Trends-in-Medicine

December 2007
by Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

FDA Panel Recommends Approval of Abbott's Xience Drug-Eluting Stent

Gaithersburg, MD
November 29, 2007

For more than three years there have been only two drug-eluting stents (DES) on the U.S. market – Johnson & Johnson's Cypher and Boston Scientific's Taxus – but two new second-generation DES may soon be available. On October 10, 2007, the FDA's Circulatory System Devices Advisory Committee voted to recommend approval of Medtronic's Endeavor. Then, seven weeks later the same advisory panel voted 9 to 1 to recommend approval of Abbott Vascular's Xience V EECSS with two conditions:

1. An appropriately-designed post-approval study be conducted, with details to be determined later by the FDA. **Passed by a vote of 9 to 1.**
2. Labeling for antiplatelet therapy be consistent with the ACC/AHA guidelines and what the FDA has recommended for other DES and include life-long aspirin. **Passed unanimously.**

Xience V, which will also be sold by Boston Scientific as Promus, is a cobalt chromium Multi-Link Vision/Mini Vision stent eluting everolimus (Novartis's Certican). Xience is coated with two layers: (1) a primer layer of PBMA [poly (nbutyl methacrylate)] and (2) a drug matrix layer consisting of a copolymer of vinylidene fluoride and hexafluoropropylene (PVDF-HFP) blended with everolimus. Two delivery systems will be available: over-the-wire and rapid exchange.

Certican is not yet approved in the U.S., but it is approved in Europe. In its briefing documents, the FDA noted that it "considers everolimus to be a 'studied drug,' that is, a molecular entity that has been previously approved or studied under IND, and for which access to these study data are available." However, the FDA noted that it would have a Pregnancy Category C rating since there are no safety studies in pregnant women.

Abbott is seeking approval for Xience V use in:

> **improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.**

Abbott also is asking for a 9-month shelf life, but the FDA briefing documents indicated that this has yet to be decided, "Although the stability data appear to support the proposed shelf life, shelf life can not be determined until the (manufacturing) specifications are finalized." There was no discussion of shelf life at the panel meeting.

The Abbott presentation to the panel was very well done, carefully touching on all the key advantages of Xience but not over-emphasizing them either: thin struts, potentially less or no stent fracture (none was seen in bench testing), a polymer that doesn't flake or web, low drug dose, deliverability, and good re-endothelialization. However, Boston Scientific may be able to counter-market on diabetic patients. The Xience data appeared worse than Taxus in diabetics. Though FDA officials said this was not a statistically valid difference, the data could be in the label, opening the door for Boston Scientific to use it against Xience.

There appears to be much more excitement about Xience than there is about Endeavor. An interventional cardiologist questioned at the panel meeting about what his cath lab will do when Xience and Endeavor are available predicted they would move from 70% Cypher and 30% Taxus to 60% Xience, 15% Endeavor, and 25% Cypher. Another cardiologist said his cath lab will go entirely to Xience except for diabetics, where Taxus will probably be used until there are more data on Xience in diabetics.

Before the advisory committee took up the Xience application, they got an update on FDA-requested cardiovascular post-approval studies from Dr. Danica Marinac-Dabic, Chief of the Epidemiology Branch in the FDA's Office of Surveillance and Biometrics. She said CDRH approved a total of 21 cardiovascular pre-market applications with post-approval study requirements resulting in 27 post-approval studies (some PMAs have more than one post-approval study).

Status of 27 Post-Approval Cardiovascular Studies
as of November 7, 2007

Status	2005	2006	2007
Reporting status			
Final report received	1	4	0
Report overdue/received	1	3	0
Report on time	5	5	8
Progress status			
Protocol pending	0	1	6
Study completed	1	4	0
Study pending	0	4	2
Study on time	6	3	0

ABBOTT PERSPECTIVE

After relatively brief overview comments from three Abbott officials, most of the Abbott presentation was handled by outside experts. Gary Johnson, Vice President of Abbott Vascular, told the panel that the pre-clinical findings showed Xience V was:

- Non-inferior and superior in late loss over a bare metal stent (BMS).
- Non-inferior and superior in late loss over Cypher and Taxus.
- Non-inferior in TVF vs. Taxus.

He pointed out that since Certican (everolimus) is not a new molecular entity (NME), the requirement for data on 2,000 treated patients did not apply. He also commented that the two-year analysis of SPIRIT-II and SPIRIT-III were consistent with the 1-year data from both trials as well as the 3-year data from SPIRIT-First.

Murthy Simhambhatla PhD, vice president and general manager of DES at Abbott Vascular, reviewed the Xience technology. Among the points he made was that Xience has a 41% reduced drug dose vs. Cypher and Endeavor for the same size stent (3.0 x 18 mm): 88 µg Xience, 150 µg Cypher, 180 µg Endeavor. In Abbott's briefing documents for the panel, it indicated 75%-80% of the everolimus on Xience is released during the first 28 days with >99% released by 120 days. At 3 days, 42% of the drug is released; at 14 days 62.5%; and at 60 days 91.3%.

Leslie Coleman DVM, director of preclinical research at Abbott Vascular, reviewed the preclinical program, emphasizing that Xience is associated with more rapid re-endothelialization than other DES and enhanced endothelial cell function vs. other DES when examined by scanning electron microscopy (SEM). Abbott officials have speculated that this is due to the stent's thinner struts.

Endothelialization in Rabbits at 14 Days by SEM

Stent	All death	p-value vs. Vision
Cypher	~ 6%	0.006
Taxus	~ 25%	0.006
Endeavor	~ 32%	0.006
Xience	~ 66%	Nss
Bare Vision	~ 80%	---

Clinical program

Dr. Gregg Stone of Columbia University Medical Center reviewed the SPIRIT clinical program. Overall, the Xience program consists of eight studies with >16,000 patients, including >14,000 patients getting a Xience stent. In the panel briefing documents, the FDA said Abbot has "continued to develop a robust clinical development program." The FDA application is based on:

- **SPIRIT-First.** The trial met both its pre-specified primary and major secondary endpoints, demonstrating superiority of Xience V vs. the bare Vision in reducing late loss and % volume obstruction.
- **SPIRIT-II.** The trial met its pre-specified primary endpoint, demonstrating superiority vs. Taxus in reducing in-stent angiographic late loss.
- **SPIRIT-III.** This pivotal trial met both its pre-specified primary and major secondary (co-primary) endpoints, demonstrating superiority of Xience vs. Taxus in reducing angiographic in-segment late loss as well as non-inferiority on the 9-month endpoint of TVF.
  - **SPIRIT-III 4.0 mm.**
  - **SPIRIT-III Japanese.**

Xience V Clinical Trials

Measurement	SPIRIT-First	SPIRIT-II	SPIRIT-III		SPIRIT-III Japan
			RCT	4.0 mm registry	
Study type/design	Multicenter, randomized, single-blind, BMS control	Multicenter, randomized single-blind, active control	Multicenter, randomized, single-blind, active control	Multicenter, single-arm, open-label	Multicenter, single-arm, open-label
Number of patients	Total: 60 Xience V: 30 Bare Vision: 30	Total: 300 Xience V: 225 Taxus: 75	Total: 1,002 Xience V: 668 Taxus: 334	80	88
Lesions	Single *de novo* lesion	Up to 2 *de novo* lesions in different epicardial vessels	Up to 2 *de novo* lesions in different epicardial vessels	Up to 2 *de novo* lesions in different epicardial vessels	Up to 2 *de novo* lesions in different epicardial vessels
RVD	3 mm by QCA	≥ 2.5 to ≤ 4.25 mm	≥ 2.5 to ≤ 3.75 mm	≥ 3.75 to ≤ 4.25 mm	≥ 2.5 to ≤ 4.25 mm
Lesions length	≤ 12 mm	≤ 28 mm	≤ 28 mm	≤ 28 mm	≤ 28 mm
Post-procedure antiplatelet therapy (Plavix or ticlopidine)	3 months plus aspirin 1 year	6 months plus aspirin 1 year	6 months plus aspirin 5 years	6 months plus aspirin 5 years	3 months plus aspirin 5 years
Primary endpoint	In-stent late loss at 180 days	In-stent late loss at 180 days	In-segment late loss at 240 days	In-segment late loss at 240 days	In-segment late loss at 240 days
Major ***secondary endpoint***	% VO at 180 days	---	TVF at 270 days	---	---
Follow-up available	3 years	1 year	1 year	1 year	Ongoing. The 270-day follow-up data lock anticipated in Feb. 2008
Angiographic follow-up	180 days and 1 year (all)	180 days (all) and 2 years (n=152)	240 days (n=564)	240 days	240 days
IVUS follow-up	180 days and 1 year (all)	180 days and 2 years (n=152)	240 days (n=240)	None	240 days

Xience Efficacy

Measurement	SPIRIT-First		SPIRIT-II		SPIRIT-III	
	Xience	Taxus	Xience	Taxus	Xience	Taxus
TVF at 9 months	7.7%	21.4%	4.5%	6.6%	7.6% * ***Co-Primary endpoint***	9.7%
TVF at 1 year	15.4%	21.4%	4.5%	9.2%	8.5%	11.1%
In-stent late loss at 180 days	0.10 mm ***Primary endpoint***	0.85 mm **	0.11 mm * ***Primary endpoint***	0.36 mm	---	---
In-segment late loss at 180 days	---	---	0.07 mm ***Secondary endpoint***	0.15 mm	0.17 mm * ***Primary endpoint***	0.28 mm
% volume obstruction	8.0% ***Secondary endpoint***	28.1%	2.5%	7.4%	6.9%	11.2%

*** p-value for non-inferiority <.001**
**** p-value for superiority <.001**

Stent Thrombosis with Xience

Stent thrombosis	SPIRIT-First	SPIRIT-II		SPIRIT-III		SPIRIT-III 4.0 mm
		Xience	Taxus	Xience	Taxus	
Per protocol at 12 months	0%	0.9%	1.3%	1.2%	1.2%	1.5%
ARC definite and probable (uncensored) at 12 months	0%	0%	1.3%	0.8%	0.9%	1.5%
24-month post hoc analysis by ARC	0%	---	---	---	---	---
36-month post hoc analysis by ARC	0%	---	---	---	---	---

Dr. Stone noted that Taxus has been a tough competitor for other drug-eluting stents, but Xience has shown itself to be non-inferior and even superior to Taxus. He concluded Xience has shown:

- Significant reductions in angiographic in-stent and in-segment late loss and restenosis.
- Comparable rates of stent thrombosis.

Abbott Meta-Analysis of SPIRIT-II and SPIRIT-III Trials

Measurement	Xience n=892	Taxus n=410	p-value
30 days			
Cardiac death	0	0	Nss
MI	1.0%	2.9%	0.02
Cardiac death or MI	1.0%	0.9%	0.02
TLR	0.3%	0.5%	Nss
MACE	1.2%	3.2%	0.02
TVR remote	0.2%	0.7%	Nss
TVF	1.5%	3.4%	0.03
1 year			
All-cause death	1.3%	1.8%	Nss, 0.48
Stent thrombosis	0.8%	0.8%	Nss, 0.93
Cardiac death	0.6%	1.0%	Nss, 0.39
MI	2.3%	4.0%	Nss, 0.08
Cardiac death or MI	2.7%	4.5%	Nss, 0.10
TLR	3.1%	5.8%	0.02
In-stent late loss	0.14 mm	0.33 mm	<.0001
In-segment late loss	0.11 mm	0.22 mm	0.0004
Restenosis in-stent	1.9%	4.9%	0.021
Restenosis in-segment	4.1%	7.8%	0.039
MACE	5.2%	10.0%	0.002
TVR remote	2.7%	3.8%	Nss, 0.32
TVF	7.6%	10.7%	Nss, 0.062

Xience Safety Data

Measurement	SPIRIT-First	SPIRIT-II		SPIRIT-III		SPIRIT-III 4.0 mm
		Xience	Taxus	Xience	Taxus	
9-month results						
All death	0.0%	0.9%	1.3%	1.1%	0.9%	1.5%
Cardiac death	0.0%	0.0%	1.3%	0.6%	0.6%	1.5%
MI	3.8%	0.9%	3.9%	2.3%	3.1%	4.4%
Cardiac death + MI	3.8%	---	---	2.9%	3.8%	5.9%
TVF	7.7%	4.5%	6.6%	7.6%	9.7%	5.9%
12-month results						
All death	0.0%	0.9%	1.3%	1.2%	1.2%	1.5%
Cardiac death	0.0%	0.0%	1.3%	0.8%	0.9%	1.5%
MI	7.7%	0.9%	3.9%	2.8%	4.1%	4.4%
Cardiac death + MI	7.7%	---	---	3.4%	4.7%	5.9%
TVF	15.4%	4.5%	9.2%	8.6%	11.3%	5.9%
MACE	---	2.7%	9.2%	6.0%	10.3%	---
TLR	---	1.8%	6.6%	3.4%	5.6%	---
TVR – remote	---	1.8%	1.3%	3.1%	4.4%	---

- Significant reduction in IVUS % volume obstruction, without positive remodeling or late acquired incomplete apposition.
- Significant reductions in MI, MACE, and TVF at 30 days, with non-significant numerical trends toward less composite cardiac death and MI as well as TVF at 1 year.
- Comparable rates of stent thrombosis.
- Significant reductions in TLR and MACE at 1 year.
- The clinical benefits of Xience vs. Taxus have been consistent in 2 consecutive randomized trials in different geographies and "as such, these findings may be considered especially robust."
- Every pre-specified primary and major secondary endpoint in the SPIRIT randomized trials were successfully met.

Ad hoc pooled analysis

Dr. Mitchell Krucoff of Duke University noted, "I don't have a lot of data on Xience vs. BMS because the program was primarily against Taxus, not BMS, but we know a lot about Taxus…On-label use of Taxus DES is safe and effective relative to BMS." He presented the available data from the 2-year pooled SPIRIT-II and SPIRIT-III safety analysis, concluding:

- The Xience design objectives were met or exceeded.
- There was no evidence of any safety signal at 2 years based on all available monitored data.
- Two-year directionality of safety endpoints were very consistent with one-year data.
- At two years, there was no evidence for safety concerns vs. Taxus.

Dr. Krucoff also reviewed Abbott's proposed and ongoing post-marketing study plans, which include:

- **SPIRIT-IV.** This 3,690-patient, single-blind, multicenter, randomized trial vs. Taxus – with overlapping stents and use in bifurcations permitted – is currently enrolling patients and continues to be blinded. The primary endpoint is ischemia-driven MACE (major adverse cardiac events) at 270 days, but all patients will be followed for five years. The DSMB met three times and found no safety-related issues.
- **SPIRIT V.** This is actually two OUS studies. The DSMB met three times and found no safety-related issues.
  1. Diabetics. A randomized, 300-patient, multicenter comparison of Xience and Taxus Liberté.

2. Registry. This single-arm, multicenter, 2,700-patient study will evaluate Xience in a "real-world" setting. This just completed enrollment.

- **SPIRIT WOMEN.** This is a 2,000-patient, all-comers study, with 1,550 patients in a registry and 450 randomized to either Xience or Cypher. Enrollment began in July 2007, and it is still enrolling.
- **XIENCE V India.** Enrollment in this 1,000-patient, single-arm, post-approval registry has not yet begun.
- **XIENCE V USA.** This single-arm, post-approval registry in ~5,000 real-world patients at up to 275 U.S. sites, with follow-up at 14, 30, and 180 days as well as at Year 1, 2, 3, 4, and 5.

Other data

In the panel briefing documents, Abbott noted that in animal models, overlapping Xience stents appeared safe, with "acceptable results." No angiographic evidence of dissection, aneurysm, angiographic filling defects, excessive narrowing, thrombosis, stent migration, or stent fractures was observed. Furthermore, neointimal growth was similar between Xience and a bare Vision.

Abbott also noted that Xience V demonstrated decreased relative thrombogenicity compared to Vision stents as well as to commercially available DES (Cypher, Taxus, and Endeavor) as measured by overall adherent thrombus weight at 2 hours. *Ex vivo* models confirmed the relative thromboresistance of Xience.

Post-approval study

Abbott's original proposal for the primary endpoint in Xience V USA, the post-marketing study, was ARC-defined stent thrombosis at Year 1. The FDA did not agree with this proposed endpoint, indicating both in the panel briefing materials and at the panel meeting that it would prefer the primary endpoint be the evaluation of stent thrombosis rates through 5 years plus a co-primary endpoint of death and MI at 1 year and then out to 5 years.

Dr. Krucoff told the panel that Abbott wanted to modify its proposal to conform with the FDA request:

- Primary endpoint: Stent thrombosis through 5 years.
- Co-primary endpoint: The composite of death and MI
- Plus monitoring of antiplatelet therapy duration.

This is a change from Abbott's original proposal and appears to satisfy criticisms in the FDA briefing documents. After the panel meeting, an Abbott official said the company will do whatever the FDA wants in terms of the post-marketing study design.

Panel questions for Abbott speakers

The panel zeroed in on several issues, but Abbott speakers appeared to offer satisfactory answers:

- **Why was there a lack of superiority on TVF in SPIRIT III**, even though there was non-inferiority? Dr. Stone explained, "I think it is pretty evident that if we had a larger number of patients, we would see a reduction in TVF (with Xience)."
- **Why was there more late acquired malapposition with Xience by the FDA analysis than the Abbott analysis?** Dr. Stone offered an explanation that the panel seemed to accept.
- **Why was the angiographic follow-up only 77%?** Dr. Stone said U.S. angiographic follow-up typically is 75%-80%, and SPIRIT-III was powered for 75% follow-up, but this did not affect the findings.
- **How would Xience compare to Johnson & Johnson's Cypher?** Dr. Stone said Cypher likely would have had similar late loss rates, but Xience probably would have "looked very good on binary restenosis and other clinical events."
- **Why didn't Abbott test a lower everolimus dose?** An Abbott official said, "We did exploratory research at lower doses…The reason we didn't go below 100 μg was to find a balanced dose between efficacy and manufacturing capability, especially with smaller stents…Just for manufacturing ability, we felt it appropriate to go with this dose."
- **Isn't the reason Xience performed so well due to its second-generation DES design?** FDA panel member, Dr. Douglas Morrison, an interventional cardiologist from Yakima WA, commented, "Would you not agree that the difference in late loss between Xience and Taxus is really pretty close to what has been shown between Cypher and Taxus?...Part of the reason Taxus is more widely used is it is really a better stent platform, easier to deliver, etc…A cobalt chromium, thin strut (Xience) seems even further along the line." Dr. Stone responded, "When you look at many of the Cypher vs. Taxus trials, even though there is less late loss, there is similar binary restenosis…and almost identical TLR. Here (with Xience), perhaps due to thinner struts, greater re-endothelialization – I'm speculating here – and less stent fracture, we are seeing a reduction in TLR…So, while we've never compared Xience to Cypher, and we don't know for sure what the result would be, you might speculate they might be similar."
- **Could lack of pre-dilatation account for the lower MI rates with Xience?** Dr. Stone said no because it was mandatory to pre-dilate in SPIRIT, though he added, "We don't have experience with Xience with a direct stent strategy…but some non-randomized comparisons have suggested that not pre-dilating may lower MI rates."

- **Why was Xience not as good in the pooled analysis of SPIRIT-II/III as in SPIRIT-II alone?** Dr. Stone called it a purely statistical anomaly and due to "random noise."
- **Please elaborate on the potential problem of differential follow-up.** Dr. Bram Zuckerman, director of the FDA's Division of Cardiovascular Devices in the Center for Devices and Radiological Health (CDRH), asked Abbott to address this issue later in the day. He asked Abbott to show in the angiographic vs. non-angiographic subsets what exactly are the clinical event rates "because they are not the same, and we really need to flush this out and see the limitations of angiographic follow-up." Dr. Stone commented, "We will show clinical outcomes in cohorts of patients and that hopefully will allay your concerns."
- **Please address the quality and adequacy of the long-term Xience data.** Abbott experts insisted there are sufficient data and that adding even a few hundred patients wouldn't provide the answers on long-term safety that the panel wanted, that only a large, long-term post-marketing study would do that.
- **When would additional patients be available for analysis?** Dr. Krucoff said another 422 patients would be available in ~8 months.
- **On incomplete apposition and remodeling:** Speaking on behalf of Abbott, Dr. Peter Fitzgerald of Stanford, the director of the core lab for SPIRIT, pointed out that:
  - Late acquired stent apposition was 1.1% with Xience and 2.3% with Taxus.
  - Vessel remodeling is less with Xience, which is a positive for Xience. He said, "With Taxus we see a statistically significant increase in that (vessel re-modeling) from baseline to follow-up and no difference for Xience. Having done just about every DES technology and having a number of Taxus arms (to review), this is a trend we see consistently (with Taxus), and we don't see it with Xience."
- **Is the difference in late loss between Xience and other DES clinically meaningful?** Dr. Stuart Pocock, professor of medical statistics at the London School of Hygiene and Tropical Medicine, showed data from a study to be published soon in the ***Journal of the American College of Cardiology*** which found that lower late loss is associated with lower TLR, with the effect more pronounced as vessels get smaller. Dr. Stone added, **"For every 100 patients treated with Xience rather than Taxus, three did not require ischemic TLR."**
- **Is Xience safe in terms of stent thrombosis?** Dr. Stone said, "You need to look beyond stent thrombosis and look at overall death and MI, and then you get a little more reasonable assurance of safety…And we've shown 30-day MI rates are reduced – perhaps because of more robust polymer. So, in the peri-procedural period, Xience appears safer…And then when you look to one and two years, all-cause death, cardiac death, and MI – at least with available data – are all on the side favoring Xience. So, at this point we are at a good point…The desire for more data is a good one, and that is why we are doing a registry and another RCT with 3,700 patients, but we won't have that until near the end of 2009."
- **Why did Abbott submit Xience with limited patient data?** Panel member Dr. John Somberg, a professor of medicine and pharmacology at Rush University Medical Center, said, "My problem is with only 422 (Xience) patients…How in good conscience can you (Abbott) bring forward this presentation where we don't have the data to measure it. We have good efficacy data, but we don't have adequate data to give us a safety signal." Dr. Stone responded:
  - "I think you have to look at the totality of the program, what I understand led to adverse outcomes …You would like a thinner polymer, thinner struts, a lower dose of drug, an easier to deliver and more flexible stent with the potential for less vessel injury."
  - "And there is the (Renu Virmani animal) data...that this was the DES that most looked like a BMS. Does that promise long-term safety? No, of course not, but at least it is another piece of reassuring data."
  - "I'm quite convinced of the efficacy of this device."
  - "If 100% of DES penetration was with Xience, there would be 30,000 patients symptom-free, without re-hospitalization, so there would be a tangible benefit."
  - "This would be the stent I would put in most of my patients."

FDA Perspective

Dr. Robert Fiorentino, a medical reviewer for the FDA, and Xu (Sherry) Yan PhD, an FDA biostatistician, raised several issues with the SPIRIT program, including:

SPIRIT-II issues:

- The study was not adequately powered to allow robust comparisons between the 2 arms with respect to clinical endpoints.
- The study was not adequately powered to detect low frequency events.

FDA View of Xience Patient Clinical Follow-Up

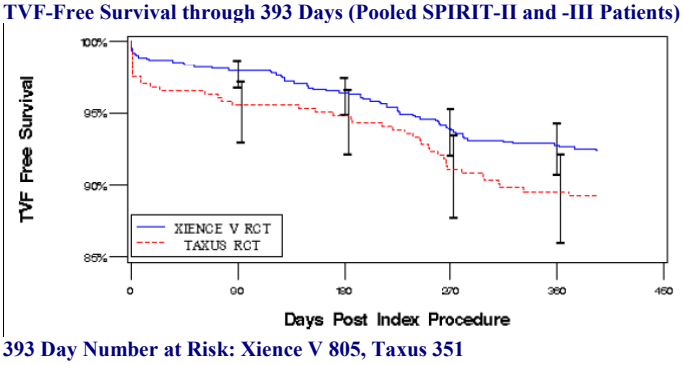
Trial	30 D	6 M	9 M	12 M	2 Y	3 Y
SPIRIT-First	27	26	26	26	26	26
SPIRIT-II	223	222	220	220	---	---
SPIRIT-III	667	662	653	646	---	---
SPIRIT-III 4.0 mm	69	67	67	67	---	---
Total	**986**	**977**	**966**	**959**	**---**	**---**

- The purpose of the two interim analyses is not clear: Abbott stated no early stopping was intended.
  - The decision boundary for superiority was not clearly specified.
  - The interim analyses results were un-blinded to Abbott but not available to the FDA.
  - The interim analyses may introduce potential bias to the study conclusions.

Pivotal SPIRIT-III Results

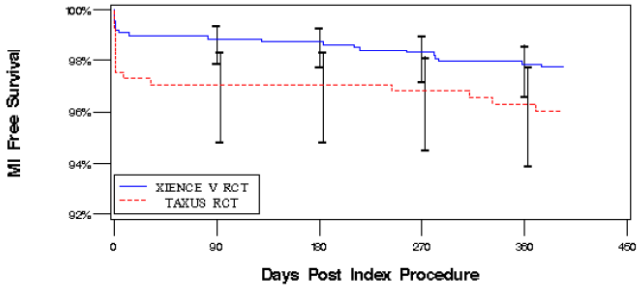
Measurement	Xience	Taxus
Primary endpoint #1: 240-day in-segment late loss	0.14 mm <0.001 for non-inferiority	0.28 mm
12-month results		
Number of patients	669	333
Primary endpoint #2: 9-month TVF	7.6% <0.001 for non-inferiority	9.7%
TVF	8.6%	11.3%
MACE	6.0%	10.3%
All Death	1.2%	1.2%
Cardiac Death	0.8%	0.9%
MI	2.8%	4.1%
Q-wave MI	0.3%	0.3%
Non-Q-wave MI	2.5%	3.8%
TLR	3.4%	5.6%
TVR	3.1%	4.4%
Stent thrombosis at 12 months		
Protocol defined	0.8%	0.6%
ARC definite + probable (TLR not censored)	1.1%	0.6%
ARC definite + probable (TLR censored)	1.1%	0.6%

TVF-Free Survival through 393 Days (Pooled SPIRIT-II and -III Patients)



393 Day Number at Risk: Xience V 805, Taxus 351
Log-rank p-value=0.0616

MI-Free Survival through 393 Days (Pooled SPIRIT-II and -III Patients)



393 Day Number at Risk: Xience V 847, Taxus 376
Log-rank p-value=0.0836

SPIRIT-III issue: Missing angiographic data.

SPIRIT-III 4.0 mm issues:

- It was observational, so the comparability of the treatment groups may be of concern.
- After 69 patients were enrolled, Abbott submitted a data analysis based on these patients.
- The primary analysis was not adjusted for covariates.
- Taxus does not have approval for a 4.0 mm DES.
- Taxus is not indicated for the treatment of RVD >3.75 mm, while the Xience V 4.0 mm is intended for the treatment of RVD between 3.75 mm and 4.25 mm.

Dr. Yan concluded:

- In SPIRIT-First, the superiority of Xience to BMS appeared to be established in terms of 180-day in-stent late loss.
- In SPIRIT-II, the superiority of Xience to Taxus appeared to be established in terms of 180-day in-stent late loss.
- In SPIRIT-III, the superiority of Xience to Taxus appeared to be established in terms of 240-day in-segment late loss, and the non-inferiority of Xience to Taxus appeared to be established in terms of 9-month ischemia-driven TVF.
- In SPIRIT-III 4.0 mm arm, the comparison of Xience and Taxus should be interpreted with caution because it is an observational study.

Diabetics

The data on Xience in diabetics was the only really negative finding, but FDA reviewers discounted the importance of this, and panel members did not focus on it either.

Clinical Events in Diabetics with Xience through Year 1

Measurement	Non-diabetics		All diabetics	
	Xience n=643	Taxus n=296	Xience n=249	Taxus n=110
TVF	6.4%	12.8%	11.1%	5.8%
All death	1.0%	2.4%	2.0%	0
Cardiac death	0.3%	1.4%	1.2%	0
MI	1.4%	4.5%	4.5%	2.9%
TLR	2.5%	7.6%	4.5%	1.0%
TVR (no TLR)	2.5%	4.1%	3.3%	2.9%
Stent thrombosis (protocol)	0.5%	1.0%	1.3%	0
Stent thrombosis – ARC definite and probable (not censored)	0.3%	0.7%	2.1%	1.0%

Panel questions for the FDA staff

- **Are there enough long-term data?** Dr. Fiorentino said more data are "months away."
- **Is Xience actually worse in diabetics than Taxus?** Panel member Dr. Valluvan Jeevanandam of the University of Chicago said, "Looking at the diabetics (in the pooled SPIRIT-II/III analysis), there is higher TVF with Xience…This is the only indication where Taxus is better than Xience." The FDA's Dr. Fiorentino responded that the difference between Xience and Taxus was statistically significant for non-diabetics (p=0.0036)." No p-value was provided for the difference between Xience and Taxus in diabetics, but Dr. Fiorentino added, "I'm hesitant to draw conclusions based on this (post hoc analysis)…I don't think we can say (either) stent performs better; the numbers are too low."
- **How does Plavix compliance correlate with stent thrombosis?** In patients with the first Plavix discontinuation before 393 days, there were similar rates of stent thrombosis with Xience and Taxus.
- **Could the course of Plavix be shortened with Xience?** There was no answer to this question.
- **Why isn't everolimus an NME?** Dr. Ashley Boam, Chief of the FDA's Interventional Cardiology Devices Branch at CDRH, explained, "We believe it is not an NME because everolimus, as Certican, was widely studied and thoroughly evaluated by CDER, so that this drug fell in the same category as sirolimus, which contrasted with other agents, such as zotarolimus, and others in development, like biolimus, that were never studied in any indication other than DES."
- **Why isn't there a comparator arm in the proposed post-marketing study?** Dr. Boam said the FDA has not requested or required that.
- **Did the FDA know the results of the SPIRIT-II and SPIRIT-III trials before asking for a pooled analysis?** Yes.
- **What is the significance of the tipping point analysis that the FDA performed?** The FDA's Dr. Yan said, "I wanted to give the panel as much information as possible…I wanted to show the panel under which data the difference in the two arms would reject non-inferiority." Dr. Pocock, the renowned U.K. medical statistician, speaking on behalf of Abbott, said, "My conclusion from the tipping point analysis is you would have to have major bias for the conclusions (relating to Xience) to no longer hold up...and it is implausible that that level of major bias would exist…So I think the tipping point analysis is interesting, but I think it suggests such major bias that would need to exist that it is plausible that the original results are valid…It would require an implausibly high level of late loss (to change the results)."

PANEL DISCUSSION

Two interventional cardiologists on the advisory committee offered their perspective on Xience.

1. Dr. Douglas Morrison, a private practitioner from Yakima WA:

- "This is by far the largest amount of data about the smallest number of patients, so that is concerning. How could that happen?"
- "Part of the reason there are so much data is not only that the same trials are repeated a number of times, but there are certain inferences in the concept of surrogacy...and there are several levels of surrogacy…We are looking at late loss for the first time as a surrogate of a surrogate of a surrogate in a subset of a randomized clinical trial."
- "I don't think very many people doing interventions would have any problem with the notion that it (Xience) is easier to deliver and that there is a broader anatomy in which you can get a good result with Xience than Taxus."
- "In my private practice: Vision is in both our hospitals as the stent of last resort. If you can't get a Vision or a Mini-Vision in, you are about to settle for a balloon result."
- "As a stent platform, I would take almost as a given that it (Xience) is a more deliverable platform than either of the currently available DES (Taxus and Cypher)."
- "I feel a lot more comfortable hearing about a drug where there is a good bit of human experience. This drug is given to a lot of patients with renal or heart transplant. The problems seem to be relatively modest. There is not a signal in the model I care about that everolimus isn't a safe drug."
- "It seems to me this (Xience) is a better stent platform than the other ones on the market (Cypher and Taxus), and now we have some patient data that it may be a better DES…Here we have a DES that is apparently approved in 64 countries and put into at least 4,000 human beings, and the total prospective randomized clinical trial data we have here on what happens two years later is ~400 patients."
- "In the interest of comparing apples to apples, we should recommend the same dual antiplatelet duration as the other (drug-eluting) stents that are approved."

2. Dr. John Hirshfeld of The Hospital of the University of Pennsylvania:

- "I am highly convinced this device is effective in reducing late loss, and I think preventing late loss overall is a good thing…The only question I would raise is if there is an optimal amount of late loss. This device has late loss comparable to Cypher, and there is always a concern that if a device is too good at inhibiting late loss, it could be (a negative)."

- In terms of efficacy, we have clear data that this is a very effective device. The meaningful issue is the safety issue …and there was a bit of a problem because we don't have as much data as we would like…It (Xience) appears safe in some axes and less safe in others."

Dr. Hirshfeld's Comparison of Xience vs. Taxus

Efficacy	Safety		
	Better	Similar	Worse
Better	++++	+++	+/–
Similar	+++	++	--
Worse	+/– ?	-- ?	---

- "To date there is not a concerted signal of a problem (with Xience). The reason to be vigilant for the potential of a problem is the extreme efficacy of this device in attenuating late loss. Intuitively, one feels the more you attenuate late loss, the more you may have stent thrombosis later down the road…We saw something like that in the data we looked at a month ago (Medtronic's Endeavor stent). I don't see a problem (with Xience), but we and the Agency need to be ongoing vigilant on this."

Panel Consideration of FDA Questions

The FDA posed six questions to the panel, which discussed each of them but took no formal votes.

Question 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?

Yes, in the short-term, but uncertain beyond 12 months.

After taking a first vote, the panel had further discussion. However, following that discussion, no panel members changed their vote.

The panel chair, Dr. Clyde Yancy, medical director of the Baylor Heart and Vascular Institute, summarized the discussion: "At least half the panel has reservations about the safety of this application. Whether or not that safety concern is a modest one because of some ambiguity or a definitive one because of inadequacy of the database, varies among the panel members. The one thing all panel members would accept is there is adequate assurance of near-term safety and in the first 12 months, but there are a number of people on the panel who would reserve the statement on safety beyond 12 months pending additional data. The concerns are it is an easily applied platform with significant clinical utility and works very well, and there is no safety signal for the data we are provided, but there is a need for additional data to resolve the issues beyond 12 months…I believe we are all of the mindset there is adequate safety out to 12 months. Past that, at least half the panel believes there are insufficient data to resolve the issue, but not to say the system is unsafe, just that the data just don't exist." The FDA's Dr. Zuckerman said, "I think you have captured that there are two viewpoints here, and the FDA is satisfied."

Panel member comments included:

- *Dr. Somberg:* "I don't think even if there were 800 patients it would be enough…Why are we racing to approve this when there are other DES available?...I think this is a good stent, and I think it would turn out to work …I favor this seeing the light of day, but I would like to see the data, and I would like to see a standard (for patient follow-up for approval)."
- "Yes, but there is minimal evidence."
- *Dr. Richard Page, an electrophysiologist from the University of Washington School of Medicine:* "There are a few of us who believe a reasonable assurance of safety has been shown."
- *Dr. Morrison, an interventional cardiologist:* "I think we have adequate data. This is as safe as Taxus."
- *Dr. Eugene Blackstone, a cardiothoracic surgeon at the Cleveland Clinic:* "Yes, short-term, but we don't know long-term."
- *Dr. Norman Kato, a cardiothoracic surgeon from California:* "For the study duration we have, it is reasonably safe, but the numbers here are very, very small…We struggled considerably with Endeavor, and that was 1,000 patients over 2 years…So, for me to drop the bar, so to speak, down from 1,000 to 200 (patients) – I'm very concerned about that."
- *Dr. Jeffrey Brinker, an interventional cardiologist at Johns Hopkins Hospital:* "There is no reason to suspect that after 12 months a stent like this will suddenly turn rogue and have a high incidence of (something). There is no reason to suggest something worse happens that is not associated with stopping antiplatelet drugs."

Question 2. If the answer to Question 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?

YES for approval, but longer follow-up needed after approval.

Panel chair summary: There is early safety out to 12 months, and the available follow-up has been sufficient…Even if there were an effort to close the loop and complete the data acquisition for the outstanding data points, there would be no statistically significant way to resolve issues about very late stent thrombosis. There might be some measurements on MI or death, but that doesn't make any panel members more comfortable. Where we will find comfort is safety at the time of deployment and out to 12 months, but there needs to be

some way to capture the safety issue beyond 12 months…My sense is that there probably already is a sense of clinical comfort with the use of this (device)."

QUESTION 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?

No. The panel recommended the label be compliant with the accepted ACC/AHA guidelines.

The panel chair said, "I think we should be consistent and respect the guidelines statement."

QUESTION 4. Do the data presented on the Xience V EECSS provide a reasonable assurance of effectiveness?

Yes, with no discussion.

QUESTION 5. Labeling – Acceptable as proposed, with no real discussion.

a. **Please comment on the INDICATIONS FOR USE section as to whether it identifies the appropriate patient populations for treatment with this device. No changes.**

b. **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. No changes.**

c. **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. No changes.**

d. **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. No changes.**

e. **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. No changes.**

f. **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. No changes.**

QUESTION 6. Post-marketing study

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

b. **Does the plan provided by the sponsor adequately address these objectives? No**

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

The panel chair summarized the changes the panel would like to see: "We suggest a very different post-approval study that puts clinical endpoints (e.g., death and MI) that are fairly comprehensive as primary endpoints. The size would still be 5,000 patients and follow-up to 5 years. The rest of the details we trust the office of post-approval studies would work out with the sponsor."

FINAL PANEL VOTE

Just before the panel voted on the overall approvability of Xience, Abbott speakers were given an opportunity to make some last minute comments. These included:

- *Dr. Pocock:* "What would you get with waiting eight months for more data? If you little more than double the size of the data, you might get 0 to 3 stent thromboses, so I don't think one would gain much insight. The relative issue on safety is in large studies."
- *Dr. Krucoff:* "I think it is important to take a step back, and the notion that low late loss is bad for safety is a notion of the past…Doing that and getting better endothelial healing is the goal of the future…Another item that has been repeated: compared to what (in the post-marketing study)? This (Xience) was compared to Taxus, a comparison that shows at least as good or superior efficacy with every indication that safety is roughly equivalent… DES have not 'taken rogue,' and there is no expectation for 'rogue behavior,' but there is a need for vigilance, and we are committed to vigilance."
- *Dr. Stone:* "If you look at where we are with 1- and 2-year hard endpoints (cardiac death and MI): At 1 year: 4.5% Taxus and 2.7% with Xience. In the 2-year dataset: 6.3% Taxus and 4.7% with Xience. So, we are favoring Xience. There is a real chance that is real and not just a chance finding. We've seen identical stent thrombosis but a reduction in peri-procedural MIs that is not chance – there is a mechanistic explanation for that – and a reduction in TVR. And some of those (TVRs) do cause death and MI. So, I hope we are on the verge of having a stent that improves outcomes. It looks safe and potentially even safer than the devices we have on the market (Cypher and Taxus)."

VOTE ON APPROVABILITY: The panel voted 9 to 1 to approve Xience V EECSS with these conditions:

1. **An appropriately-designed post-approval study be conducted, with details to be determined later by the FDA. Passed by a vote of 9 to 1.**
2. **Labeling for antiplatelet therapy be consistent with the ACC/AHA guidelines and what the FDA has recommended for other DES and include life-long aspirin. Passed unanimously.**

Two other conditions were proposed but rejected:

1. **The post-approval study have a concurrent control group.**

   Failed by a vote of 6 No to 5 Yes (chair broke the initial tie).

2. **That the outstanding two-year data from SPIRIT-III be acquired before approval.**
   Failed with no second. This was proposed by Dr. Somberg but did not even receive a second.

Following the vote, individual members offered comments on their vote. These included:

- *Dr. Hirshfeld, an interventional cardiologist:* "It (Xience) looks like it will be a nice adjunct to our armamentarium."
- *Sharon Lise-Normand, PhD, a statistician with Harvard School of Public Health:* "I voted for approval with conditions because the sponsor (Abbott) showed effectiveness with a reasonable sample size for clinical endpoints. Late loss was on a much smaller sample size…I had no prior reasons to suspect a safety issue, and the data didn't show a safety issue."
- *Dr. Somberg, the only vote against approval:* "I thought the safety data in 12-24 months was inadequate, and it was a bad precedent to establish…To have inadequate data leave the stent thrombosis issues unaddressed for many years."
- *Dr. Warren Laskey, medical cardiologist at the University of New Mexico School of Medicine:* "The study met the pre-specified endpoints…There is something very gratifying in returning to a technology that works very well (Vision) and the thin struts."
- *Dr. Page:* "I feel a reasonable assurance of safety was demonstrated as well as reasonable assurance of safety…I think this represents a step forward for interventional cardiology and our patients."
- *Dr. Blackstone:* "I was convinced the efficacy data were there. I thought the safety data, especially for the first 12 months, also showed the device was safe. There was encouraging information, especially about late restenosis that may well offset my conscience about long-term data that may come on thrombosis."
- *Dr. Valluvan Jeevanandam, a cardiothoracic surgeon at the University of Chicago:* "I think their 12-month endpoints have shown efficacy and safety at least at 12 months, and with post-marketing studies we can see the long-term effects."
- *Dr. Yancy, the panel chair:* "I would have voted for approval with conditions because of the less than full data set on safety but the good efficacy data."

The FDA's Dr. Zuckerman told the panel members they can have confidence the post-marketing study will be done: "Post-approval studies in the past – the very near past – have not been done with the diligence one might expect. The landscape has changed significantly. The first presentation today was from the Division of Postmarket Surveillance. Before we sign off on PMAs today, we have to have a good idea of the post-marketing study design. We would not hesitate to call a post-approval panel if we felt we still had issues, etc. So, the general construct, while it may not have been working well in the past, we are committed to changing it right now, and I wouldn't worry so much that it wouldn't be completed."

♦