

FDA Executive Summary

SPIRIT II and III 2-year Completer Analysis

Background

In the original Panel Pack materials mailed out on November 6, 2007, the clinical dataset provided by Abbott Vascular and reviewed by FDA consisted of:

- SPIRIT FIRST – follow-up through 36 months
- SPIRIT II – follow-up through 12 months
- SPIRIT III – follow-up through 12 months

Although Abbott Vascular has submitted complete 1 year data on subjects in both SPIRIT II and SPIRIT III to the FDA, *complete* data on these subjects out to 2 years is currently unavailable. Given the time elapsed since enrollment was completed, a number of subjects in these trials have become eligible for 2 year follow-up. Further, some proportion of these eligible subjects will have completed their 2 year follow-up assessment on an ongoing basis.

In order to provide as complete a dataset as possible, Abbott Vascular proposed to provide an additional analysis of data from those subjects who had completed their 2 year follow-up by a specific cut-off date. Abbott Vascular agreed to provide these data by November 5, so that FDA could review this additional information prior to the Panel meeting.

Therefore, Abbott Vascular has performed an *ad hoc* analysis on a subset of combined SPIRIT II and III subjects with 2 year follow-up as of October 30, 2007. FDA has agreed to receive and review such an analysis to give the applicant an opportunity to present the most up-to-date data available on the XIENCE V™ stent at the upcoming Panel meeting, despite the limitations of such an analysis.

Methodology

As of October 30, 2007, 603 subjects who were enrolled in the SPIRIT II and SPIRIT III trials had completed their two year follow-up (n=529) or were terminated early (n=74). Subjects who were terminated early included those who withdrew from the study, were lost to follow-up or died. Abbott was able to determine which investigational sites had subjects who completed their 2 year follow-up by October 30, 2007. Data on these subjects was subsequently monitored and clinical events sent for adjudication as needed and to apply ARC definitions of stent thrombosis (to allow analysis by both per protocol and ARC definitions).

- SPIRIT II protocol-defined stent thrombosis was reviewed by 3 independent physicians contracted to form a Clinical Events Committee (CEC) by Abbott Vascular. The same CEC members reviewed events applying the ARC

definitions. The Independent Core Lab, Cardialysis, provided information related to revascularizations to the CEC for their review.

- SPIRIT III protocol-defined stent thrombosis was adjudicated by an independent Cardiac Events Committee (CEC) at Duke Clinical Research Institute (DCRI). ARC-defined stent thrombosis was adjudicated by an independent CEC at Harvard Clinical Research Institute (HCRI).

Results

Of the 603 subjects who were completers or early terminators, 422 subjects received XIENCE V and 181 subjects received TAXUS. The contribution of subjects according to the study in which they were enrolled is as follows:

- SPIRIT II: XIENCE V 186 patients, TAXUS 65 patients.
- SPIRIT III: XIENCE V 236 patients, TAXUS 116 patients

Baseline demographics appear to be similar to that in the overall SPIRIT II and III cohorts, with possible exceptions including Unstable Angina, Prior MI and MI Within Two Months. Baseline lesion characteristics were generally comparable, with possible exceptions of lesion eccentricity and ACC/AHA lesion classes.

For comparison, one year (393 days) TVF rates in the subset of subjects with 2-year data (XIENCE V: 8.4% vs. TAXUS 13.0%) were numerically higher than that observed in the overall analysis (XIENCE V: 7.7% vs. TAXUS 10.8%). No formal statistical comparisons were performed to evaluate differences in outcomes between the 2 year completer cohort and the overall combined SPIRIT II and III analysis.

Not unexpectedly, clinical events from 0 to 758 days in the 2 year cohort were numerically higher than the one year data. As shown in Table 1 below, rates of cardiac death and MI from 1 to 2 years were low in the 2 year completer cohort.

Table 1

394 to 758 days	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)
Cardiac Death	0.5% (2/379)	0.0% (0/153)
QMI	0.0% (0/379)	0.0% (0/153)
NQMI	1.1% (4/379)	0.7% (1/153)

In the 2-year completer cohort, there were two additional *Protocol Defined* stent thromboses observed in the XIENCE V arm and none in the TAXUS arm:

Table 2

Protocol Defined	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)

Very Late Stent Thrombosis (394 - 758 days) [95% Confidence Interval] ¹	0.5% (2/378) [0.06%, 1.90%]	0.0% (0/153) [0.00%, 2.38%]
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¹ By Clopper-Pearson exact confidence interval

In contrast, as outlined in Table 3, there was one *ARC Definite + Probable* stent thrombosis in the XIENCE V arm between 1 and 2 year follow-up. The applicant notes that the one very late event (394 – 758 days) reported for XIENCE V came from a subject enrolled in the SPIRIT II trial.

Table 3

ARC Defined	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)
Very Late Stent Thrombosis (394 - 758 days) Definite/Probable [95% Confidence Interval] ¹	0.3% (1/377) [0.01%, 1.47%]	0.0% (0/153) [0.00%, 2.38%]

¹ By Clopper-Pearson exact confidence interval

As presented in Table 4, total stent thrombosis rates at 2 years for the completer cohort were numerically similar between the XIENCE V and TAXUS stents:

Table 4

Total Stent Thrombosis (0 - 758 days)	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)
Protocol defined [95% Confidence Interval] ¹	1.6% (6/379) [0.58%, 3.41%]	1.9% (3/155) [0.40%, 5.55%]
ARC Definite/Probable [95% Confidence Interval] ¹	1.3% (5/379) [0.43%, 3.05%]	1.3% (2/155) [0.16%, 4.58%]

Summary

For the 2 year analysis cohort presented by the applicant, rates of additional cardiac death, myocardial infarctions and stent thrombosis events occurring between one and two years of follow-up were low.

Key Limitations

- This is an ad hoc analysis presented for the purpose of providing information on 2 year data available to the applicant by the arbitrarily chosen cut-off date of Oct. 30, 2007; it should not be interpreted as an interim analysis.
- Data is derived from a subset of the total SPIRIT II and III study cohorts and contains only data that was available to the applicant. It is possible that the data

available for this analysis, or subjects from which the data were derived, have characteristics that are different from the remaining subjects not included (i.e., due to sampling bias).

- Events that occurred in subjects who had not yet reached the 2 year follow-up window may not be included in this analysis.
- Absent from the data are subjects who were eligible for 2 year follow-up, but have not yet been assessed (for whatever reason).
- It is possible that there are subjects who have had their 2 year follow-up, but did not have their data reported to the applicant by the October 30, 2007 cutoff.
- Inclusion of data from sites that submitted 2 year data was non-random.
- Adjudication of clinical events and determination of ARC-defined stent thromboses were not performed by the same committee for each subject.