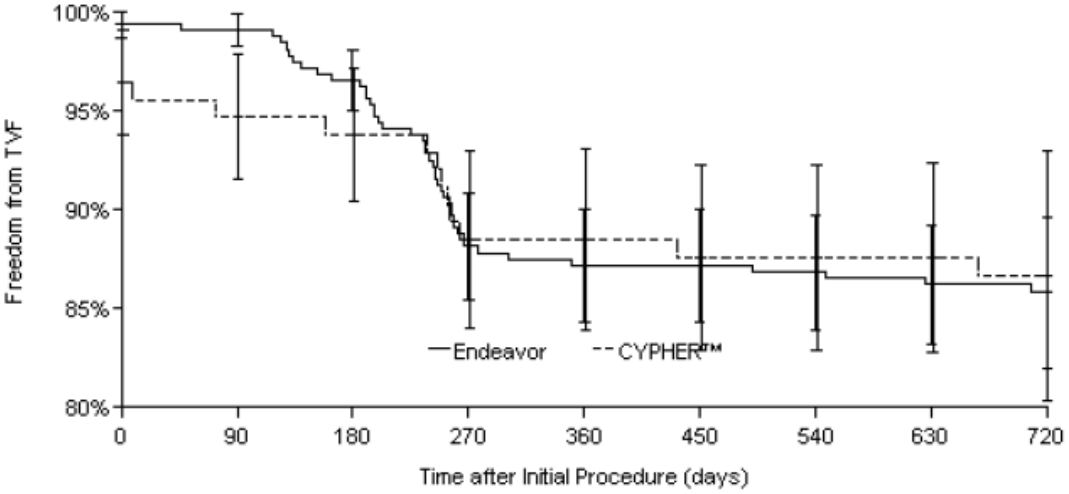
Safety & Effectiveness Measures	ENDEAVOR (N= 323 Patients)	CYPHER™ (N= 113 Patients)	Difference [95% CI]	P-value†
Late Stent Thrombosis to 360 days	0.0% (0/320)	0.0% (0/112)	0.0% [--,--]	--
Late Stent Thrombosis to 720 days	0.0% (0/313)	0.0% (0/112)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 720 Days	0.6% (2/313)	0.9% (1/112)	-0.3% [-2.2%,1.7%]	1.000
Perforation to 720 Days	0.0% (0/313)	0.9% (1/112)	-0.9% [-2.6%,0.8%]	0.264
Target Vessel Revascularization to 30 days	0.0% (0/323)	0.9% (1/113)	-0.9% [-2.6%,0.8%]	0.259
Target Vessel Revascularization to 270 days	11.2% (36/321)	8.0% (9/113)	3.3% [-2.8%,9.3%]	0.375
Target Vessel Revascularization to 360 days	12.2% (39/320)	8.0% (9/112)	4.2% [-2.0%,10.3%]	0.295
Target Vessel Revascularization to 720 days	13.7% (43/313)	9.8% (11/112)	3.9% [-2.8%,10.6%]	0.325
Target Vessel Failure to 30 days	0.6% (2/323)	4.4% (5/113)	-3.8% [-7.7%,0.1%]	0.014
Target Vessel Failure to 270 days	11.8% (38/321)	11.5% (13/113)	0.3% [-6.5%,7.2%]	1.000
Target Vessel Failure to 360 days	12.8% (41/320)	11.6% (13/112)	1.2% [-5.8%,8.2%]	0.868
Target Vessel Failure to 720 days	14.4% (45/313)	13.4% (15/112)	1.0% [-6.4%,8.4%]	0.875
Target Lesion Revascularization to 30 days	0.0% (0/323)	0.0% (0/113)	0.0% [--,--]	--
Target Lesion Revascularization to 270 days	6.2% (20/321)	3.5% (4/113)	2.7% [-1.6%,7.0%]	0.346
Target Lesion Revascularization to 360 days	6.6% (21/320)	3.6% (4/112)	3.0% [-1.4%,7.4%]	0.347
Target Lesion Revascularization to 720 days	7.0% (22/313)	4.5% (5/112)	2.6% [-2.2%,7.3%]	0.498

Kaplan-Meier Estimate	ENDEAVOR III (N= 323 Patients)	CYPHER™ (N= 113 Patients)	P-value†
*MACE-Free at 720 days	90.9%	88.5%	0.464
*TLR-Free at 720 days	93.0%	95.5%	0.336
*TVR-Free at 720 days	86.4%	90.2%	0.304
*TVF-Free at 720 days	85.8%	86.7%	0.867

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – CYPHER.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary endpoint is in-segment late lumen loss at 8 months as measured by QCA.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).

Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment,
retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
*MACE free– No Death, MI, emergent CABG or target lesion revascularization.

Figure 8-2. Survival Free from Target Vessel Failure (at 720 days)



TVF	0	90	180	270	360	450	540	630	720
Endeavor									
# Entered	323	321	318	310	281	274	268	264	262
# Censored	0	2	0	2	4	6	3	0	102
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	2	1	8	27	3	0	1	2	1
% Survived	99.4%	99.1%	96.6%	88.1%	87.2%	87.2%	86.9%	86.2%	85.8%
SE	0.4%	0.5%	1.0%	1.8%	1.9%	1.9%	1.9%	2.0%	2.6%
CYPHER™									
# Entered	113	109	107	106	100	98	97	97	95
# Censored	0	0	0	0	2	0	0	2	38
# Incomplete	0	0	0	0	0	0	0	0	0
# Events	4	2	1	6	0	1	0	0	1
% Survived	96.5%	94.7%	93.8%	88.5%	88.5%	87.6%	87.6%	87.6%	86.7%
SE	1.7%	2.1%	2.3%	3.0%	3.0%	3.1%	3.1%	3.2%	4.2%
Tests Between Groups									
	Test	Chi-Square	Deg Frdm	P-value					
	Wilcoxon	0.01	1	0.906					
	Log-Rank	0.03	1	0.867					

8.4 ENDEAVOR II Trial

Purpose: The purpose of the ENDEAVOR II trial was to demonstrate the safety and efficacy of the **Endeavor** Stent with 10 µg/mm zotarolimus compared to the DRIVER Stent for the treatment of single *de novo* lesions in native coronary arteries 2.25-3.5 mm in diameter.

Conclusion: Based on acute procedural results, 8-month angiographic, 9, 12, 24 and 36 month follow-up the **Endeavor** Stent has demonstrated similar safety and superior efficacy compared with the DRIVER Control Stent.

Design: This was a prospective, multi-center, double-blind, two-arm randomized controlled trial to evaluate the safety and efficacy of the **Endeavor** Stent in subjects with *de novo* lesions of the native coronary arteries. Seventy-two (72) study sites in Asia, Australia, Europe, Israel and New Zealand enrolled subjects into this trial. The primary endpoint for this trial was the target vessel failure (TVF) rate, defined as a composite of target vessel revascularization (TVR), recurrent Q or non-Q wave myocardial infarction (MI), or cardiac death that could not be clearly attributed to a vessel other than the target vessel at 270 days post index procedure. To be eligible, patients were required to have symptomatic ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters ≥2.25 mm and ≤3.5 mm and lesion lengths of ≥14 mm and ≤27 mm that were amenable to percutaneous treatment with stenting.

Patients were randomized in a double-blind fashion (1:1 randomization) to one of two treatments: **Endeavor** Stent or Uncoated DRIVER Coronary Stent System (DRIVER). A total of 1,197 patients were enrolled in the clinical trial – 598 patients were randomized to the **Endeavor** Stent and 599 were randomized to the control. A total of 600 patients were pre-specified to receive angiographic follow-up at 8 months. Following the index procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 12 weeks.

Clinical follow-up through the 1080 days follow-up period is available on 1,156 patients. Angiographic follow-up was completed on 529 patients at eight months. Clinical follow-up is available through 1080 days.

Demographics: Patients were well matched for baseline demographics with no statistically significant differences between treatment arms. Factors evaluated included age (mean 62 years), gender (24% female), diabetes (20%), prior MI (41%), hypertension requiring treatment (66%), hyperlipidemia requiring treatment (79%), ejection fraction (mean 61%), CSS Angina Class (54% Class III or IV), IIb/IIIa inhibitor use (12%), LAD (45%), LCX (22%), RCA (33%), reference vessel diameter (mean 2.75 mm), minimum lumen diameter (mean 0.83 mm), percent diameter stenosis (70%), and lesion length (mean 14.2 mm).

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent angiographic core lab assessed angiographic outcomes in a blinded fashion, and an independent intravascular ultrasound core laboratory assessed IVUS outcomes in a blinded fashion. An independent Clinical Events Committee adjudicated clinical events and an independent Data Monitoring Committee monitored the trial.

Results: In selected patients, elective **Endeavor** Stent placement in native coronary artery *de novo* lesions resulted in reduction of the incidence of TVF at 1080 days compared to Control (12.8% vs. 21.4%, $p < 0.001$). **Table 8-6** summarizes the results of the primary endpoint of target vessel failure (TVF) at 270 days post index procedure. Overall Major Adverse Cardiac Events (MACE) defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target lesion revascularization (TLR) were reduced in the **Endeavor** Stent group at 1080 days compared to control (12.0% vs. 20.7%, $p < 0.001$). The rate of early stent thrombosis was lower in the **Endeavor** Stent arm when compared to the control (0.5% vs. 1.2%, $p = 0.342$).

Table 8-6: Primary endpoint from Endeavor II trial

Study	Primary Endpoint	Test/Control	Parameter in % or Mean ± SD	p-value
Endeavor II	Target Vessel Failure at 9 months post-procedure	Endeavor Driver	7.9% (47/592) 15.1% (89/591)	< 0.001

By follow-up angiography at 8-months, there was significantly lower in-stent late loss (0.62 vs. 1.03, $p < 0.001$) and in-segment late loss (0.36 vs. 0.72, $p < 0.001$) in Endeavor stent as

compared to the Driver stent. Mean in-stent percent diameter stenosis was significantly reduced (27.9% vs. 42.2%, p < 0.001). Additionally, in-stent and in-segment binary angiographic restenosis were significantly reduced (9.5% vs. 33.2%, p < 0.001 and 13.3% vs. 34.7%, p < 0.001). There was no significant increase in proximal or distal edge late loss or BAR for the **Endeavor** Stent arm.

Examination by IVUS at 8 months showed that neointimal hyperplasia (NIH) volume was significantly reduced in the **Endeavor** Stent arm (30.2 mm^3 vs. 53.5 mm^3, p < 0.001). There was no evidence of late stent incomplete apposition in either treatment arm at 8 months.

Table 8-7 summarizes the principal effectiveness and safety results of the ENDEAVOR II Trial through 1080 days. **Figure 8-3** provides of the cumulative percent of patients who are TVF-Free through 1080 days.

Table 8-7: Principal Effectiveness and Safety Results (to 1080 Days)

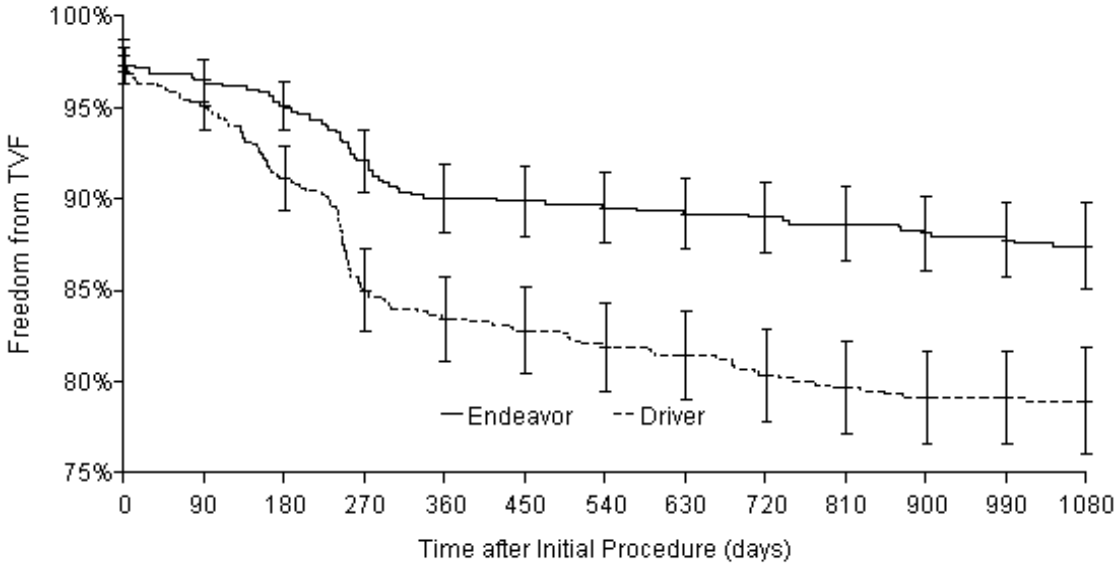
Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
Lesion Success	99.7% (587/589)	100.0% (590/590)	-0.3% [-0.8%,0.1%]	0.249
Device Success	98.8% (585/592)	99.2% (586/591)	-0.3% [-1.5%,0.8%]	0.773
Procedure Success	97.3% (573/589)	97.1% (573/590)	0.2% [-1.7%,2.0%]	1.000
Device-Specific Procedure Success	96.5% (571/592)	96.4% (570/591)	0.0% [-2.1%,2.1%]	1.000
Post- Procedure Minimal Lumen Diameter (MLD, in mm)				
In-Stent	2.59±0.43 (588)	2.61±0.44 (589)	-0.02 [-0.07,0.03]	0.436
In-Segment	2.21±0.49 (589)	2.24±0.49 (590)	-0.03 [-0.09,0.03]	0.302
Post-Procedure % Diameter Stenosis (%DS)				
In-Stent	6.04±10.43 (588)	6.23±10.03 (589)	-0.18 [-1.36,0.99]	0.757
In-Segment	20.39±10.26 (589)	20.11±9.38 (590)	0.28 [-0.84,1.41]	0.622
Eight-Month Follow-Up MLD (mm)				
In-Stent	1.99±0.56 (264)	1.62±0.70 (265)	0.37 [0.26,0.48]	<0.001
In-Segment	1.86±0.55 (264)	1.56±0.67 (265)	0.30 [0.19,0.40]	<0.001
Eight-Month Follow-up %DS				
In-Stent	27.91±17.30 (264)	42.24±21.73 (265)	-14.33 [-17.68,-10.97]	<0.001
In-Segment	32.67±16.27 (264)	44.33±20.45 (265)	-11.66 [-14.82,-8.50]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.62±0.46 (264)	1.03±0.59 (263)	-0.41 [-0.50,-0.32]	<0.001
In-Segment	0.36±0.46 (264)	0.72±0.61 (263)	-0.36 [-0.45,-0.27]	<0.001
Eight-Month Binary Restenosis				
In-Stent	9.5% (25/264)	33.2% (88/265)	-23.7% [-30.4%,-17.1%]	<0.001
In-Segment	13.3% (35/264)	34.7% (92/265)	-21.5% [-28.5%,-14.4%]	<0.001
Eight-Month Volume Obstruction (%)	17.34±10.27 (90)	29.55±17.58 (81)	-12.22 [-16.51,-7.92]	<0.001
Eight-Month Minimal Lumen Area (mm^2)	4.99±1.66 (122)	3.98±1.72 (107)	1.01 [0.57,1.45]	<0.001
Eight-Month NIH Volume (mm^3)	30.15±21.66 (90)	53.51±39.80 (81)	-23.36 [-32.91,-13.81]	<0.001
In-Hospital MACE	2.5% (15/597)	2.9% (17/596)	-0.3% [-2.2%,1.5%]	0.725

Safety & Effectiveness Measures	Endeavor (N=598 patients)	Driver (N=599 patients)	Difference [95% CI]	P-value†
MACE to 30 Days	2.9% (17/596)	3.7% (22/594)	-0.9% [-2.9%,1.2%]	0.421
MACE to 270 Days	7.3% (43/592)	14.4% (85/591)	-7.1% [-10.6%,-3.6%]	<0.001
MACE to 360 Days	8.8% (52/590)	15.6% (92/589)	-6.8% [-10.5%,-3.1%]	<0.001
MACE to 720 Days	9.9% (58/587)	18.1% (106/586)	-8.2% [-12.2%,-4.3%]	<0.001
MACE to 1080 Days	12.0% (69/577)	20.7% (120/579)	-8.8% [-13.0%,-4.5%]	<0.001
Death to 1080 Days	3.3% (19/577)	4.5% (26/579)	-1.2% [-3.4%,1.0%]	0.362
Vascular Complications to 1080 Days	0.5% (3/577)	1.2% (7/579)	-0.7% [-1.8%,0.4%]	0.342
Major Bleeding to 1080 Days	1.2% (7/577)	2.4% (14/579)	-1.2% [-2.7%,0.3%]	0.185
Early Stent Thrombosis	0.5% (3/596)	1.2% (7/594)	-0.7% [-1.7%,0.4%]	0.224
Late Stent Thrombosis to 270 days	0.0% (0/592)	0.0% (0/591)	0.0% [--,--]	--
Late Stent Thrombosis to 360 days	0.0% (0/590)	0.0% (0/589)	0.0% [--,--]	--
Late Stent Thrombosis to 720 days	0.0% (0/587)	0.0% (0/586)	0.0% [--,--]	--
Late Stent Thrombosis to 1080 days	0.0% (0/577)	0.0% (0/579)	0.0% [--,--]	--
Cerebrovascular Accident (CVA) to 1080 Days	1.0% (6/577)	1.2% (7/579)	-0.2% [-1.4%,1.0%]	1.000
Perforation to 1080 Days	0.5% (3/577)	0.3% (2/579)	0.2% [-0.6%,0.9%]	0.686
Target Vessel Revascularization to 30 days	1.2% (7/596)	1.2% (7/594)	-0.0% [-1.2%,1.2%]	1.000
Target Vessel Revascularization to 270 days	5.6% (33/592)	12.5% (74/591)	-6.9% [-10.2%,-3.7%]	<0.001
Target Vessel Revascularization to 360 days	7.5% (44/590)	14.1% (83/589)	-6.6% [-10.2%,-3.1%]	<0.001
Target Vessel Revascularization to 720 days	8.3% (49/587)	16.4% (96/586)	-8.0% [-11.8%,-4.3%]	<0.001
Target Vessel Revascularization to 1080 days	9.5% (55/577)	17.6% (102/579)	-8.1% [-12.0%,-4.2%]	<0.001
Target Vessel Failure to 30 days	3.2% (19/596)	3.7% (22/594)	-0.5% [-2.6%,1.6%]	0.638
Target Vessel Failure to 270 days	7.9% (47/592)	15.1% (89/591)	-7.1% [-10.7%,-3.5%]	<0.001
Target Vessel Failure to 360 days	10.0% (59/590)	16.6% (98/589)	-6.6% [-10.5%,-2.8%]	<0.001
Target Vessel Failure to 720 days	11.1% (65/587)	19.8% (116/586)	-8.7% [-12.8%,-4.6%]	<0.001
Target Vessel Failure to 1080 days	12.8% (74/577)	21.4% (124/579)	-8.6% [-12.9%,-4.3%]	<0.001
Target Lesion Revascularization to 30 days	0.8% (5/596)	1.2% (7/594)	-0.3% [-1.5%,0.8%]	0.579
Target Lesion Revascularization to 270 days	4.6% (27/592)	11.8% (70/591)	-7.3% [-10.4%,-4.2%]	<0.001
Target Lesion Revascularization to 360 days	5.9% (35/590)	13.1% (77/589)	-7.1% [-10.5%,-3.8%]	<0.001
Target Lesion Revascularization to 720 days	6.5% (38/587)	14.2% (83/586)	-7.7% [-11.1%,-4.2%]	<0.001
Target Lesion Revascularization to 1080 days	7.3% (42/577)	14.7% (85/579)	-7.4% [-11.0%,-3.8%]	<0.001

Kaplan-Meier Estimate	Endeavor (N=598 patients)	Driver (N=599 patients)	P-value†
*MACE-Free at 1080 days	88.3%	79.6%	<0.001
*TLR-Free at 1080 days	92.8%	85.4%	<0.001
*TVR-Free at 1080 days	90.6%	82.6%	<0.001
*TVF-Free at 1080 days	87.4%	78.9%	<0.001

† p-values and confidence intervals are unadjusted for multiple comparisons (except for primary endpoint).
N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter.
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
Difference = ENDEAVOR – DRIVER.
CI = Confidence interval
P-values are based on the Fisher's Exact test for dichotomous outcomes, Log-Rank test for event-free survival outcomes, and the two-sample t-test for continuous outcomes.
The primary end point is Target Vessel Failure at 9 months.
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
Device Specific Procedure Success: Defined as device success and no in-hospital MACE.
MLD = Minimal luminal diameter.
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair
Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
Target vessel revascularization (TVR) is defined as repeat PCI or CABG of the target vessel. These may include a hematoma requiring treatment, retroperitoneal bleed
Target vessel failure (TVF) is defined as the composite endpoint comprised of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization. Target vessel failure includes any target vessel revascularization and MI. Target vessel failure will be reported when: MI occurs in territory not clearly attributed to a vessel other than the target vessel, target vessel revascularization is performed.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
* MACE free– No Death, MI, emergent CABG or target lesion revascularization.

Figure 8-3. Survival Free from Target Vessel Failure (at 1080 days)



TVF	0	90	180	270	360	450	540	630	720	810	900	990	1080
Endeavor													
# Entered	597	584	570	561	541	525	522	519	515	512	503	500	497
# Censored	0	6	1	2	4	2	1	2	2	7	0	1	108
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	13	8	8	18	12	1	2	2	1	2	3	2	2
% Survived	97.8%	96.5%	95.1%	92.1%	90.0%	89.9%	89.5%	89.2%	89.0%	88.6%	88.1%	87.8%	87.4%
SE	0.6%	0.8%	0.9%	1.1%	1.2%	1.3%	1.3%	1.3%	1.3%	1.3%	1.4%	1.4%	1.6%
Driver													
# Entered	596	580	565	540	500	485	478	473	470	460	453	450	448
# Censored	0	2	1	4	6	3	0	0	4	3	0	2	109
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# Events	16	13	24	36	9	4	5	3	6	4	3	0	1
% Survived	97.3%	95.1%	91.1%	85.0%	83.5%	82.8%	81.9%	81.4%	80.3%	79.6%	79.1%	79.1%	78.9%
SE	0.7%	0.9%	1.2%	1.5%	1.5%	1.6%	1.6%	1.6%	1.7%	1.7%	1.7%	1.7%	2.0%
Tests Between Groups													
	Test	Chi-Square	Deg Frdm	P-value									
	Wilcoxon	15.19	1	<0.001									
	Log-Rank	15.19	1	<0.001									

8.5 ENDEAVOR I Trial

Purpose: The purpose of this study was to demonstrate the safety and efficacy of the **Endeavor** Stent for the treatment of single *de novo* lesions in native coronary arteries. This study provides the longest follow-up experience available.

Conclusion: In selected patients, use of the **Endeavor** Stent provided favorable IVUS, angiographic, and clinical results through 1440 days of follow-up.

Design: This is a prospective, multi-center, non-randomized, single-arm study that enrolled 100 subjects at eight (8) study sites in Australia and New Zealand. To be eligible, a patient was required to have a *de novo* ischemic lesion (≤ 15 mm in length) of a native coronary artery with reference vessel diameter of 3.0 mm to 3.5 mm. The study allowed for use of 18 mm **Endeavor** Stents. A total of 100 patients were treated with the **Endeavor** Stent. After the procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 12 weeks. Angiographic follow up was performed at 4 and 12 months post-procedure. Clinical follow-up is available through 1440 days.

Demographics: Patients had a mean age of 59 years, there were 21% females, 16% had a history of diabetes mellitus, and 47% had a prior MI. Forty-three (43) percent of the lesions treated were in LAD, 23% were in LCX, 34% were in RCA, mean reference vessel diameter pre-procedure was 2.96 mm, mean pre-procedure minimal lumen diameter was 0.88 mm, mean pre-procedure percent diameter stenosis was 70.3%, and the mean lesion length was 10.9 mm (43% of patients had a lesion length < 10 mm and 56% of patients had a lesion length between 10 mm and 19.9 mm). No patients received IIb/IIIa inhibitors in this study.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical research coordinators at the study sites. An independent Angiographic Core Laboratory and an independent IVUS Core Laboratory analyzed all baseline and follow-up angiograms and IVUS images. An independent Clinical Events Committee adjudicated clinical events and an independent Data Safety Monitoring Board monitored the trial.

Results: The primary safety endpoint of 30-day MACE was 1.0%. The cumulative MACE rate at 12, 24, 36 and 48 months was 2%, 3.0%, 6.1% and 7.2% respectively. There was minimal late lumen loss and consequential binary angiographic restenosis by 4 months, at 12-month in-stent late lumen loss was 0.58±0.44 mm and in-stent binary restenosis occurred in 4.3% of patients.

Table 8-8 summarizes the principal effectiveness and safety results of the ENDEAVOR I Trial through 1440 days.

Table 8-8: Principal Effectiveness and Safety Results

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Lesion Success	100.0% (100/100)
Device Success	100.0% (100/100)
Procedure Success	100.0% (100/100)
Device-Specific Procedure Success	100.0% (100/100)
Post- Procedure Minimal Lumen Diameter (MLD, in mm)	
In-Stent	2.84±0.35 (100)
In-Segment	2.52±0.42(100)
Post-Procedure % Diameter Stenosis (%DS)	
In-Stent	5.37±7.51 (100)
In-Segment	16.54±8.40 (100)
4-Month Follow-Up MLD (mm)	
In-Stent	2.52±0.44 (98)
In-Segment	2.29±0.46 (98)
4-Month Follow-up %DS	
In-Stent	14.40±13.10 (98)

Safety & Effectiveness Measures	Endeavor (N=100 patients)
In-Segment	22.36±12.08 (98)
4-Month Late Loss (mm)	
In-Stent	0.32±0.37 (98)
In-Segment	0.22±0.43 (98)
4-Month Binary Restenosis	
In-Stent	2.0% (2/98)
In-Segment	3.1% (3/98)
4-Month Volume Obstruction (%)	4.46±6.05 (94)
4-Month Minimal Lumen Area (mm^2)	5.96±1.66 (95)
4-Month NIH Volume (mm^3)	6.10±7.39 (94)
12-Month Follow-Up MLD (mm)	
In-Stent	2.26±0.49 (92)
In-Segment	2.08±0.47 (92)
12-Month Follow-up %DS	
In-Stent	21.75±15.35 (92)
In-Segment	28.00±13.41 (92)
12-Month Late Loss (mm)	
In-Stent	0.58±0.44 (92)
In-Segment	0.43±0.44 (92)
12-Month Binary Restenosis	
In-Stent	4.3% (4/92)
In-Segment	5.4% (5/92)
12-Month Volume Obstruction (%)	9.73±8.50 (86)
12-Month Minimal Lumen Area (mm^2)	5.69±1.74 (86)
12-Month NIH Volume (mm^3)	14.15±11.82 (86)
In-Hospital MACE	0.0% (0/100)
MACE to 30 Days	1.0% (1/100)
MACE to 270 Days	2.0% (2/100)
MACE to 360 Days	2.0% (2/98)
MACE to 720 Days	3.0% (3/99)
MACE to 1080 Days	6.1% (6/98)
MACE to 1440 Days	7.2% (7/97)
Death to 1440 Days	4.1% (4/97)
Vascular Complications to 1440 Days	3.1% (3/97)
Major Bleeding to 1440 Days	2.1% (2/97)
Early Stent Thrombosis	1.0% (1/97)
Late Stent Thrombosis to 270 days	0.0% (0/100)
Late Stent Thrombosis to 360 days	0.0% (0/98)
Late Stent Thrombosis to 720 days	0.0% (0/98)
Late Stent Thrombosis to 1080 days	0.0% (0/97)
Late Stent Thrombosis to 1440 days	0.0% (0/97)
Cerebrovascular Accident (CVA) to 1440 Days	1.0% (1/97)

Safety & Effectiveness Measures	Endeavor (N=100 patients)
Perforation to 1440 Days	0.0% (0/97)
Target Vessel Revascularization to 30 days	1.0% (1/100)
Target Vessel Revascularization to 270 days	2.0% (2/100)
Target Vessel Revascularization to 360 days	2.0% (2/98)
Target Vessel Revascularization to 720 days	4.0% (4/99)
Target Vessel Revascularization to 1080 days	5.1% (5/98)
Target Vessel Revascularization to 1440 days	5.2% (5/97)
Target Vessel Failure to 30 days	1.0% (1/100)
Target Vessel Failure to 270 days	2.0% (2/100)
Target Vessel Failure to 360 days	2.0% (2/99)
Target Vessel Failure to 720 days	4.0% (4/99)
Target Vessel Failure to 1080 days	5.1% (5/98)
Target Vessel Failure to 1440 days	5.2% (5/97)
Target Lesion Revascularization to 30 days	1.0% (1/100)
Target Lesion Revascularization to 270 days	2.0% (2/100)
Target Lesion Revascularization to 360 days	2.0% (2/99)
Target Lesion Revascularization to 720 days	2.0% (2/99)
Target Lesion Revascularization to 1080 days	3.1% (3/98)
Target Lesion Revascularization to 1440 days	3.1% (3/97)

Kaplan-Meier Estimate	Endeavor (N=100 patients)
*MACE-Free at 1440 days	92.9%
*TLR-Free at 1440 days	96.9%
*TVR-Free at 1440 days	94.9%
*TVF-Free at 1440 days	94.9%

N = the maximum number of eligible patients, n = Number of patients with evaluable data. Denominators indicate the total number of patients with available data for related parameter
The numbers are % (Count / Sample Size) or Mean + SD (sample size).
The primary endpoint was 30-Day Major Adverse Cardiac Event (MACE) and late lumen loss (QCA) at 4 months
Lesion Success defined as Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Procedure Success: Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Device Success: Attainment of < 50 % residual stenosis of the target lesion using only the assigned device.
MLD = Minimal luminal diameter .
% DS = Percent Diameter Stenosis.
In-segment measurement or in-segment is defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.
In-stent measurement or in-stent is defined as the measurements within the boundaries of the stent.
VOLUME OBSTRUCTION (%) is defined as stent intimal hyperplasia and is calculated as 100 x (Stent Volume - Lumen Volume)/Stent Volume.
Neointimal Hyperplastic Volume as measured by intravascular ultrasound (IVUS).
Major adverse cardiac events (MACE) is defined as death, MI (Q wave and non-Q wave), emergent cardiac bypass surgery, or target site revascularization (repeat PTCA or CABG).
Early stent thrombosis: Defined as 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 is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Late stent thrombosis: Myocardial infarction > 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.
Vascular complications may include: Hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia/nerve injury, vascular event requiring transfusion or surgical repair

Major Bleeding: Procedure-related hemorrhagic event that requires a transfusion or surgical repair. These may include hematoma requiring treatment, retroperitoneal bleed.
CVA/Stroke: The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.
The following survival estimates are by Kaplan-Meier Methods:
*TLR free - No target lesion revascularization
*TVR free – No target vessel revascularization
*TVF free – No cardiac death, MI or target vessel revascularization.
* MACE free– No Death, MI, emergent CABG or target lesion revascularization.

9.0 Individualization of Treatment

See also **Precautions-5.6 Use in Special Populations** and **Precautions-5.7 Lesion/Vessel Characteristics.**

The risks and benefits described above should be carefully considered for each patient before use of the **Endeavor** Zotarolimus-Eluting Coronary Stent System. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anticoagulation. Stenting is generally avoided in patients at risk of bleeding and for those with contraindicated anticoagulation therapy.

10.0 Patient Counseling Information

Physicians should consider the following in counseling the patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a zotarolimus eluting stent implant
- Discuss the risks/benefits issues for this particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term
- Discuss the risks of early discontinuation of the antiplatelet therapy

The following information is provided in the package or online for physicians to provide to their patients:

- A Patient Guide which includes information on the **Endeavor** Zotarolimus-Eluting Coronary Stent System, coronary artery disease, and the implantation procedure.
- A Patient Implant Card that is used to record information about the patient and the stent.

11.0 How Supplied

STERILE: **FOR SINGLE USE ONLY**. This product is sterilized with ethylene oxide (EO) and is nonpyrogenic. Do not use if the package is opened or damaged. Do not resterilize. Return product if package is opened or damaged to Medtronic Returned Goods. Contact your local Medtronic, Inc. Representative for return information.

CONTENTS: One (1) **Endeavor** Zotarolimus-Eluting Multi Exchange II (MX^2) Coronary Stent System.

- One (1) Patient Implant Card
- One (1) Reference card to the electronic Instructions for Use

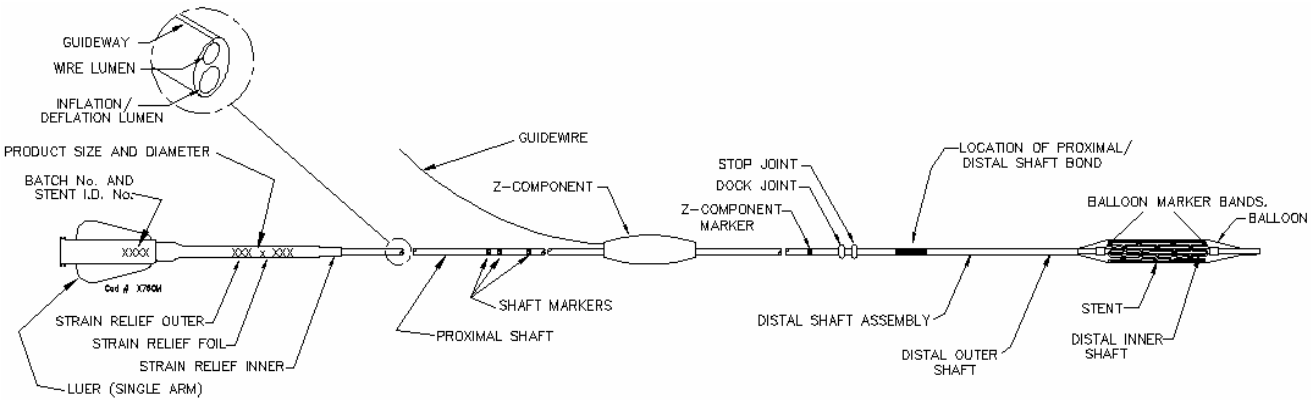
STORAGE: Store in the original container. Store at 25 ºC (77 ºF); excursions permitted to 15-30 ºC (59-86 ºF). Use by the “Use By” date noted on the package.

DISPOSAL INSTRUCTIONS:

After use, dispose of product and packaging in accordance with hospital, administrative and/ or local government policy.

12.0 Operator's Manual

Figure 12-1. Diagram of the Endeavor Zotarolimus-Eluting Coronary Stent System Multi Exchange II (MX^2) Delivery System



12.1 Access to Package Holding Sterile Stent Delivery System

Tear open the outer foil pouch to reveal the inner pouch. Do not drop or hand the inner pouch into the sterile field. Remove the inner pouch from the outer foil pouch. Peel open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
Note: The outer surface of the inner pouch is not sterile.

12.2 Inspection Prior to Use

Before opening the product, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Do not use after the "Use By" date. If the sterile package is intact, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the product if any damage to the packaging is noted.

A protective sheath covers the stent mounted on the balloon. After removal of the sheath, visually inspect the stent to ensure that it has not been damaged or displaced from its original position (between proximal and distal marker bands) on the balloon.

Remove the accessories pouch from the hoop, open it and place the accessories on a sterile table. The stent delivery system is packaged with the Z-component in its most proximal position on the proximal shaft. Holding the luer steady, withdraw the delivery system from the packaging hoop. The release mechanism in the hoop will advance the Z-component to its distal position on the proximal shaft in preparation for use. It is normal to feel some minor resistance as the Z-component is released. During removal the proximal shaft may be coiled in a single or double loop to allow for easier handling.

Upon removal of the catheter, confirm that the Z-component is in its most distal position on the proximal shaft. There are two small bumps proximal to the proximal/distal joint, which are referred to as the stop joint and the dock joint, as shown in Figure 12-1. The Z-component is located on the dock joint when it is in its most distal position on the shaft. The dock joint is used to hold the Z-component stationary during guidewire backloading. The stop joint prevents the Z-component from advancing any further distally along the proximal shaft. A white marker (the Z-component marker) on the shaft just proximal to the Z-component indicates that the Z-component is near its most distal position. There will also be resistance to movement of the shaft through the Z-component when it is in this position. If the Z-component is not in its most distal position, advance it distally along the proximal shaft until it is positioned against the stop joint on the dock joint.

Note: The Z-component design features an outer grip, which is free to rotate relative to the central portion of the Z-component.

12.3 Materials Required

Quantity	Material
1	20 cc syringe
1	12 cc syringe
1,000 u /500 cc	Heparinized normal saline
1	Guidewire [≤ 0.014 inch (0.36 mm) diameter]
1	Rotating hemostatic valve
1	Inflation device
1	Torque device
optional	Stopcock (3-way minimum)
N/A	Contrast medium diluted 1:1 with heparinized normal saline
N/A	Appropriate anticoagulation and antiplatelet drugs
N/A	Guiding catheter [≥ 6 F (1.6 mm, 0.064 inch) inner diameter]

12.4 Preparation Precaution

- DO NOT use product if the protective sheath is not present or the stent is damaged/displaced.
- AVOID manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- DO NOT apply negative or positive pressure to the balloon during the delivery system preparation.

12.4.1 Guidewire Lumen Flush

Step	Action
1.	Remove protective sheath covering from the stent/balloon. Care should be taken not to disrupt the stent.
2.	Flush Stent Delivery System guidewire lumen with heparinized normal saline through the distal end of the catheter by attaching the blunt end of a syringe to the distal end of the catheter and flushing the guidewire lumen until fluid exits from the guideway and/or the Z- component. Alternatively the stent delivery system guidewire lumen may be flushed by attaching the flushing cannula to the syringe and placing it in the white funnel of the Z-component and flushing the guidewire lumen until fluid exits the distal end of the catheter.
3.	Verify that the stent is positioned between the proximal and distal balloon markers.

12.4.2 Delivery System Preparation

This step may be carried out prior to the guidewire lumen flush, described in section 12.4.3 above, while the delivery system is in the hoop.

Step	Action
1.	Fill a 20 cc syringe with 5 cc of contrast/heparinized normal saline mixture (1:1).
2.	Attach to delivery system by holding the luer steady and rotating the syringe to connect and apply negative pressure for 20-30 seconds. **Note:** If attaching to delivery system in hoop prior to removal, hold the retainer and rotate the syringe to connect to luer.
3.	Slowly release pressure to allow negative pressure to draw mixture into balloon lumen.
4.	Detach syringe and leave a meniscus of mixture on the hub of the balloon lumen.
5.	Prepare inflation device in standard manner and purge to remove all air from syringe and tubing.
6.	Attach inflation device to catheter directly ensuring no bubbles remain at connection.

7. Leave on ambient pressure (neutral position).
   Note: Do not pull negative pressure on inflation device after balloon preparation and prior to delivering the stent.
8. Visually inspect the stent to ensure the stent is placed within the area of the proximal and distal balloon markers.

12.5 Delivery Procedure

Step	Action
1.	Prepare vascular access site according to standard PTCA practice.
2.	Pre-dilate the lesion/vessel with appropriate diameter balloon having a ratio of 1:1 with the diameter of the vessel. Pre-dilatation must be performed using a balloon with the following three characteristics: • A diameter at least 0.5 mm smaller than the treatment stent. • A length equal to or shorter than the lesion length to be dilated. • A length shorter than the stent to be implanted.
3.	Maintain neutral pressure on inflation device. Open rotating hemostatic valve to allow for easy passage of the stent. **Note:** If resistance is encountered, **do not force passage**. Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine**.**
4.	Ensure guiding catheter stability before advancing the **Endeavor** Coronary Stent Delivery System into the coronary artery. Carefully advance the distal tip of the **Endeavor** Coronary Stent Delivery System over the proximal end of the guidewire. Ensure that the guidewire exits the stent delivery system catheter through the Z-component. **Note:** If Z-component is not located in most distal position against the stop joint on dock joint, advance it forward to this position before backloading proximal end of guidewire into stent delivery system. **Note:** If the Z-component moves during backloading, advance it to its most distal position and hold stationary while backloading the guidewire.
5.	While maintaining guidewire position advance the stent delivery system over the guidewire through the hemostatic valve adapter using conventional angioplasty techniques.
6.	Carefully advance the stent delivery system through the guiding catheter until the Z-component is positioned against the hemostatic valve adapter and cannot advance any further. **Note:** Once the distal section of the delivery system is in the guide catheter, the ideal position of the Z-component is adjacent to the hemostatic valve adapter (during shaft advancement, retraction, etc.).
7.	Gradually tighten the hemostatic valve adapter or adjust the spring loaded cap seal to control back flow. **Excessive hemostatic valve tightening may affect movement of the proximal shaft.**

8. While maintaining guidewire position and with the Z-component adjacent to hemostatic valve adapter advance the stent delivery system over the guidewire through the hemostatic valve adapter using conventional angioplasty techniques.
   Note: Holding the hemostatic valve adapter and guidewire will ensure the Z-component stays properly positioned adjacent to hemostatic valve adapter during proximal shaft advancement into the guiding catheter; holding the Z-component is not necessary.
   Note: Initial resistance may be felt during the first push as the dock joint moves away from the Z-component. If resistance to movement is encountered while advancing the catheter after the first push, this may indicate that the hemostatic valve adapter has been overtightened.
   Note: In order to minimize shaft friction and reduce the likelihood of kinking, advance the catheter using short straight strokes (not at an angle) into the Z-component.
   Note: The guidewire may be held in any position that is most comfortable to user.
9. **Note:** If the physician encounters resistance of the stent delivery system prior to exiting the guiding catheter, **do not force passage**. Resistance may indicate a problem and may result in damage to the stent if it is forced. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. (See Section 12.11-Stent/Delivery System Removal Precautions).
10. While maintaining guidewire position advance the stent delivery system over the guidewire to the target lesion under direct fluoroscopic visualization.
    Utilize the proximal and distal radiopaque markers on the balloon as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Section 12.11-Stent/Delivery System Removal Precautions).
    Note: Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.

12.6 Contrast Medium Injection Preparation (if performed)

Step	Action
1.	Connect a 12cc (or smaller) syringe filled with contrast medium diluted 1:1 with heparinized normal saline to the system.
2.	If air aspiration is desired prior to contrast injection, ensure that the Z-component is positioned adjacent to the hemostatic valve adapter and securely close it around the proximal shaft. Retract the contrast injection syringe slowly. **Note: Aggressive pulling of vacuum during aspiration may cause air to be drawn in.**
3.	Check that there is no air in the hemostatic valve adapter. **Note:** If air is found in the system, purge prior to performing injection of contrast medium as per standard procedure.
4.	Perform injection of contrast medium as per standard PTCA.

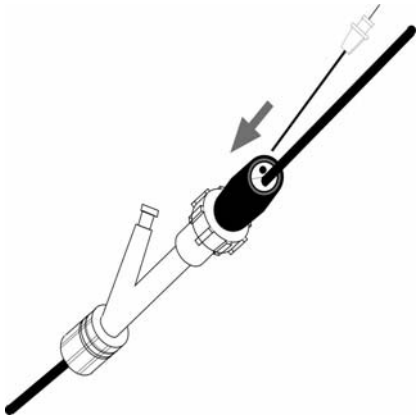
12.7 Deployment Procedure

Step	Action
1.	Prior to stent expansion, utilize high-resolution fluoroscopy to verify the stent has not been damaged or shifted during positioning.
2.	Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3.	Do not exceed Rated Burst Pressure. The **Endeavor** Stent should not be expanded to a diameter beyond 0.5 mm of its nominal expansion.
4.	Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

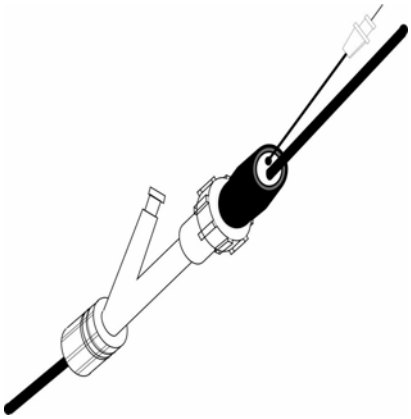
12.8 Guidewire Interchange (if performed)

Step	Action
1.	Tighten the hemostatic valve adapter around the proximal shaft.
2.	Maintain delivery system position by holding the delivery system shaft proximal to the Z-component and withdraw the guidewire.
3.	Taking care not to damage the guidewire tip, insert the guidewire into the Wire Introducer Tool packaged with this device.
	Note: Guidewires should only be loaded into the Z-component using the Wire Introducer Tool packaged with the device.
4.	Insert the Wire Introducer Tool and guidewire into the white funnel located at the proximal end of the Z-component while ensuring that the Z-component remains adjacent to the hemostatic valve adapter.
5.	Advance the guidewire into Z-component and guidewire lumen of proximal shaft.
6.	Remove the Wire Introducer Tool from the guidewire by tracking proximally over guidewire.
7.	Begin to advance the guide wire. Prior to exiting the guide catheter and advancing the guide wire into the coronary arteries, utilize fluoroscopy to verify that the wire is within the distal wire lumen of the catheter. If the wire has exited the proximal wire lumen remove the guide wire and the catheter and discard both.

Figure 12-1. Wire Introducer Tool and Guidewire on Z-component



Wire Introducer Tool and Guidewire prior to insertion into Z-component.



Wire Introducer Tool and Guidewire in place on Z-component

12.9 Removal Procedures

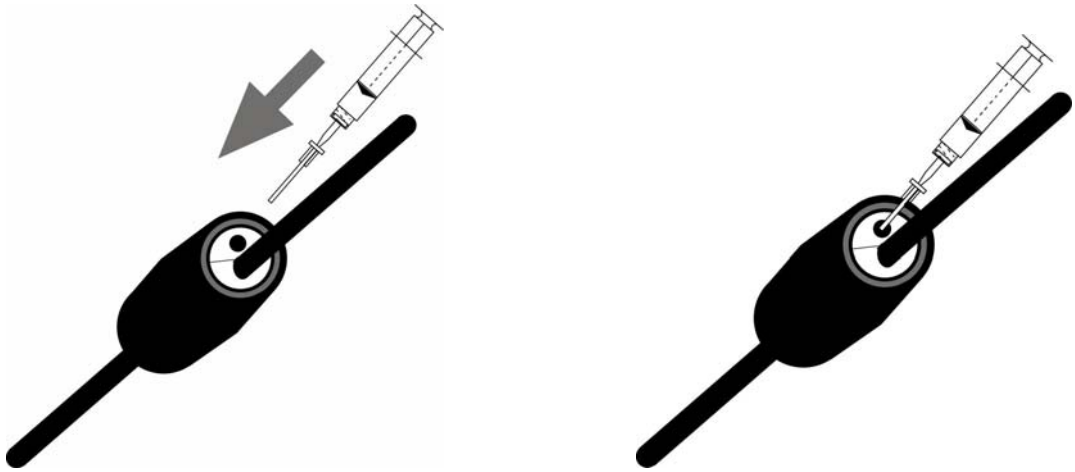
Step	Action
1.	Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 15 seconds, for full balloon deflation. Longer stents may require more time for deflation.
2.	Open the hemostatic valve to allow removal of the delivery system.
3.	Maintain position of guiding catheter and guidewire to prevent it from being drawn into the vessel. Very slowly, withdraw the balloon from the stent maintaining negative suction.

4. While maintaining guidewire position, withdraw the catheter shaft until the white Z-component marker is proximal to the Z-component. This indicates that the Z-component is near its most distal position.
   Note: When resistance is met the Z-component will be positioned against the stop joint on the dock joint. While maintaining guidewire position remove the catheter from the guide catheter. After removal of the delivery system from the guide catheter, tighten the hemostatic valve around the guidewire.
   Remove the catheter from the proximal end of the guidewire.
5. Prior to setting the delivery system aside wipe the proximal shaft with a sterile saline soaked gauze.
   Note: If it is intended to reintroduce the delivery system, go to Section 12.10-Reintroduction of **Endeavor** MX^2 Coronary Stent System.
6. Repeat angiography and visually assess the vessel and the stent for proper expansion.
   Note: Observation of the patient and angiographic evaluation of the stent site should be performed periodically within the first 30 minutes after stent placement. If stent placement is associated with the onset of thrombus or suspected thrombus in the region of the stented segment, intracoronary infusions of a thrombolytic agent is recommended.

12.10 Reintroduction of Endeavor MX^2 Coronary Stent System (If performed)

Step	Action
	If the delivery system is removed from the patient and is intended to be reintroduced later in the procedure, immediately wipe down the outside of the shaft with a sterile saline soaked gauze. Prep the stent delivery system for reintroduction as shown in steps 1-6 below.
1.	Retract the Z-component to its most proximal position on the stent delivery catheter.
2.	Fill a 20 cc syringe with 20 cc of heparinized saline solution.
3.	Attach the syringe to the flushing cannula provided.
4.	Insert the flushing cannula and attached syringe into the white funnel at the proximal end of the Z-component as shown in Figure 12-2 below.
5.	While holding the delivery system over a saline basin, flush the guidewire lumen until fluid exits the distal end of the catheter while advancing the Z-component to its most extended distal position. Note: Flushing medium may seep from the guideway during flushing.
6.	Reintroduce the delivery system into the patient following step 12.5.

Figure 12-2. Flushing Cannula and Syringe on Z-Component



Flushing cannula and syringe prior to insertion into Z -component

Flushing cannula and syringe in place on Z-component.

12.11 Stent / Delivery System Removal Precautions

If removal of a stent system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the stent system and cautiously withdraw the stent system into the guide catheter.

Should unusual resistance be felt at any time, when withdrawing the stent towards the guide catheter, the stent delivery system and the guiding catheter should be removed as a single unit. This must be done under direct visualization with fluoroscopy.

When removing the Stent Delivery System and guiding catheter as a single unit:

- **Do not retract the Stent Delivery System into the guiding catheter**. Maintain guidewire placement across the lesion and carefully pull back the stent delivery system until the proximal balloon marker of the stent delivery system is aligned with the distal tip of the guiding catheter.
- The guiding catheter and the stent delivery system should be carefully removed from the coronary artery as a single unit.
- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten, allowing safe withdrawal of the stent delivery system into the guiding catheter and the subsequent removal of the stent delivery system and the guiding catheter from the arterial sheath.

Failure to follow these steps and/or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent and/or stent delivery system components such as the balloon.

12.12 In-vitro Information

Table 12-1: Inflation Pressure Recommendations						
Pressure				Stent Nominal Inner Diameter (mm)		
atm	**kPa**	**bar**		**2.5**	**3.0**	**3.5**
6	**608**	**6.08**		2.3	2.9	3.3
7	**709**	**7.09**		2.3	2.9	3.4
8	**811**	**8.11**		2.4	3.0	3.4
9	**912**	**9.12**	Nominal	2.4	3.0	3.5
10	**1013**	**10.13**		2.5	3.1	3.5
11	**1115**	**11.15**		2.5	3.1	3.6
12	**1216**	**12.16**		2.5	3.2	3.6
13	**1317**	**13.17**		2.6	3.2	3.6
14	**1419**	**14.19**		2.6	3.2	3.7
15	**1520**	**15.20**		2.6	3.3	3.7
16	**1621**	**16.21**	RBP*	2.6	3.3	3.8
17	**1723**	**17.23**		2.7	3.3	3.8
18	**1824**	**18.24**		2.7	3.4	3.8

*Do not exceed the rated burst pressure (RBP)

12.13 Further Dilatation of Stented Segment

The stent delivery balloon may not be used for post-dilatation. Post-dilatation may be performed with appropriately sized (length and diameter) balloons to ensure that the stent is in full contact with the vessel wall. To achieve this, a balloon to artery ratio of 1.0 to 1.1:1.0 should be used to leave a residual diameter stenosis of near 0% (with a recommended maximum of no greater than 10%). Whenever possible, avoid the use of grossly oversized balloons (balloon:artery ratio > 1.2).

Precaution: Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilatation Limits
2.50 mm	3.00 mm
3.00 mm	3.50 mm
3.50 mm	4.00 mm

All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. This further expansion should be performed using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

13.0 Reuse Precaution Statement

For single use only. Do not resterilize or reuse.

14.0 Disclaimer of Warranty and Limitation of Remedy

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ATTACHMENT 9D Draft Endeavor Patient Guide

This educational booklet is provided to all patients for whom the stent procedure is being considered as general information about treatment options for coronary artery disease.

For more information on treatment options for coronary artery disease, visit www.Medtronic.com.

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Zotarolimus-Eluting
Coronary Stent System

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This booklet is provided to doctors for use in educating their patients about the options available for treating coronary artery disease. This information does not replace medical advice. Only a doctor can diagnose your health problem and determine which treatment is best for you.

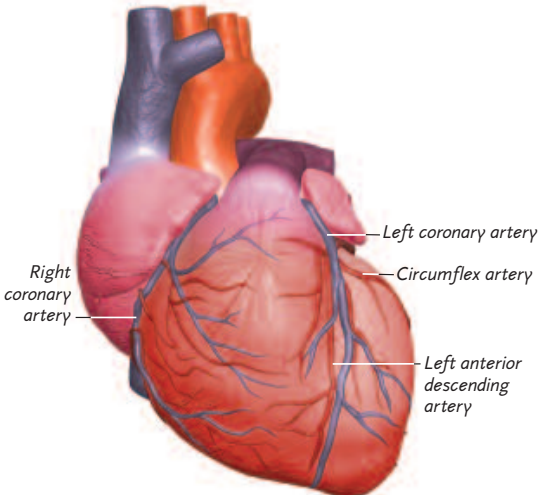


Figure 1. Coronary arteries

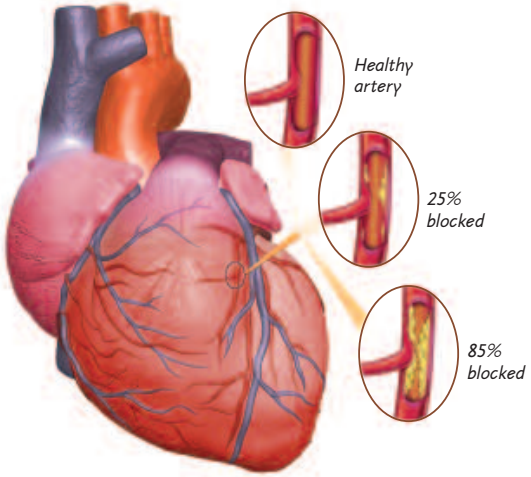


Figure 2. Plaque deposits build up inside the coronary arteries, decreasing blood flow

Your Heart

Your heart is a muscle that pumps blood throughout your body. The blood carries oxygen and nutrients that your body needs to work correctly. For the heart to be able to function properly, it also needs a constant supply of oxygen-filled blood. The vessels that supply this blood to the heart are called *coronary arteries* (see **Figure 1**). If these arteries become blocked or narrowed, treatment is usually required to restore blood flow and the vital supply of oxygen to the heart.

Coronary Artery Disease

Coronary artery disease occurs when a waxy substance called *plaque* builds up on the inside of your arteries, in a process known as *atherosclerosis*. These plaque deposits can cause a narrowing of the inside of the arteries, which decreases the supply of blood and oxygen (see **Figure 2**). When atherosclerosis occurs in the arteries that supply your heart, it is called coronary artery disease. When it occurs in the arteries that supply oxygen-rich blood to your arms and legs, it is called peripheral vascular disease.

The reduced blood flow to the heart can lead to chest pain (called *angina*) and numbness in the arms and shoulders. In some cases, it can cause a heart attack (*myocardial infarction* or *MI*), or even death.

TABLE 1. RISK FACTORS FOR CORONARY ARTERY DISEASE

- High blood pressure (also called hypertension)
- High levels of cholesterol and triglycerides in your blood
- Diabetes
- Obesity and overweight
- Gender (sex)
- Smoking
- Lack of physical activity
- Age over 65 years
- Family history of coronary artery disease

Figure 3. Healthy artery

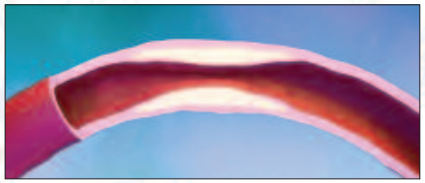


Figure 4. Artery with plaque

Risk Factors

Several factors can increase your risk of coronary artery disease (see **Table 1**). The more risk factors you have, the higher your risk.

Some proven risk factors are beyond your control, such as your age, sex and family history. Other risk factors can be managed or eliminated to lower your risk. These risk factors are smoking, diabetes, high blood pressure, high cholesterol, obesity and having a sedentary lifestyle. Your doctor can support your efforts to make healthier choices regarding your diet, tobacco use, activity level and stress management. For more information on steps you can take to prevent heart disease, see Page 23.

Diagnosis

When making a diagnosis, your doctor will consider:

- Your current symptoms and previous medical history.
- Your family history.
- Your risk factors.

Before deciding on a treatment plan, your doctor may also recommend that you have a chest X-ray and/or blood tests. You may also have a test to measure how well your heart is functioning. A baseline *electrocardiogram* (ECG or EKG) records your heart's electrical activity while you sit quietly. An exercise ECG, or "stress test," shows how your heart responds to increasing physical activity. Both tests are designed to show if your heart is not working properly due to a lack of oxygen.

Coronary Angiogram

Your doctor also may perform a special X-ray test called a coronary *angiogram* (also called a *cardiac catheterization*). It will show the exact location and

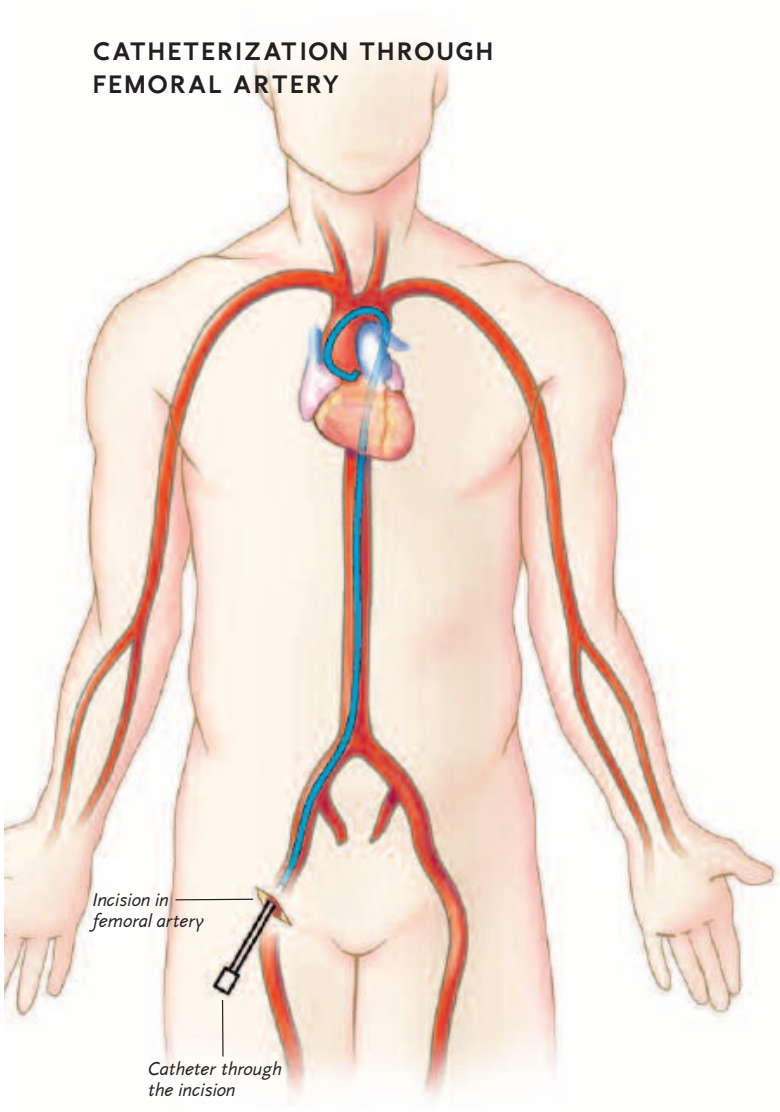


Figure 5. Heart catheterization through femoral artery

extent of your narrowed or blocked coronary arteries. This test, which usually takes 20 to 40 minutes, is performed in a cardiac catheterization laboratory ("cath lab"), a room designed especially for the procedure.

For the procedure, you will be given a mild sedative to help you relax. Small sticky patches, called electrodes, will be placed on your chest to monitor your heart rate and rhythm. Your doctor will insert a short, hollow tube into an artery in your arm or leg, after numbing the area with a local anesthetic (see **Figure 5**).Through this tube, the doctor can move small metal wires, called guidewires, and thin, flexible shafts, called catheters, to the arteries in your heart. A special dye will be injected through the catheter and into your bloodstream to allow your doctor to view your arteries on an X-ray monitor, much like a television screen.

Results of this angiogram can help your doctor decide which treatment option is best for you. It is normal to feel a warm but temporary "flush" when the dye is injected. Tell your doctor or nurse if you feel any pain or discomfort during the procedure.

Treatment Options for Coronary Artery Disease

Your doctor will recommend a treatment plan for you, depending on your symptoms, test results and medical history. The plan may include medications to relieve your chest pain and/or to expand the coronary arteries, increasing blood flow to your heart.

However, because medicine alone may not clear blocked arteries, you may need more treatment, including surgery, angioplasty and/or stenting.

BALLOON ANGIOPLASTY

Figure 6a. Artery narrowed by plaque deposits

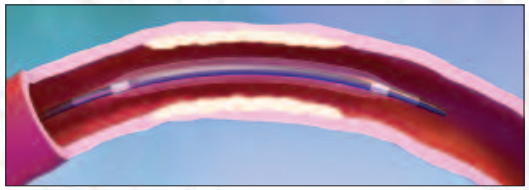


Figure 6b. Balloon is inflated to flatten plaque and reopen the artery

Figure 6c. Balloon is deflated and withdrawn, restoring blood flow

Surgery

Coronary artery bypass grafting is a common surgical procedure that removes a section of artery or vein from another part of your body. This vessel is then connected (grafted) to the coronary artery at the blockage site. This creates a new path for blood to flow around (bypass) the blocked artery and to your heart. Often, several blocked arteries are bypassed during the same operation. Most coronary bypass patients remain in the hospital for about a week, followed by a recovery period at home.

Balloon Angioplasty

Balloon angioplasty is performed in the catheterization laboratory—the same room where you may have had a coronary angiogram. Like with coronary angiograms, your doctor will inject a special dye through a catheter into your bloodstream, which allows your doctor to view your arteries on the X-ray monitor. A local anesthetic will be used to numb the puncture site, and you may be given a sedative to help you relax. A catheter with a small balloon on its tip is inserted through an artery in your groin or your forearm and threaded through your arteries until it reaches your blocked coronary artery. Then the balloon is inflated to flatten the plaque against the wall of the artery. This increases blood flow through the artery (see **Figures 6a–c**).

It is normal to have some chest pain when the balloon is inflated. Tell your doctor or nurse if you feel any pain or discomfort during the procedure.

STENTING PROCEDURE

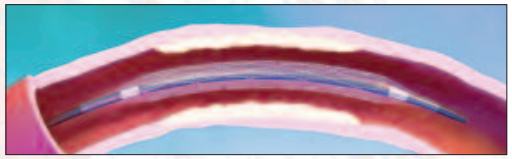


Figure 7a. The unexpanded stent is delivered to the treatment area via a special catheter

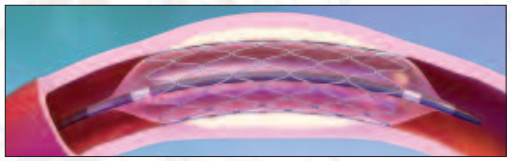


Figure 7b. The balloon is inflated to expand the stent

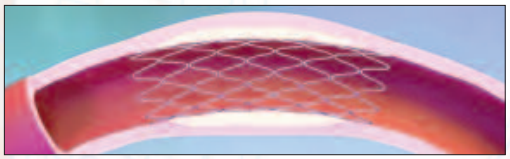


Figure 7c. The balloon is deflated and withdrawn from the body, leaving the stent to support the artery and maintain good blood flow

Stenting

Your doctor also may recommend placing a coronary stent in the narrowed part of your artery during the balloon angioplasty procedure (see **Figures 7a–c**). A stent is a tiny, expandable, mesh-like tube made of metal that acts as a scaffold inside the artery and helps keep the artery open after balloon angioplasty.

Implanting the stent does not require open surgery. Instead, your doctor will make a small incision in your groin or forearm and insert a catheter into the artery, similar to the balloon angioplasty procedure. A specially designed balloon catheter is used to deliver the stent to the blocked area of the coronary artery. The balloon is inflated to expand the stent. As the stent expands, it helps flatten the plaque against the artery wall, increasing blood flow. Once the stent is fully expanded, the balloon is deflated and removed from your body. The stent is designed to stay in your artery permanently.

Stenting is less invasive than traditional surgery. It involves a shorter hospital stay—usually one to three days—and faster recovery than surgery. However, a condition called *restenosis* occurs in some patients who receive conventional stents. This is the renarrowing of the artery where the stent was placed, due to the overgrowth of normal tissue within the stent during the healing process.

Figure 8. A stent is a tiny, expandable mesh-like tube that helps support the artery, increasing blood flow

Drug-Eluting Stents

To help prevent restenosis, *"drug-eluting" stents* have been developed. These stents provide the same structural support as conventional (uncoated) stents, but they also have a drug applied to them. The drug is released over time, helping to prevent restenosis by limiting the overgrowth of normal tissue within the stent.

Medtronic Endeavor Zotarolimus-Eluting Coronary Stent

Medtronic's Endeavor zotarolimus-eluting coronary stent has a drug (called zotarolimus) contained within a biocompatible polymer that coats the surface of the stent. The Endeavor stent provides mechanical support in the artery, and the zotarolimus drug is released into the artery wall around the stent. The zotarolimus drug is designed to limit the growth of scar tissue, which results in restenosis.

Contraindications

You should not receive the Endeavor stent if you have known hypersensitivity to:

> Drugs such as zotarolimus, rapamycin, tacrolimus, everolimus or any other analogue or derivative.
> The cobalt-based alloy (cobalt, nickel, chromium and molybdenum).
> The polymer (phosphorylcholine) or its individual components (including but not limited to polymethacrylates).

Coronary artery stenting is contraindicated for use in:

> Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
> Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

Before You Receive an Endeavor Stent

Your doctor might tell you to take aspirin and other medications before your stent procedure. Tell your doctor which medications you are currently taking and whether you have a history of bleeding problems.

Potential Adverse Events Associated with the Endeavor Stent

The risk of using the Endeavor stent are similar to those that are associated with standard stent procedures. If the stent clots, you may need another angioplasty. It may also lead to a heart attack, the need for urgent bypass surgery or death. Even with successful stent implants, there is a chance of renarrowing in the first six months. This may require more therapy, such as repeat angioplasty and/or bypass surgery, to reopen the artery and to increase blood flow to the heart. The risks from using balloon catheters after stent implants are similar to the risks that may occur during the stent implant. These may be serious enough to require surgery or cause death.

The Endeavor stent is composed of an alloy containing the following metals: cobalt, chromium, molybdenum and nickel. Other permanently placed devices such as artificial hip joints, heart pacing wires and blood vessel filters have used similar alloys. The risk of the material for use as a stent is thought to be minimal.

Other risks from these devices are the same as treatment procedures for a narrowed heart artery. Some problems with standard balloon angioplasty and stenting include but are not limited to:

Most Likely Risks

> Bruise or bleeding at the catheter insertion site in the groin or arm.
> Pain at the catheter insertion site.
> Irregular heartbeats, possibly life-threatening.
> Chest pains during and after the procedure.
> Decreased or increased blood pressure.
> Renarrowing of the heart artery.

Rare Risks

> Tearing, puncture or rupture of the heart artery.
> Air, pieces of devices or fragments of clots blocking the coronary artery.
> Complete blockage of the heart artery, which may require a repeat procedure to reopen the heart artery.
> Bleeding around the heart.
> Heart attack.
> Damage to the stent or injury to the heart artery requiring emergency heart surgery.
> Bleeding requiring transfusion or surgery.
> Allergic reaction (may include X-ray dye, cobalt, chromium, nickel, zotarolimus [an analog of rapamycin] and phosphorylcholine [the stent's base coating]).
> Infection.
> Nerve injury.
> Aneurysm (weakening of a portion of the wall of a blood vessel).
> Failure to release the stent from the catheter.
> Stent misplacement in the artery.
> Movement of the stent from where it was placed.
> The balloon used to expand the stent may break.
> Shock.
> Stroke.
> Death.

The actual risks of the zotarolimus drug are not yet fully known. Your exposure to zotarolimus is directly related to the total amount of stent length implanted. The risks that might occur include but may not be limited to:

> Blood in the urine and/or diarrhea.
> Diarrhea.
> Dry skin.
> Fatigue.
> Headache.
> Infection.
> Pain (abdominal, joint, injection site).
> Skin reaction (at injection site).
> Tingling feeling around the mouth.

What to Expect After Your Stent Procedure

Immediately After Procedure

You will be asked to lie flat for four to six hours following the procedure and to not bend your leg or arm, depending on which area your doctor used to insert the catheters. Pressure will also be placed on the area.

A vascular closure device may be used to seal the puncture site in your groin or arm. You will be allowed to get up and walk around sooner if this type of device is used. Your hospital stay may range from one to three days.

Medications will be prescribed for you before and after stent placement. Aspirin and antiplatelet medications (also called platelet inhibitors) are the most commonly prescribed. They help prevent a blood clot (thrombus) from forming and adhering to the surface of the stent. You may need to have periodic blood tests while taking these medications. Your doctor or nurse will give you instructions about your medications before you leave the hospital.

Caution: If you have any chest pain, discomfort or bleeding from your puncture site, call your doctor immediately. If your doctor is unavailable, call for an ambulance to take you to the nearest hospital emergency room.

Take All Medications as Instructed

After you leave the hospital, your cardiologist may instruct you to take a small daily dose of aspirin indefinitely. Your doctor will tell you how long you should continue taking the antiplatelet drugs. It is very important that you take these medications exactly as your doctor instructs you:

> Follow your medication schedule exactly to avoid possible complications after you receive your stent. Do not miss any doses.

- Call your doctor if you cannot keep taking your medications because of side effects such as rash, bleeding or upset stomach.
- **Caution:** Do not stop taking your prescribed medications unless you are instructed to do so by the doctor who performed your stent procedure.
- **Caution:** Notify your cardiologist or family doctor if you are scheduled to see the dentist while on antiplatelet medication. Your doctor may prescribe antibiotics to avoid the potential of an infection.

Follow-Up Care

You will be discharged to the care of your cardiologist or family doctor. You should be able to return to your normal activities soon.

Caution: Notify your doctor immediately if you experience chest pain (angina) or notice any changes such as more severe or frequent chest discomfort, especially in the first month after a procedure. These symptoms may indicate a renarrowing in your coronary arteries.

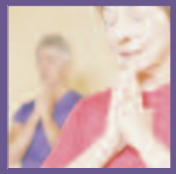
Your doctor will ask you to return for follow-up visits. The first visit is usually two to four weeks after your stent is implanted, with follow-up visits every six months for the first year. Be sure to keep all appointments for follow-up care, including blood tests.

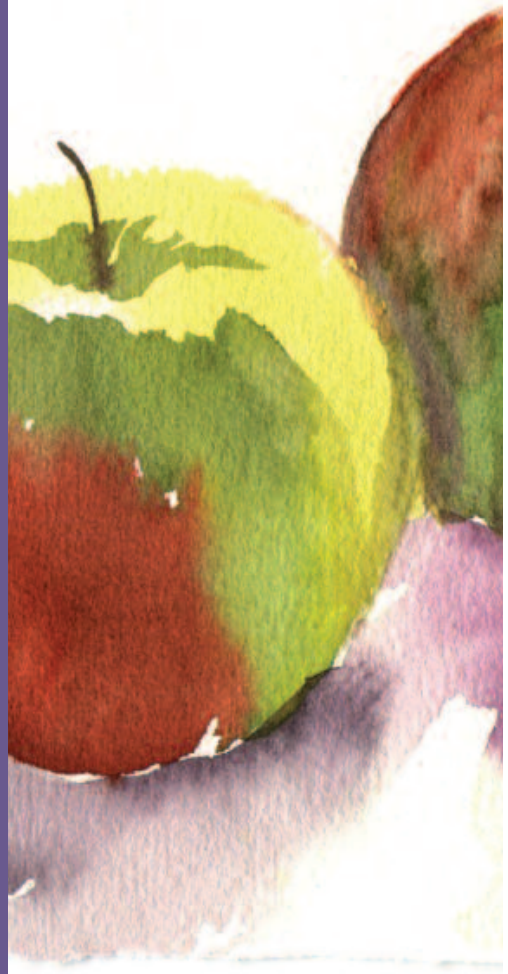
Keep Your ID Card Handy

Caution: Show your identification card if you report to an emergency room. This card identifies you as a patient who has had a stent implanted.

If you require a magnetic resonance imaging (MRI) scan, tell your doctor or MRI technician that you have a stent implant.

PREVENTION





Preventing Coronary Artery Disease

Coronary artery disease can be treated effectively, but it has no cure. You can help to prevent your coronary artery disease from progressing by carefully following your doctor's advice. Your doctor may prescribe medications to help control your blood pressure, diabetes and/or high cholesterol. Your doctor may also recommend some lifestyle changes. Among the healthy choices you can make:

Stop smoking. If you smoke, quitting is the single most important thing you can do to lower your risk of coronary artery disease. Chemicals in cigarette smoke may make it easier for plaque to build up on your artery walls. And smoking increases your heart rate and blood pressure, raising your risk of heart attack and stroke. If you're ready to quit, ask your doctor for advice—he or she can recommend smoking cessation aids to help you quit.

Increase your activity. A sedentary lifestyle increases your risk. Your doctor can recommend an activity program tailored for your situation. Regular exercise can help you lower your blood pressure and blood cholesterol and reach a healthy weight. It can also help you manage the daily stresses of modern life more easily.

Choose a healthy diet. A diet low in saturated fats and cholesterol and rich in lean protein, fresh fruits, vegetables and whole grains can help you achieve a healthy weight and control your blood pressure and cholesterol levels.

Manage your stress. Stress is an inescapable aspect of modern day living, but you can help lessen its negative health effects by practicing the "relaxation response." Research has shown that relaxation techniques can improve your ability to cope with stressful events while decreasing your heart rate, blood pressure and stress hormone levels.

Frequently Asked Questions

How long will the stent stay in my body?
Stents are designed to stay in your body permanently.

What are the restrictions or cautions?
If you require magnetic resonance imaging (MRI), tell your doctor or MRI technician that you have an implanted stent.

When can I resume my regular activities?
Your doctor will advise you. Many patients can return to work and follow their normal routine about a week after their stent procedure.

Will my stent set off the metal detector at airport security checkpoints?
No, your stent implant will not trigger alarms at security checkpoints.

Will I be able to feel the stent inside me?
No, you will not be able to feel the stent once it has been implanted in your artery.

Could I have recurring symptoms?
Yes, it is possible that you will experience symptoms again, either due to a new blockage in the treated region or another blockage in your arteries. Your doctor will monitor your progress.

How can I help prevent a recurrence of symptoms?
While there is no sure way to prevent a recurrence of symptoms, you can reduce the risk through exercise, not smoking and eating a healthy diet. Your doctor can advise you about lifestyle changes.

Glossary

Angina. Pain or discomfort in the chest because of reduced blood flow and oxygen supply to the heart muscle.

Angiogram. Special X-ray test that indicates the number, exact location and extent of narrowed or blocked coronary arteries.

Antiplatelet medications. Drugs that inhibit the function of platelets, the blood cells that clump together to begin the process of blood clot formation. Examples include aspirin and Plavix® (also known as clopidogrel).

Atherosclerosis. Disease process involving the buildup of a waxy substance called plaque on the inside of arteries.

Balloon angioplasty. Nonsurgical medical procedure in which a specially designed balloon catheter is used to open a narrowed or blocked artery.

Cardiac catheterization. Procedure in which a thin, hollow tube (catheter) is inserted into an artery for the purposes of visualizing the heart and blood vessels, and diagnosing and treating heart disease.

Cardiac catheterization laboratory. A room designed especially for the catheterization procedure.

Coronary arteries. Blood vessels on the outside of the heart that provide oxygen-filled blood to the heart.

Coronary artery bypass graft. Common surgical procedure that grafts an artery from your chest or a vein from your leg to create an alternate route around a narrowed or blocked coronary artery.

Drug-eluting stent (DES). Used to refer to stents that carry drugs that help keep arteries from renarrowing after a stent has been implanted.

Electrocardiogram (ECG or EKG). Medical test in which several electronic sensors are placed on your body to monitor electrical activity associated with the heartbeat.

Myocardial infarction (MI). Damage or death of an area of your heart muscle, resulting from a blocked blood supply to the area.

Plaque. Waxy substance consisting of fats and cholesterol that can build up on the inner lining of your arteries.

Restenosis. Renarrowing of an artery at the site of angioplasty and/or a stent implant, due to the over-growth of normal tissue.

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