

Panel Questions

Evaluation of Safety and Effectiveness

The sponsor has conducted three multi-center, randomized, clinical investigations, referred to as SPIRIT FIRST (n=60 at 9 sites), SPIRIT II (n=300 at 31 sites), and SPIRIT III RCT (n=1002 at 80 sites) with the XIENCE V Everolimus-Eluting Coronary Stent System in patients with symptomatic heart disease due to de novo native coronary artery lesions the following patient population:

Table 1: XIENCE V Trials Patient Population		
Trial	Reference Vessel Diameter (RVD)	Lesion Length (mm)
SPIRIT FIRST	3.0 mm	≤ 12 mm
SPIRIT II	≥ 2.5 mm to ≤ 4.25 mm	≤ 28 mm
SPIRIT III RCT	≥ 2.5 mm to ≤ 3.75 mm	≤ 28 mm
SPIRIT III 4.0 mm arm	≥ 3.75 mm to ≤ 4.25 mm	≤ 28 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:

The XIENCE V EECSS is intended for improving coronary luminal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions (length ≤ 28mm) with reference vessel diameter of 2.5mm to 4.25mm.

Table 2: XIENCE V EECSS Device Matrix & Nominal Drug Dosages (µg)						
Diameter	Stent Length					
	8 mm	12 mm	15 mm	18 mm	23 mm	28 mm
2.50 mm	37	56	75	88	113	132
2.75 mm	37	56	75	88	113	132
3.00 mm	37	56	75	88	113	132
3.50 mm	53	75	98	113	151	181
4.00 mm	53	75	98	113	151	181

Safety

The safety endpoints evaluated at 9 and 12 months in the SPIRIT 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 3: Safety Data at 9 months							
	SPIRIT FIRST	SPIRIT II		SPIRIT III		SPIRIT III 4.0 mm	Combined* SPIRIT II & III RCT
		XIENCE V	TAXUS	XIENCE V	TAXUS		
All death	0.0% (0/26)	0.9% (2/222)	1.3% (1/76)	1.1% (7/658)	0.9% (3/321)	1.5% (1/68)	1.0% (9/880)
Cardiac death	0.0% (0/26)	0.0% (0/222)	1.3% (1/76)	0.6% (4/657)	0.6% (2/320)	1.5% (1/68)	0.5% (4/877)
MI	3.8% (1/26)	0.9% (2/220)	3.9% (3/76)	2.3% (15/657)	3.1% (10/320)	4.4% (3/68)	1.9% (17/877)
Cardiac Death + MI	3.8% (1/26)	-	-	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	2.4% (21/877)
TVF	7.7% (2/26)	4.5% (10/220)	6.6% (5/76)	7.6% (50/657)	9.7% (31/320)	5.9% (4/68)	6.8% (60/877)

*XIENCE V arms from SPIRIT II and SPIRIT III RCT were combined in a post-hoc analysis at FDA’s request.

Table 4: Safety Data at 12 months							
	SPIRIT FIRST	SPIRIT II		SPIRIT III		SPIRIT III 4.0 mm	Combined* SPIRIT II & III RCT
		XIENCE V	TAXUS	XIENCE V	TAXUS		
All death	0.0% (0/26)	0.9% (2/222)	1.3% (1/76)	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	1.3% (11/877)
Cardiac death	0.0% (0/26)	0.0% (0/222)	1.3% (1/76)	0.8% (5/653)	0.9% (3/320)	1.5% (1/68)	0.6% (5/873)
MI	7.7% (2/26)	0.9% (2/220)	3.9% (3/76)	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	2.3% (20/873)
Cardiac Death + MI	7.7% (2/26)	-	-	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	2.7% (24/873)
TVF	15.4% (4/26)	4.5% (10/220)	9.2% (7/76)	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	7.7% (67/873)

*XIENCE V arms from SPIRIT II and SPIRIT III RCT were combined 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 5: Stent Thrombosis at 12 months							
	SPIRIT FIRST	SPIRIT II		SPIRIT III		SPIRIT III 4.0 mm	Combined* SPIRIT II & III RCT
		XIENCE V	TAXUS	XIENCE V	TAXUS		
Protocol	0.0% (0/26)	0.5% (1/220)	1.3% (1/76)	0.8% (5/647)	0.6% (2/317)	1.4% (1/69)	0.7% (6/867)
ARC definite + probable, uncensored	0.0% (0/26)	0% (0/220)	1.3% (1/76)	1.1% (7/652)	0.6% (2/319)	0.0% (0/68)	0.8% (7/868)

*XIENCE V arms from SPIRIT II and SPIRIT III RCT were combined in a post-hoc analysis at FDA's request.

Table 6: SPIRIT FIRST Stent Thrombosis at 24 and 36 months		
	SPIRIT FIRST 24 months	SPIRIT FIRST 36 months
Protocol	0.0% (0/ 26)	0.0% (0/ 26)
ARC definite + probable, uncensored	0.0% (0/ 26)	0.0% (0/ 26)

1. Do the data submitted to date on the XIENCE™ V EECSS 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 7 and 8 summarize the available long-term follow-up data and important clinical outcomes for patients treated with XIENCE V 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 7: Patient Clinical Follow-Up						
	30d	6m	9m	12m	2y	3y
SPIRIT FIRST	27	26	26	26	26	26
SPIRIT II	223	222	220	220	-	-
SPIRIT III RCT	667	662	653	646	-	-
SPIRIT III 4.0 mm	69	67	67	67	-	-
Total	986	977	966	959	-	-

Note: Total patients followed up in XIENCE™ V arm

Note: Patient follow-up data as presented in the SPIRIT I, II and III year clinical report

Table 8: Outcomes at latest available clinical follow-up				
	SPIRIT FIRST (n=26)	SPIRIT II (n=223)	SPIRIT III RCT (n=669)	SPIRIT III 4.0 mm (n=69)
Follow-up	3 years	1 year	1 year	1 year
Death	0.0% (0/26)	0.9% (2/222)	1.2% (8/665)	1.5% (1/68)
Cardiac Death	0.0% (0/26)	0.0% (0/222)	0.8% (5/653)	1.5% (1/68)
MI	7.7% (2/26)	0.9% (2/220)	2.8% (18/653)	4.4% (3/68)
TVF	15.4% (4/26)	4.5% (10/220)	8.6% (56/653)	5.9% (4/68)
TLR	7.7% (2/26)	1.8% (4/220)	3.4% (22/653)	1.5% (1/68)
TVR non TL	0.0% (0/26)	1.8% (4/220)	3.1% (20/653)	0.0% (0/68)
Stent thrombosis				
Protocol	0.0% (0/26)	0.5% (1/220)	0.8% (5/647)	1.4% (1/69)
ARC definite + probable (TLR- uncensored)	0.0% (0/26)	0.0% (0/220)	1.1% (7/648)	0.0% (0.68)

Antiplatelet Therapy

In the clinical studies conducted on the XIENCE V stent to date, the recommended post-procedure antiplatelet regimen was aspirin for 5 years and clopidogrel (or ticlopidine) for a minimum of 6 months, with the exception of SPIRIT FIRST. In the SPIRIT FIRST study, the recommended duration of clopidogrel (or ticlopidine) use was 3 months.

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

Table 9: Antiplatelet Therapy Use at 6 months for XIENCE V Patients				
	SPIRIT FIRST (N=26)	SPIRIT II (N=223)	SPIRIT III RCT (N= 669)	SPIRIT III 4.0 mm (N=69)
Aspirin	100% (26/26)	99.5% (220/221)	96.6% (645/668)	95.7% (66/69)
Clopidogrel or Ticlopidine	69.2% (18/26)	90.1% (201/223)	94.5% (632/669)	97.1% (67/69)
Aspirin + Clopidogrel or Ticlopidine	69.2% (18/26)	90.5% (200/221)	92.8% (620/668)	94.2% (65/69)

Note: Per treatment evaluable analysis for SPIRIT FIRST, intent-to-treat analysis for SPIRIT II, SPIRIT III RCT and 4.0 mm arm.

Note: No SPIRIT FIRST subject was on Ticlopidine.

Note: SPIRIT FIRST protocol requires a minimum of 3 months Clopidogrel usage post index procedure; SPIRIT II and SPIRIT III protocols require a minimum of 6 months on Clopidogrel or Ticlopidine post index procedure.

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

“In XIENCE V clinical trials, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 6 months post-procedure for the majority of subjects (3 months in SPIRIT FIRST subjects). Aspirin was administered concomitantly with clopidogrel bisulfate or ticlopidine hydrochloride and continued for 5 years to reduce thrombosis risk. See **Section 9.0 – Clinical Studies**, for more specific information. American Heart Association/ American College of Cardiology/ Society for Cardiovascular Angiography and Interventions joint guidelines for Percutaneous Coronary Intervention (PCI) recommend that patients who receive a drug eluting stent and in patients not at high risk for bleeding events should ideally receive dual antiplatelet therapy up to 12 months.

It is very important that the patient complies with the post-procedural antiplatelet recommendations. Prematurely discontinuing prescribed antiplatelet medication could result in higher stent thrombosis, myocardial infarction or death risk. Prior to Percutaneous Coronary Intervention (PCI), if a surgical or dental procedure is anticipated that requires 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 choice. Following PCI, should a surgical or dental procedure be recommended, procedural risks and benefits should be weighed against the risk associated with prematurely discontinuing antiplatelet therapy.

Patients who prematurely discontinue antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, their antiplatelet therapy should be restarted as soon as possible per treating physician discretion.”

3. **Do you believe that the language in the proposed XIENCE V stent label adequately conveys a recommended course of dual antiplatelet therapy following XIENCE V stent implantation?**
 - a. **If no, please discuss the appropriate modifications that should be made to the label.**
 - 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. This language has been included in the proposed labeling presented here. Do you agree that this language is appropriate?**

Effectiveness

The angiographic endpoint for the SPIRIT FIRST and SPIRIT II studies was in-stent late loss at 180 days. The angiographic endpoint for SPIRIT III was in-segment late loss at 240 days. The clinical effectiveness endpoint for SPIRIT III was TVF at 270 days, where TVF is a composite of cardiac death, MI, and TVR. Study success for SPIRIT III depends on meeting both the angiographic effectiveness and clinical effectiveness endpoints. The TVF composite 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 10: Effectiveness Data									
	SPIRIT FIRST			SPIRIT II			SPIRIT III		
	XIENCE V	Vision	p-value Superioriy	XIENCE V	Taxus	p-value Non-inferiority	XIENCE V	Taxus	p-value Non-inferiority
TVF At 9 months	7.7%*	21.4%*	-	4.5%	6.6%	-	7.6%**	9.7%**	<0.0001
TVF at 1 year	15.4%	21.4%	-	4.5%	9.2%	-	8.6%	11.3%	-
In-stent late loss at 180 days	0.10±0.23	0.85±0.36	<0.0001	0.11±0.27	0.36±0.39	<0.0001			

In-segment late loss at 8 months			-				0.14 ± 0.41	0.28 ± 0.48	<0.0001
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4. In the SPIRIT FIRST study, the XIENCE V EECSS was demonstrated to be superior to the bare metal VISION stent with respect to in-stent late loss along with reduced rates of TVF and percent volume obstruction. In the SPIRIT II and SPIRIT III trials, XIENCE V EECSS was found to be non-inferior to Taxus with respect to 180 day in-stent late loss for SPIRIT II and 240 day in-segment late loss for SPIRIT III. Additionally since each study found that XIENCE V was non-inferior to Taxus, a superiority analysis was performed and XIENCE V EECSS was found to be superior to TAXUS (p < 0.0001 for SPIRIT II and p=0.0037 for SPIRIT III). Do the data presented on the XIENCE V EECSS provide a reasonable assurance of effectiveness?

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.**

Post-Approval Study

The postmarket study has been designed to:

- Evaluate clinical outcomes in a cohort of real world patients receiving the XIENCE V Everolimus Eluting Coronary Stent System (EECSS) during commercial use by various physicians with a range of coronary stenting experience
- Evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications
- Determine clinical device and procedural success during commercial use
- Evaluate patient health status (symptoms, physical function, and quality of life) by the Seattle Angina Questionnaire

6a. Are the objectives identified above appropriate? Should additional objectives be considered?

6b. Does the plan provided by the sponsor adequately address these objectives?

6c. If not, how should the sponsor's plan be modified?

Issues identified in the review are that the study is not currently designed for evaluation of stent thrombosis rates beyond 1 year, the study does not currently include an endpoint related to death and MI, and it is unclear if 5-year follow-up is sufficient for long-term stent thrombosis evaluation.

7. Should the study protocol be revised to address these issues?