

Panel Questions

Evaluation of Safety and Effectiveness

The sponsor has conducted three multi-center, randomized, clinical investigations, referred to as ENDEAVOR II (n=1197 at 72 sites), ENDEAVOR III (n=436 at 29 sites), and ENDEAVOR IV (n=1548 at 80 sites) with the Endeavor Zotarolimus-Eluting Coronary Stent System in the following patient population:

Patients with *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.25 mm (ENDEAVOR II) or ≥ 2.5 mm (ENDEAVOR III and IV) to ≤ 3.5 mm.

For this PMA application, the sponsor is requesting approval for use in the following patient population with the stent sizes designated in Table 1 with their nominal drug dosages:

Patients with *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5 mm to ≤ 3.5 mm.

Table 1: Endeavor Coronary Stent System Device Matrix & Nominal Drug Dosages								
Diameter	Stent Length							
	8mm	9mm	12mm	14mm	15mm	18mm	24mm	30mm
2.5mm	84 μ g		120 μ g	144 μ g		180 μ g	240 μ g	300 μ g
3.0mm		90 μ g	120 μ g		150 μ g	180 μ g	240 μ g	300 μ g
3.5mm		90 μ g	120 μ g		150 μ g	180 μ g	240 μ g	300 μ g

Safety

The safety endpoints evaluated at 9 and 12 months in the Endeavor studies are shown in Tables 2 and 3, respectively. (Please refer to Section 7 of FDA’s executive summary memorandum provided in the panel package for additional details regarding safety outcomes of each trial.)

Table 2: Safety Data at 9 months										
	ENDEAVOR I	ENDEAVOR II		ENDEAVOR II CA	ENDEAVOR III		ENDEAVOR IV		ENDEAVOR PK	Pooled* Endeavor
		Endeavor	Driver		Endeavor	Cypher	Endeavor	Taxus		
All death	0.0%	1.2%	0.5%	0.7%	0.6%	0.0%	0.7%	0.8%	4.8%	0.9%
Cardiac death	0.0%	0.8%	0.5%	0.7%	0.0%	0.0%	0.4%	0.3%	4.8%	0.6%
MI	1.0%	2.7%	3.9%	5.1%	0.6%	3.5%	1.5%	2.5%	2.4%	2.2%
Death + MI	1.0%	3.7%	4.4%	5.5%	1.2%	3.5%	2.2%	3.3%	7.1%	3.0%
TVF	2.0%	7.9%	15.1%	13.0%	11.8%	11.5%	6.8%	7.4%	11.9%	8.6%

*Endeavor arms across ENDEAVOR I, II, IICA, III, IV, and PK pooled in a post-hoc analysis at FDA’s request.

Table 3: Safety Data at 12 months										
	ENDEAVOR I	ENDEAVOR II		ENDEAVOR II CA	ENDEAVOR III		ENDEAVOR IV		ENDEAVOR PK	Pooled* Endeavor
		Endeavor	Driver		Endeavor	Cypher	Endeavor	Taxus		
All death	0.0%	1.4%	0.7%	0.7%	0.6%	0.9%	-	-	-	0.9%
Cardiac death	0.0%	1.0%	0.7%	0.7%	0.0%	0.0%	-	-	-	0.6%
MI	1.0%	2.7%	3.9%	5.5%	0.6%	3.6%	-	-	-	2.7%
Death + MI	1.0%	3.9%	4.6%	5.8%	1.3%	4.5%	-	-	-	3.5%
TVF	2.0%	10.0%	16.6%	15.8%	12.8%	11.6%	-	-	-	11.4%

*Endeavor arms across ENDEAVOR I, II, IICA, III, IV, and PK pooled in a post-hoc analysis at FDA’s request.

Stent thrombosis data (evaluated per protocol and per the ARC definitions) are shown in Tables 4 through 7. (Please refer to section 7 of FDA’s executive summary memorandum provided in the panel package for additional details regarding stent thrombosis data from each trial.)

Table 4: Stent Thrombosis at 9 months										
	ENDEAVOR I	ENDEAVOR II		ENDEAVOR II CA	ENDEAVOR III		ENDEAVOR IV		ENDEAVOR PK	Pooled* Endeavor
		Endeavor	Driver		Endeavor	Cypher	Endeavor	Taxus		
Protocol	1.0%	0.5%	1.2%	0.0%	0.0%	0.0%	0.8%	0.1%	0.0%	0.5%
ARC definite + probable, censored	1.0%	0.5%	1.4%	0.0%	0.0%	0.0%	0.9%	0.1%	0.0%	0.5%
ARC definite + probable, uncensored	1.0%	0.5%	1.4%	0.0%	0.0%	0.0%	0.9%	0.1%	0.0%	0.5%

*Endeavor arms across ENDEAVOR I, II, IICA, III, IV, and PK pooled in a post-hoc analysis at FDA’s request.

Table 5: Stent Thrombosis at 12 months										
	ENDEAVOR I	ENDEAVOR II		ENDEAVOR II CA	ENDEAVOR III		ENDEAVOR IV		ENDEAVOR PK	Pooled* Endeavor
		Endeavor	Driver		Endeavor	Cypher	Endeavor	Taxus		
Protocol	1.0%	0.5%	1.2%	0.0%	0.0%	0.0%	-	-	-	0.3%
ARC definite + probable, censored	1.0%	0.7%	1.4%	0.0%	0.0%	0.0%	-	-	-	0.4%
ARC definite + probable, uncensored	1.0%	0.7%	1.4%	0.0%	0.3%	0.0%	-	-	-	0.5%

*Endeavor arms across ENDEAVOR I, II, IICA, III, IV, and PK pooled in a post-hoc analysis at FDA's request.

Table 6: Stent Thrombosis at 24 months										
	ENDEAVOR I	ENDEAVOR II		ENDEAVOR II CA	ENDEAVOR III		ENDEAVOR IV		ENDEAVOR PK	Pooled* Endeavor
		Endeavor	Driver		Endeavor	Cypher	Endeavor	Taxus		
Protocol	1.0%	0.5%	1.2%	0.0%	0.0%	0.0%	-	-	-	0.3%
ARC definite + probable, censored	1.0%	0.9%	1.4%	0.0%	0.0%	0.0%	-	-	-	0.5%
ARC definite + probable, uncensored	1.0%	0.9%	1.4%	0.0%	0.3%	0.0%	-	-	-	0.5%

*Endeavor arms across ENDEAVOR I, II, IICA, III, IV, and PK pooled in a post-hoc analysis at FDA's request.

Table 7: Stent Thrombosis at 36 months										
	ENDEAVOR I	ENDEAVOR II		ENDEAVOR II CA	ENDEAVOR III		ENDEAVOR IV		ENDEAVOR PK	Pooled* Endeavor
		Endeavor	Driver		Endeavor	Cypher	Endeavor	Taxus		
Protocol	1.0%	0.5%	1.2%	-	-	-	-	-	-	0.6%
ARC definite + probable, censored	1.0%	0.9%	1.4%	-	-	-	-	-	-	0.9%
ARC definite + probable, uncensored	1.0%	0.9%	1.6%	-	-	-	-	-	-	0.9%

*Endeavor arms across ENDEAVOR I, II, IICA, III, IV, and PK pooled in a post-hoc analysis at FDA's request.

1. Do the data submitted to date on the Endeavor DES provide adequate assurance of safety in the population identified in the proposed indications for use?
2. If the answer to #1 is yes, does the application include adequate follow-up in a sufficient portion of the patient population? If no, how much additional follow-up (i.e., number of patients or duration of follow-up) is needed prior to approval to confirm a reasonable assurance of safety? Tables 8 and 9 summarize the available long-term follow-up data and important clinical outcomes for patients treated with Endeavor stents. (Please refer to Section 7 of FDA's executive summary memorandum provided in the panel package for additional details regarding outcomes of each trial.)

Table 8: Patient Follow-Up							
	30d	6m	9m	12m	2y	3y	4y
ENDEAVOR I	100	100	100	99	99	98	97
ENDEAVOR II	596	593	592	590	587	577	-
ENDEAVOR II CA	296	295	293	292	288	-	-
ENDEAVOR III	323	321	321	320	313	-	-
ENDEAVOR IV	770	766	740	-	-	-	-
ENDEAVOR PK	43	43	42	-	-	-	-
Total	2128	2118	2088	1301	1287	675	97

Table 9: Outcomes at latest available clinical follow-up						
	ENDEAVOR I (n=97)	ENDEAVOR II (n=577)	ENDEAVOR II CA (n=288)	ENDEAVOR III (n=313)	ENDEAVOR IV (n=740)	ENDEAVOR PK (n=42)
Follow-up	4 years	3 years	2 years	2 years	9 months	9 months
Death	4.1%	3.3%	1.4%	1.6%	0.7%	4.8%
Cardiac Death	0.0%	1.6%	0.7%	0.0%	0.4%	4.8%
MI	1.0%	3.3%	5.9%	0.6%	1.5%	2.4%
TVF	5.2%	12.8%	16.3%	14.4%	6.8%	11.9%
TLR	3.1%	7.3%	7.3%	7.0%	4.2%	2.4%
TVR	5.2%	9.5%	12.5%	13.7%	5.5%	7.1%
Stent thrombosis						
Protocol	1.0%	0.5%	0.0%	0.0%	0.8%	0.0%
ARC definite + probable (TLR-censored)	1.0%	0.9%	0.0%	0.0%	0.9%	0.0%
ARC definite + probable (TLR-uncensored)	1.0%	0.9%	0.0%	0.3%	0.9%	0.0%

Antiplatelet Therapy

In the clinical studies conducted on the Endeavor stent to date, the recommended post-procedure antiplatelet regimen was aspirin indefinitely and clopidogrel (or ticlopidine) for a minimum of 3 months, with the exception of ENDEAVOR IV. In the ENDEAVOR IV study, the recommended duration of thienopyridine use was 6 months.

Table 10 shows the use of dual antiplatelet therapy through 6 months in ENDEAVOR II, II CA, III, and IV as reported by the patient at their follow-up visit:

	ENDEAVOR II (N=598)	ENDEAVOR II CA (N=296)	ENDEAVOR III (N= 323)	ENDEAVOR IV (N=773)
Aspirin	96.9% (561/579)	95.1% (272/286)	95.9% (303/316)	95.8% (713/744)
Clopidogrel	65.5% (377/576)	59.4% (170/286)	90.1% (264/293)	94.8% (697/735)
Ticlopidine	2.1% (12/569)	0% (0/287)	6.1% (2/33)	29.4% (5/17)
Aspirin + Clopidogrel or Ticlopidine	64.8% (375/579)	55.9% (161/288)	81.6% (258/316)	92.3% (687/744)

In the labeling for the Endeavor stent, the Sponsor proposes the following language with regard to antiplatelet therapy use:

“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.”

- 3. Do you believe that the language in the proposed Endeavor stent label adequately conveys a recommended course of dual antiplatelet therapy following Endeavor stent implantation?**
 - a. If no, should the label explicitly state that the recommended course of dual antiplatelet therapy be at least 6 months following Endeavor stent implantation?**
 - b. Following the FDA Advisory Panel Meeting on DES thrombosis in December 2006, the labels for the currently approved DES (Cypher and Taxus) had language added to their labels referencing the ACC/AHA/SCAI consensus statement recommending dual antiplatelet therapy for 12 months following DES implantation in patients who are not at high risk for bleeding. Should this recommendation also be included in the Endeavor stent label?**

Effectiveness

The primary endpoint for the ENDEAVOR II and IV studies was target vessel failure (TVF) at 9 months which is a composite of safety (cardiac death and MI) and effectiveness outcomes (TVR). The angiographic effectiveness endpoint for the ENDEAVOR III and IV studies was late lumen loss at 8 months. The TVF composite, clinical effectiveness (TLR and TVR), and angiographic effectiveness data from these trials are presented in the Table 11. (Please refer to Section 7 of FDA’s executive summary memorandum provided in the panel package for additional details regarding effectiveness outcomes of each trial.)

Table 11: Effectiveness Data									
	Endeavor II			Endeavor III			Endeavor IV		
	Endeavor	Driver	p*	Endeavor	Cypher	p**	Endeavor	Taxus	p**
TVF at 9m	7.9%	15.1%	<0.001	11.8%	11.5%	-	6.8%	7.4%	0.0005
TLR at 9m	4.6%	11.8%	-	6.2%	3.5%	-	4.2%	2.7%	-
TVR at 9m	5.6%	12.5%	-	11.2%	8.0%	-	5.5%	5.0%	-
In-segment late loss at 8m	0.36±0.46m	0.72±0.61m	<0.001	0.36±0.46m	0.13±0.33mm	<0.001	0.36±0.47mm	0.23±0.45mm	0.023

*test for superiority; **test for non-inferiority

4. Do the data presented on the Endeavor stent provide a reasonable assurance of effectiveness?
 - a. In the ENDEAVOR II study, the Endeavor stent was demonstrated to be superior to the bare metal Driver stent with respect to TVF along with reduced rates of TLR, and TVR. Has a reasonable assurance of effectiveness of the Endeavor stent been demonstrated versus bare metal stent implantation?
 - b. In the ENDEAVOR III study, the Endeavor stent did not meet its primary non-inferiority endpoint of in-segment late lumen loss at 8 months post-stent implantation compared with the Cypher stent. In ENDEAVOR IV, the Endeavor stent met its primary clinical endpoint of TVF, but failed to meet its major secondary non-inferiority endpoint of in-segment late lumen loss at 8 months post-stent implantation compared to the Taxus stent. Do the data from ENDEAVOR III and IV demonstrate a reasonable assurance of effectiveness of the Endeavor stent?

Product Labeling

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling (Section 9).

- 5a. Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations for treatment with this device.**
- 5b. Please comment on the CONTRAINDICATIONS section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.**
- 5c. Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.**
- 5d. Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.**
- 5e. Given the information on the drug substance proposed for inclusion in the labeling, please comment whether modifications are needed or whether any additional information should be added to the labeling to maximize benefits and minimize adverse events.**
- 5f. Please comment on the remainder of the labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.**