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First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in *de novo* native coronary artery lesions: Endeavor I Trial

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KEYWORDS

Stent, ABT-578, Hyperplasia, Restenosis, Coronary Angiography, Intravascular Ultrasound

Abstract

Aims: The Endeavor I study was the first clinical study evaluating the safety and feasibility of the Endeavor stent system in the treatment of symptomatic coronary artery disease. The Endeavor Stent System comprises a new cytostatic, antiproliferative and immunosuppressive agent in the same class of drugs as sirolimus, (ABT-578), a phosphorylcholine polymer-based coating, and an established cobalt-alloy stent with thin struts, (Driver™ stent).

Methods and results: One hundred consecutive patients with symptomatic ischemic heart disease due to *de novo*, obstructive lesions of native coronary arteries were treated with the Endeavor stent system at eight centers in Australia and New Zealand according to contemporary practice. The acute lesion, procedure, and device-deployment success rates were all 100%. Independent core laboratories analyzed quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) data immediately after stent implantation, and at 4 and 12 month follow-up. At 12 months, in-stent late lumen loss was 0.61±0.44 mm; in-segment late lumen loss was 0.43±0.44 mm, and neointimal hyperplasia volume was 14.2±11.8 mm^3 (corresponding to a percent volume obstruction of 9.7%±8.5%). By QCA and IVUS, the pattern of neointimal hyperplasia was greatest within stent and not at the stent edges. The binary angiographic restenosis rate (defined as >50% diameter stenosis) at 4 and 12 months was 2.1% (2/97) and 5.4% (5/93) respectively. The cumulative incidence of major adverse cardiac events (MACE, defined as death, myocardial infarction, emergent cardiac surgery or repeat revascularization of the index lesion), was 1% at 30 days and 2% at 4 and 12 months.

Conclusion: This 100 patient pilot study demonstrates that the Endeavor stent system is a reliable and safe treatment for obstructive coronary disease, providing durable event free clinical outcomes to 12 months by suppression of neointimal proliferation of the target lesion. The results support further pivotal evaluation in larger randomized clinical trials.

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Introduction

The use of endoluminal metallic stents became common practice during percutaneous coronary intervention after clinical trials indicated that stenting decreased restenosis rates when compared with conventional balloon angioplasty[1,2]. Restenosis rates in patients who receive coronary stents, however, can be as high as 20% to 40% after 6 months[1-5]. Stents coated with antiproliferative agents to inhibit neointimal hyperplasia represent a promising new technology for preventing restenosis. The use of sirolimus- or paclitaxel-eluting stents has been associated with significantly lower restenosis rates compared with conventional bare metal stents[6-11]. Mid and long term safety are still in question with late stent thrombosis attributed in part to polymer exposition and degradation or stent malapposition[12-14]. As the first generation of drug eluting stents has reduced the problem of restenosis with stenting, there is great interest in testing newer stent systems with greater flexibility that facilitates better deliverability to the target lesion.

A novel drug eluting stent platform, known as the Endeavor stent, combining the approved Driver™ chromium-cobalt-nickel alloy coronary stent system with an antiproliferative agent, ABT-578, and a biomimetic phoshorylcholine polymer, has been developed as a collaborative effort between Medtronic Vascular (Santa Rosa, CA., USA) and Abbott Laboratories (Abbott Park, Chicago, IL, USA). ABT-578 is a sirolimus analogue, that binds with a specific intracellular receptor $FKBP_{12}$ to form a trimeric complex with the mammalian target of rapamycin (mTOR), thereby blocking mTOR's signal transduction and inducing cell-cycle arrest in the G1 phase, limiting cell division[15,16]. The phosphorylcholine polymer, PC Technology, mimics a neutral and naturally occurring phospholipid. Clinical investigators have demonstrated the safety of PC coating in stent treated patients[17-19]. Also, stents coated with PC technology release drugs such as ABT-578 in a controlled and predictable fashion. The action of ABT-578, in combination with the favorable performance properties of the Driver™ stent, provide a novel and potentially valuable platform for the treatment of symptomatic patients with coronary artery disease.

The objectives of the ENDEAVOR I "first in human" multicenter prospective study of the Endeavor stent system were: (1) to assess the early feasibility and safety of implanting the Endeavor stent system in human coronary arteries, based on the device success rates and incidence of major adverse cardiac events (MACE) at 30 days; and (2) to assess the medium and long-term safety and efficacy of the Endeavor stent system, based on target lesion late lumen loss and neointimal hyperplastic volume, and the cumulative incidence of adverse events at 4 and 12 months.

Methods

The study was designed as a prospective, multi-center, non-randomized, single-arm study. One hundred subjects with symptomatic ischemic heart disease attributable to a native coronary artery stenosis, and amenable to treatment by percutaneous stenting, were enrolled in the ENDEAVOR 1 Trial from January 2003 through April 2003.

Data collection and core laboratories

All clinically relevant baseline and follow-up variables were collected on case report forms and processed by the Harvard Clinical Research Institute (HCRI, Harvard Medical School, Boston, MA). All data was independently monitored at the clinical site for validity. All clinical and coronary endpoints were determined by independent core laboratories (quantitative angiography, intravascular ultrasound, and ECG) and all clinical events were adjudicated by a coordinated independent clinical events committee at HCRI (non-involved cardiologists in the Boston medical area).

Quantitative coronary angiography (QCA). Coronary angiograms were obtained at baseline, at the completion of the stenting procedure, and at 4- and 12-month follow-up, and then submitted to the angiographic core laboratory (Brigham and Women's Angiographic Core Laboratory, Boston, MA) for analysis. Quantitative angiographic measurements of the target lesion were obtained within the stent boundaries (in-stent measurements) and within the stent boundaries plus 5 mms proximal and distal to the stent (in-segment measurements). Reference and minimum lumen diameters and lesion length were determined using an automated edge-detection algorithm (Cardiovascular Measurement System, Medis; Medical Imaging Systems, Nuenen, The Netherlands[20]).

Intravascular ultrasound (IVUS). IVUS examinations were performed at the completion of the stenting procedure, and at 4- and 12-month follow-up. IVUS images were obtained from 40MHz Atlantis IVUS catheters (Boston Scientific, Natick, MA) during automated, motorized pullback at 0.5 mm/sec in accordance with guidelines provided by the IVUS Core Laboratory. Qualitative assessment and quantitative determinations of the areas and volumes of the vessels, stents, and lumens were made by the IVUS core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, CA[21]).

Study patients

Study patients included single and multiple vessel coronary artery disease but only a single lesion per patient was treated in this trial. The target lesion must have been *de novo*, non-restenotic and in a native coronary artery. Lesions ≥50% and ≤100% diameter stenosis with a length ≤15 mm, in vessels with a reference diameter 3.0 mm to 3.5 mm, were included. Major exclusion criteria were a left ventricular ejection fraction <30%, significant (>50%) stenosis proximal or distal to the target lesion, occurrence of myocardial infarction (MI) within the preceding 72 hours, and a coronary interventional procedure of any kind within 30 days before or planned within 30 days after implantation of the stent system.

Clinical follow-up for all patients was performed at 30 days (telephone contact), 4 months (angiographic and IVUS measurements), 9 months (telephone contact), and at 12 months (angiographic and IVUS measurements). In addition, patients were consented to have yearly telephone follow-ups for 5 years from the date of the procedure. The study was conducted according to the Declaration of Helsinki, the medical ethical committees of all sites approved the protocol, and written informed consent was obtained from every patient.

Stent system

The Driver stent platform for the Endeavor stent system was CE mark approved in November 19, 2002 and received pre-market approval from the United States Food and Drug Administration in October 2003 for the treatment of coronary lesions. This cobalt-alloy stent has a low profile, and a strut thickness of 0.0036 inches (91 μm), designed to improve tracking and crossing in tortuous anatomy. In a prospective, multicenter, randomized registry study of 298 patients with symptomatic ischemic heart disease due to *de novo* or restenotic nonstented native lesions of a single vessel, the Driver™ stent platform was found safe and effective[22].

The polymer, phosphorylcholine, is a synthetic copy of the predominant phospholipid in the outer membrane of red blood cells and has high biovascular compatibility. In animal studies, phosphorylcholine-coated stents have demonstrated significantly less platelet adhesion compared with uncoated stents[19,23]. In the SOPHOS (Study of PHosphorylcholine coating On Stents) trial, the phosphorycholine-coated BiodivYsio stent was found safe and effective for the treatment of native coronary artery lesions[18].

The drug, a synthetic analog of sirolimus, ABT-578, binds with the intracellular protein FKBP-12 to form a trimeric complex with the mammalian target of rapamycin (mTOR), thereby blocking mTOR signal transduction, inducing cell-cycle arrest in the G1 phase, and limiting cell division[15,16]. The Endeavor stent system carries 10 μg of ABT-578 per millimeter of stent length. The drug is localized mainly on the ablumenal (arterial wall) side of the stent by means of the proprietary coating technique. For this study the stent system was available in a single length of 18 mm and in diameters of 3.0 mm and 3.5 mm.

Treatment procedure

Eight sites in Australia and New Zealand participated in this study. Stents were deployed according to a standardized procedure. Heparin was administered to maintain activated clotting time ≥250 sec or between 200 sec and 250 sec if a glycoprotein IIb/IIIa receptor inhibitor was administered. Patients received aspirin (300 mg to 325 mg daily), starting before the procedure, and clopidogrel (300 mg loading dose 6 hours before or at the procedure and 75 mg per day thereafter for 12 weeks). Pre-dilation was mandatory and undertaken with a balloon length shorter than the stent. Post-dilation, if required was also carried out with a balloon less than or equal to the stent length. Only 3.0 and 3.5 mm diameter Endeavor stents of 18 mm length were used in this study.

Endpoint definitions

Clinical endpoints were determined and summarized at each study follow-up milestone. Death was defined as the occurrence of any death during the study period. Myocardial Infarction (MI) was defined as any clinical event (peri-procedure or recurrent clinical presentation) in which there was evidence of myocardial necrosis (CK-MB >3 times normal), and further distinguished into Q- and Non-Q MI based on the development of Q waves in two or more contiguous lead on a standard 12-lead ECG. Target Lesion Revascularization (TLR) was defined as any percutaneous interven-

tion or bypass surgery performed on the index target lesion at any time after the index procedure. Target Vessel Revascularization (TVR) was defined as any percutaneous intervention or bypass surgery performed on the index target vessel at any time after the index procedure, and Target Vessel failure (TVF) was defined as TVR or death or MI. Major Adverse Cardiac Events (MACE) was defined as TLR or death or MI. Stent thrombosis (ST) was defined as a thrombotic occlusion or stenosis of the stented target lesion, or in the absence of an angiogram, an ST-segment elevation MI in the territory of the index vessel.

Angiographic endpoints were determined at the baseline index procedure, and at 4 month and 12 month angiographic follow-up. Lesion length was measured as the length of contiguous coronary narrowing (defined as percent diameter stenosis >20%) containing both the target hemodynamically obstructive and adjacent non-obstructive plaque. Acute Gain was defined as the MLD immediately after the procedure minus the MLD at baseline. Late loss was defined as the MLD immediately after the procedure minus the MLD at 8-month follow-up. Percent diameter stenosis was defined as (1 - (MLD/reference vessel diameter) times 100). Binary angiographic restenosis (BAR) was defined as a >50% diameter stenosis at follow-up. Acute lesion success was defined as achievement of a target lesion percent diameter stenosis <50%); device success was defined as acute lesion success with the intended Endeavor stent; and procedure success was defined as device success without in-hospital death, myocardial infarction or emergent surgery.

Intravascular ultrasound (IVUS) endpoints were also assessed immediately after the baseline procedure, and at 4 and 12 months. Qualitative IVUS parameters used for safety evaluation included, stent edge dissection (defined as disruptions of plaque immediately adjacent to the stent ends where the flap could be clearly differentiated from the underlying plaque) and stent incomplete apposition (defined as ≥ 1 stent struts clearly separated from the vessel wall with evidence of blood speckle behind the strut).

Quantitative IVUS measurements were performed using commercially available planimetry software (Echoplaque, Indec Systems) according to previously validated and published protocols[24]. External elastic lamina (EEL), stent, and lumen area were manually traced for serial cross sections with the axial distance of nearly 0.5 mm throughout the stented segment. NIH area was computed as stent minus lumen area. Volumetric analysis was performed by means of Simpson's method for the entire stented segment.

In detailed analysis, NIH growth was analyzed as a NIH area/volume divided by the corresponding stent area/volume to adjust for the different stent sizes. The entire in-stent NIH growth was evaluated as percent NIH volume (NIH volume x 100 / stent volume: % NIV). The most severe luminal obstruction by NIH growth within the stent segment was determined as the maximum of percent NIH area (NIH area x 100 / stent area: % NIA).

Primary Safety Endpoint. The primary safety endpoint was MACE at 30 days, analyzed on an intent-to-treat basis. Consented subjects who met eligibility criteria were analyzed regardless of the subsequent sequence of events.

Primary Efficacy Endpoint. The primary efficacy endpoint was angiographic in-stent late loss at 4 months, analyzed on an intent-

to-treat basis. All eligible subjects who received a stent and follow-up angiography were included in the primary efficacy endpoint analysis.

Study objective and statistical analysis

The main objective of this study was to demonstrate the ease-of-use (feasibility) and acute safety of the ABT-578 Coated Driver Coronary Stent System while gathering preliminary information on mid- and long-term safety and efficacy of the device. The trial was therefore designed to minimize the number of subjects exposed to the device while still providing enough information for a preliminary indication of safety and feasibility. A sample size of 100 subjects was deemed sufficient to provide reasonable confidence in the estimates of safety and efficacy generated by this study.

Based on observations from contemporary stenting trials, the expected incidence of MACE at 30 days was estimated to be approximately 4%, reflecting a true event rate of 4 or fewer subjects in this pilot study. However, the random error of estimating a true 4% rate with 95 subjects (assuming 5% loss to follow-up at 30 days) is 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 was 7.9%. Thus, the proposed 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.

An in-stent late loss of approximately 0.8 - 1.0 mm±0.55 mm (mean±SD) has observed in contemporary bare metal stenting trials[25]. Assuming a 20% loss to follow-up, this trial had 89% power to detect a late loss difference of 0.2 mm or greater from 0.8 mm. These estimates were derived using a one group t-test with a two-tailed alpha value of 0.05.

Analysis and reporting of results. All analyses are made under intention-to-treat, defined as the set of all subjects with qualifying stenosis in which treatment with the Endeavor system was intended, i.e., all patients in whom a guidewire was used to initiate the procedure. Analyses of angiographic and IVUS data, collected at baseline, 4, and 12 months follow-up were analyzed on all patients with technically successful paired data for the pairwise comparisons. Categorical variables were tested using contingency tables 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. All statistical tests were 2-sided, and a p-value <0.05 was considered statistically significant.

Results

Demographics. Baseline clinical characteristics for the 100 enrolled patients are shown in (Table 1) demonstrated a mean age of 59 years (range 35-76). The population was 79% men, and 47% of the subjects had a prior MI, while 16% had a history of diabetes mellitus. The age, sex distribution and risk factor profile were consistent with other contemporary study samples of patients presenting with ischemic symptoms due to a discrete, *de novo* lesion in a single, native coronary artery[26].

Subjects and follow-up. Procedural and lesion characteristics (Table 2) were summarized for a total of 107 implanted stents in

Table 1. Patient characteristics

	N = 100
Age (years, mean±SD)	58.8±10.1
Male sex (%)	79
Diabetes mellitus (%)	16
Hyperlipidemia (%)[a]	91.8
Hypertension (%)	53
Current smoker (%)	34
Prior myocardial infarction (%)	47
Prior percutaneous coronary intervention (%)	19
Ejection fraction (%, mean±SD)	65.2±12.3

a Hyperlipidemia was defined as a low-density lipoprotein cholesterol level above 3.4 mmol per liter.

Table 2. Lesion characteristics

	N = 100
Target artery (%)	
Left anterior descending coronary artery	42
Left circumflex coronary artery	23
Right coronary artery	35
ACC-AHA class (%)	
A	17
B1	34
B2	44
C	5
Diameter of reference vessel (mm)	2.96±0.47
Minimal lumen diameter (mm)	0.88±0.33
Diameter stenosis (%)	70.3±9.8
Length of lesion (mm)	10.9±3.1

Values are mean±SD. ACC, American College of Cardiology; AHA, American Heart Association.

100 patients; in seven patients two stents were implanted. Complete clinical follow up at 12 months was available for all patients. At 4 months, three patients were lost to QCA follow-up (97% follow-up) and 95 patients had technically successful IVUS (95% follow-up). At 12 months, nine patients were lost to QCA follow-up (91% follow-up) and 86 patients had technically successful IVUS (86% follow-up). Angiographic estimates at 12 months were made on 93 subjects: 91 who had actual 12 month follow-up plus two subjects whose 4 month data was carried forward because they underwent target lesion revascularization at 4 months.

Clinical results. The acute lesion success, device success, and procedure success were all 100%. Table 3 summarizes the composite and component adverse event rates at 30 days, 4 months and 12 months. The in-hospital incidence of major adverse cardiac events (MACE) was 0%, while MACE at 30 days was experienced by one subject (1%, non-Q wave MI post procedure, day 10 associated with stent thrombosis and repeat revascularization via percutaneous intervention then bypass surgery). At 360 days, the cumulative MACE rate was 2% (one additional subject had a target lesion revascularization 112 days post procedure). Both the 30-day 1% MACE rate and the 12-month 2% MACE rate were well less than the

Table 3. Cumulative composite and component clinical endpoint rates at 30 days, 4 months, and 12 months

Variable	30 days N = 100	4 months N = 100	12 months N = 100
Any MACE (%)	1	2	2
Death (%)	0	0	0
Myocardial infarction (%)	1	1	1
Q wave (%)	0	0	0
Non-Q wave (%)	1	1	1
Target lesion revascularization (%)	0	1	1
CABG (%)	1	0	0
PTCA (%)	1	0	1
Target vessel failure (%)	0	2	2
Stent Thrombosis	1	1	1

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

tolerable upper safety boundary of 8% ≤8 patients) that was pre-specified in the clinical protocol. There were no deaths over the 12 month study period.

The Kaplan-Meier estimate of freedom from MACE at 12 months was 98% [95% CI: 94.1,100.0]. The cumulative incidence of TVF at 12 months was 2.0% (2/100). The TLR-free survival rate at 12 months post-procedure was also 98.0% and the cumulative incidence of TLR at 12 months was 2.0% (2/100).

Angiographic and IVUS results at 4 and 12 months follow-up. Figure 1,2 and Table 4 present the QCA results after the index stenting procedure at 4 months and 12 months after the index stenting procedure at 4 months and 12 months. Binary angiographic restenosis was seen in 2 of 97 patients (2.1%) at 4 months. In-segment late lumen loss at 4 months follow-up was 0.21±0.40 mm, and in-stent late loss was 0.33±0.36mm. The proximal and distal edge late lumen losses were 0.12±0.42mm and 0.09±0.36mm respectively at 4 months and 0.29±0.46mm and 0.21±0.36 mm at 12 months. At 12 months follow-up, five subjects had binary angiographic restenosis (5.4%), and in-segment late lumen loss was 0.43±0.44 mm, and in-stent late loss was 0.61±0.44 mm. The in-stent late loss of 0.61 mm was statistically lower than the 0.8 mm standard that was pre-specified (p<0.001), and also lower than the recently reported Driver platform which had an in-stent late loss of 0.93 mm[22].

Table 5 presents the IVUS results immediately after the index stenting, at 4 months and at 12 months. Of the 99 IVUS examinations that were suitable for evaluation at the index procedure, 95 studies were evaluated at 4 months. IVUS examinations received in 2 patients were not analyzable and two further patients did not undergo IVUS, one as a result of reaching an endpoint. At 12 months, 86 IVUS studies were available for evaluation.

At the baseline IVUS procedure, 11 stent edge dissections were identified. Five were intimal edge dissections, 3 were medial edge dissections and a further 3 were treated with additional stents. At 4 months no edge dissections were identified and all 8 non-stented edge dissections had healed. Incomplete stent strut apposition was identified in 12 patients at the baseline study. Eight of these had
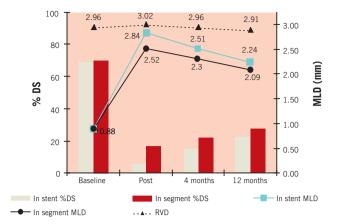

Figure 1. Quantitative coronary angiographic analysis of stent edge effect.

In-stent and In-segment minimum lumen diameter and% diameter stenosis at the 3 specified time points. Line plots reflect minimum lumen diameter (MLD), circles indicate in-segment MLD while squares refer to in-stent MLD. Triangles refer to the reference vessel diameter. Bar graphs indicate% diameter stenosis in-stent and in-segment respectively at each time point.

Table 4. Serial quantitative coronary angiography

Measure	In-stent	In-segment
Minimal lumen diameter (mm)		
After procedure (n=100)	2.84±0.35	2.52±0.42
At 4 months (n=97)	2.51±0.44	2.30±0.44
At 12 months (n=93)	2.24±0.49	2.09±0.47
Stenosis (% of lumen diameter)		
After procedure	5.4±7.5	16.5±8.4
At 4 months	14.6±13.1	21.9±11.2
At 12 months	22.4±15.6	27.8±13.2
Acute gain (mm)[a]	1.96±0.38	1.64±0.42
Late lumen loss (mm)[b]		
At 4 months	0.33±0.36	0.21±0.40
At 12 months	0.61±0.44	0.43±0.44
Late loss index[c]		
At 4 months	0.17±0.19	0.11±0.24
At 12 months	0.32±0.24	0.26±0.29
Binary restenosis (% of patients)[d]		
At 4 months	2.1	2.1
At 12 months	3.3	3.3
Cumulative	5.4	5.4

Values are mean ± SD.
[a] Acute gain was defined as the immediate dimensional change in the minimal lumen diameter (mm) that occurred after the final post-dilation as compared with the minimal lumen diameter at baseline and measured by quantitative coronary angiography from the average from two orthogonal views.
[b] Late lumen loss was defined as the difference between minimal lumen diameter immediately after the placement of the stent and the minimal lumen diameter at 4 months.
[c] Late loss index was defined as the slope of the line of regression of acute gain and late loss.
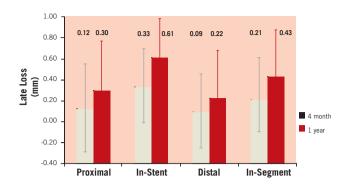[d] Binary restenosis was defined as >50% diameter stenosis.

Figure 2. Bar graph showing the mean late lumen loss associated with implantation of the Endeavor stent at 4 and 12 months in the 5 mm segment proximal to the stent, in-stent, 5 mm segment distal to the stent an in-segment.

Table 5. Serial intravascular ultrasound measurements

Measure	After stenting procedure	4 months	12 months
EEM volume (mm^3)	299.7±78.9	321.4±88.3	309±82.5
Stent volume (mm^3)	144.7±32.8	150.7±37.3	150.7±36.2
Neointimal hyperplastic volume (mm^3)		6.1±7.4	14.2±11.8
Lumen volume (mm^3)	144.6±32.8	144.6±39.1	136.6±37.4
Volume obstruction (%)[a]		4.5±6.1	9.7±8.5

Values are mean ± SD.
EEM, external elastic membrane.
[a] Volume obstruction is the ratio of neointimal hyperplastic volume to stent volume.

resolved at 4 months and 4 were preserved incomplete appositions. Late acquired apposition was not seen in any patient at either 4 or 12 months.

IVUS derived minimal lumen cross sectional area was 6.2±1.4mm^2 post procedure and 6.0±1.7 mm^2 and 5.7±1.8 mm^2 at 4 months and 12 months respectively. The neointimal hyperplastic volume was 6.1±7.4 mm^3 and 14.2±11.8 mm^3 at 4 and 12 months respectively. The percent neointimal volume obstruction was 4.5± 6.1% at 4 months and 9.7±8.5% at 12 months.

Discussion

In this study we report the first-in-human safety and efficacy of the Endeavor drug-eluting stent system comprising the Driver™ stent, phosphorylcholine PC technology coating and ABT-578, a sirolimus like analogue. To the best of our knowledge this is the first report of a DES system based on a new generation thin strut, Chromium-cobalt alloy stent.

The trial was comparatively large for a first in human study as the main objective was to demonstrate acute safety of the Endeavor stent system while gathering invaluable but preliminary information on mid-and long-term safety and efficacy. A sample size of 100 patients was calculated to be sufficient to provide reasonable confi-

dence in the estimates of safety and efficacy and thus provide a strong platform on which to establish larger randomized clinical studies, namely the three planned (Endeavor 2, 3 and 4) multicentre pivotal randomized trials. In addition to its large size for a pilot study, it is the first to evaluate restenosis during the biological restenosis period, at 4 and 12 months. Moreover there were other technical specifications that insured the percutaneous procedure was aligned with best contemporary clinical practices, such as the requirement for pre and post dilation to be undertaken with balloons less than or equal to the stent length in accordance with data of the effect of balloon length on restenosis with drug-eluting stents[25,27].

This study was conducted in 8 high volume centers performing more than 1000 procedures per year by operators performing at least 200 cases per year. Device, lesion and procedural success was achieved in 100% of patients. In part, the high success rates are likely a function of the excellent performance characteristics of the Driver stent and delivery system and the type of lesions and vessels treated. Comprehensive clinical follow-up was achieved in all patients at 4 and 12 months underpinning the calculated power of the trial to provide a meaningful estimate of the true MACE rate. The proposed test for demonstration of acute safety and feasibility was observation of a 30 day MACE rate of <7.9% or observation of MACE in fewer than 8 patients. To this end, the primary safety endpoint of MACE at 30 days was successfully achieved with a 1% MACE rate. Mid and longer term clinical safety was sustained with a 4 and 12 month MACE rate of only 2%, that is one further MACE event between 30 days and 12 months. Angiographic follow up was achieved in 97% of patients at 4 months and 93% at 12 months. Repeat intravascular ultrasound assessment was achieved in 95 and 86% of patients at 4 and 12 months respectively. Excellent levels of patient retention in the invasive components of the follow up study insured this power was maintained.

We observed an instent late loss of 0.33±0.36 mm at 4 months with further progression to 0.61±0.44 at 12 months, and in segment late loss of 0.21±0.40 progressing to 0.43±0.44 at 12 months. This modest angiographic late loss was associated with a low cumulative binary restenosis of 5.4% at 12 months and low TLR (2%, which includes one patient with a stent thrombosis at 10 days, and thus only one patients had TLR for clinical restenosis) TVR and TVF (2%) rates.

Although not readily comparable due to differences in patient, vessel, lesion and procedural factors and the timing of follow up studies in-stent and in-segment late loss appear to be marginally greater than observed with Sirolimus[8,28,29], Everolimus[30] and Paclitaxel when delivered on a polymer coating[6,31] in early phase clinical trials. However clinical endpoints such as MACE, TLR and TVF are at the very least similar if not better.

The present study also provides important insights into the nature, distribution and time dependence of neointimal proliferation within this stent system. We observed a modest decrement in minimal in stent lumen area (MLA) of approximately 0.5 mm^2 over 12 months. This was similar in magnitude to the loss of MLA observed in the cohort of patients undergoing IVUS in the SIRIUS study between the baseline and 8 month interrogations[32].

There was an approximate doubling of the neointimal hyperplastic volume and thus percent volume obstruction between 4 and

12 months in our study highlighting the importance of later angiographic and IVUS follow up in DES studies and the need to consider this when comparing studies with different and singular follow-up time points. At twelve months we observed a mean of 9.7% neointimal volume obstruction within the Endeavor stent system which is comparable to that observed in the IVUS follow up cohorts of TAXUS II[6,33] and TAXUS IV but marginally greater than observed in Sirius, Future I and II and Ravel[8,12,29,30,34]. Importantly our IVUS studies confirmed appropriate healing of peristent dissections and no evidence of late acquired malapposition. There were no late (>30-day) subacute thromboses.

The present data provide a strong foundation for larger scale clinical trials of the Endeavor platform including the 1200 patient Endeavor II powered primarily for clinical endpoints. Such studies will provide greater insight into the benefit of this system in patients with somewhat more complex lesions.

Conclusion

The Endeavor stent system is safe and feasible with complete acute lesion, procedure, and device-deployment success. Treatment of patients with symptomatic ischemic heart disease and single-vessel *de novo* lesions, with the Endeavor stent system resulted in sustained clinical effectiveness and only modest changes in vessel lumen dimensions up to 12 months. The healing process translated in mild neointimal proliferation or late lumen loss but this needs to be prospectively tested to determine the optimum balance between biologic response and adequate clinical anti-restenotic properties.

The present Endeavor I, first-in-human study will be augmented by a comprehensive clinical research program of trials powered to meet clinical endpoints. Endeavor II is a multicenter, double blind, randomized study to evaluate the Endeavor stent system compared with the Driver™ bare metal stent in the treatment of 1200 patients with symptomatic ischemic heart disease and single-vessel *de novo* lesions, including lesions up to 27 mm in length and small vessels (≥2.25 mm reference vessel diameter). Endeavor III is a multicentre, double blind, randomized study to compare the Endeavor stent system with a sirolimus-eluting stent in the treatment of 436 patients. Randomization in Endeavor III will occur on a 2 to 1 basis; the primary endpoint is late lumen loss at 8 months. Endeavor IV is a multicentre, double blind, randomized study to compare the Endeavor stent system with a paclitaxel-eluting stent in the treatment of >1500 patients. The primary endpoint of Endeavor IV is target vessel failure at 9 months. The present study provides a sound and safe platform for these larger scale studies. We await their outcome with considerable interest.

Acknowledgements

References

1. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med.* 1994;331:496-501.

2. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med.* 1994;331:489-95.

3. Elezi S, Kastrati A, Neumann FJ, Hadamitzky M, Dirschinger J, Schomig A. Vessel size and long-term outcome after coronary stent placement. *Circulation.* 1998;98:1875-80.

4. de Feyter PJ, Kay P, Disco C, Serruys PW. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. *Circulation.* 1999;100:1777-83.

5. Mudra H, di Mario C, de Jaegere P, Figulla HR, Macaya C, Zahn R, Wennerblom B, Rutsch W, Voudris V, Regar E, Henneke KH, Schachinger V, Zeiher A. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS Study). *Circulation.* 2001;104:1343-9.

6. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation.* 2003;108:788-94.

7. Holmes DR, Jr., Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, Brown C, Fischell T, Wong SC, Midei M, Snead D, Kuntz RE. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation.* 2004;109:634-40.

8. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.

9. 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. *N Engl J Med.* 2003;349:1315-23.

10. 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. *N Engl J Med.* 2004;350:221-31.

11. 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. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation.* 2004;109:1942-7.

12. Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A, Guagliumi G, Wijns W, Lindeboom WK, Ligthart J, de Feyter PJ, Morice MC. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with *de novo* native coronary artery Lesions) trial. *Circulation.* 2002;106:798-803.

13. Degertekin M, Serruys PW, Tanabe K, Lee CH, Sousa JE, Colombo A, Morice MC, Ligthart JM, de Feyter PJ. Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for *de novo* coronary lesions: an intravascular ultrasound analysis. *Circulation.* 2003;108:2747-50.

14. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, Midwall J, Simonton CA, Keim E, Wang P, Kuntz RE, Moses JW. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with *de novo* coronary artery lesions) substudy. *Circulation.* 2004;109:2273-8.

15. Braun-Dullaeus RC, Mann MJ, Dzau VJ. Cell cycle progression: new therapeutic target for vascular proliferative disease. *Circulation.* 1998;98:82-9.

16. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. *Circulation.* 2001;104:852-5.

17. Zheng H, Barragan P, Corcos T, Simeoni JB, Favereau X, Roquebert PO, Guerin Y, Sainsous J. Clinical Experience With a New Biocompatible Phosphorylcholine-Coated Coronary Stent. *J Invasive Cardiol.* 1999;11:608-614.

18. Boland JL, Corbeij HA, Van Der Giessen W, Seabra-Gomes R, Suryapranata H, Wijns W, Hanet C, Suttorp MJ, Buller C, Bonnier JJ, Colombo A, Van Birgelen C, Pieper M, Mangioni JA, Londero H, Carere RG, Hamm CW, Bonan R, Bartorelli A, Kyriakides ZS, Chauhan A, Rothman M, Grinfeld L, Oosterwijk C, Serruys PW, Cumberland DC. Multicenter evaluation of the phosphorylcholine-coated biodivYsio stent in short *de novo* coronary lesions: The SOPHOS study. *Int J Cardiovasc Intervent.* 2000;3:215-225.

19. Atalar E, Haznedaroglu I, Aytemir K, Aksoyek S, Ovunc K, Oto A, Ozmen F. Effects of stent coating on platelets and endothelial cells after intracoronary stent implantation. *Clin Cardiol.* 2001;24:159-64.

20. Popma JJ, Lansky AJ, Yeh W, Kennard ED, Keller MB, Merritt AJ, DeFalco RA, Desai A, Pacera JH, Schnabel JF, Niedermeyer V, Baim DS, Detre KM. Reliability of the quantitative angiographic measurements in the New Approaches to Coronary Intervention (NACI) registry: a comparison of clinical site and repeated angiographic core laboratory readings. *Am J Cardiol.* 1997;80:19K-25K.

21. Takahashi T, Honda Y, Russo RJ, Fitzgerald PJ. Intravascular ultrasound and quantitative coronary angiography. *Catheter Cardiovasc Interv.* 2002;55:118-28.

22. Sketch MH, Jr., Ball M, Rutherford B, Popma JJ, Russell C, Kereiakes DJ. Evaluation of the Medtronic (Driver) cobalt-chromium alloy coronary stent system. *Am J Cardiol.* 2005;95:8-12.

23. Whelan DM, van der Giessen WJ, Krabbendam SC, van Vliet EA, Verdouw PD, Serruys PW, van Beusekom HM. Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. *Heart.* 2000;83:338-45.

24. Potkin BN, Bartorelli AL, Gessert JM, Neville RF, Almagor Y, Roberts WC, Leon MB. Coronary artery imaging with intravascular high-frequency ultrasound. *Circulation.* 1990;81:1575-85.

25. Mauri L, Orav EJ, O'Malley AJ, Moses JW, Leon MB, Holmes DR, Jr., Teirstein PS, Schofer J, Breithardt G, Cutlip DE, Kereiakes DJ, Shi C, Firth BG, Donohoe DJ, Kuntz RE. Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. *Circulation.* 2005;111:321-7.

26. O'Malley AJ, Normand SL, Kuntz RE. Application of models for multivariate mixed outcomes to medical device trials: coronary artery stenting. *Stat Med.* 2003;22:313-36.

27. Mauri L, O'Malley AJ, Cutlip DE, Ho KK, Popma JJ, Chauhan MS, Baim DS, Cohen DJ, Kuntz RE. Effects of stent length and lesion length on coronary restenosis. *Am J Cardiol.* 2004;93:1340-6, A5.

28. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, Seixas AC, Staico R, Mattos LA, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation.* 2001;103:192-5.

29. Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, Kozuma K, Van Langenhove G, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation.* 2001;104:2007-11.

30. Grube E, Sonoda S, Ikeno F, Honda Y, Kar S, Chan C, Gerckens U, Lansky AJ, Fitzgerald PJ. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation.* 2004;109:2168-71.

31. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for *de novo* coronary lesions. *Circulation.* 2003;107:38-42.

32. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, Leon MB, Moses JW, Yock PG, Honda Y, Kuntz RE, Fitzgerald PJ. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. *J Am Coll Cardiol.* 2004;43:1959-63.

33. Tanabe K, Serruys PW, Degertekin M, Guagliumi G, Grube E, Chan C, Munzel T, Belardi J, Ruzyllo W, Bilodeau L, Kelbaek H, Ormiston J, Dawkins K, Roy L, Strauss BH, Disco C, Koglin J, Russell ME, Colombo A. Chronic arterial responses to polymer-controlled paclitaxel-eluting stents: comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS-II trial. *Circulation.* 2004;109:196-200.

34. Degertekin M, Serruys PW, Foley DP, Tanabe K, Regar E, Vos J, Smits PC, van der Giessen WJ, van den Brand M, de Feyter P, Popma JJ. Persistent inhibition of neointimal hyperplasia after sirolimus-eluting stent implantation: long-term (up to 2 years) clinical, angiographic, and intravascular ultrasound follow-up. *Circulation.* 2002;106:1610-3.