

SECTION 6.0 XIENCE V EECSS CLINICAL EXPERIENCE INDIVIDUAL TRIAL SUMMARIES

Introduction

The current clinical experience for the XIENCE™ V EECSS consists of the three clinical trials: SPIRIT FIRST, SPIRIT II, and SPIRIT III. SPIRIT II and SPIRIT III also include clinical pharmacokinetic substudies.

The initial clinical safety and performance of XIENCE V EECSS were demonstrated in the **SPIRIT FIRST** clinical trial, a randomized, controlled, single-blinded evaluation of XIENCE V in the treatment of patients with *de novo* native coronary artery lesions. A total of 60 patients (28 in the XIENCE V treatment group and 32 in the VISION® bare metal stent control group) were enrolled at 9 investigational sites outside the United States. The primary endpoint was in-stent late loss at 6 months. The SPIRIT FIRST trial showed a significant benefit for XIENCE V over the VISION stent. In-stent late loss of 0.10 ± 0.23 mm in the everolimus eluting stent group represented an 88% reduction relative to the control group (0.85 ± 0.36 mm) ($p < 0.0001$). A low 6-month major adverse cardiac event (MACE) rate of 7.7% supported the clinical safety of the XIENCE V EECSS. The SPIRIT FIRST trial has demonstrated that the clinical safety observed at 6 months was sustained out to 3 years as demonstrated by no observations of late stent thrombosis events, and continued low TVF and MACE rates.

The **SPIRIT II** clinical trial was a continuation in the assessment of the safety and performance of the XIENCE V EECSS versus the TAXUS® EXPRESS² Paclitaxel-Eluting Coronary Stent System (PECSS) in the treatment of patients with a maximum of two *de novo* native coronary artery lesions located in two different epicardial vessels (from 2.5 mm to 4.25 mm in diameter and up to 28 mm in length, including overlapping stents). A total of 300 subjects were enrolled into the SPIRIT II clinical study at 28 international sites. Of the 300 subjects enrolled, 223 were randomized to receive the XIENCE V EECSS and 77 were randomized to receive the TAXUS PECSS (3:1 XIENCE V:TAXUS randomization). The primary endpoint was in-stent late loss at 180 days. The data indicated that XIENCE V EECSS was non-inferior to the TAXUS PECSS for in-stent late loss at 180 days. Pre-specified secondary analysis also showed superiority in terms of in-stent late loss for the XIENCE V EECSS compared to the TAXUS PECSS. The XIENCE V in-stent late loss was 0.11 mm while the TAXUS in-stent late loss was 0.36, which represents a 72% reduction in late loss. Lower rates on key clinical endpoints were observed for the XIENCE V compared to the TAXUS such as ischemia driven MACE (2.7% and 6.5%, respectively) and protocol-defined stent thrombosis (0.5% and 1.3%). Ischemia-drive MACE at 180 days was sustained through 1 year for XIENCE V, and no new instances of late stent thrombosis were observed in either group at 1 year.

The **SPIRIT III** clinical trial was designed to demonstrate safety and effectiveness of the XIENCE V EECSS. The SPIRIT III clinical trial is a prospective, randomized, active-controlled, single-blinded, parallel two-arm multi-center clinical trial utilizing either the XIENCE V stent on a Rapid Exchange (RX) delivery system or the FDA approved,

commercially available TAXUS EXPRESS² Paclitaxel-Eluting Coronary Stent System. The SPIRIT III protocol allowed for dual vessel treatment and planned stent overlap.

The SPIRIT III RCT study was designed to enroll 1,002 subjects (randomized 2:1 XIENCE V:TAXUS) at up to 80 sites in the US. The primary endpoint for the SPIRIT III RCT was in-segment late loss at 240 days, and the major secondary endpoint was ischemia-driven Target Vessel Failure (TVF) at 270 days. The XIENCE V in-segment late loss at 240 days was 0.14 mm, compared to the TAXUS EXPRESS² in-segment late loss of 0.28 mm. These data demonstrated non-inferiority (p-value < 0.0001) and superiority (p-value =0.0037) for the XIENCE V in terms of in-segment late loss at 240 days. XIENCE V was also found to be non-inferior (p-value <0.0001) to TAXUS EXPRESS² in terms of the major secondary endpoint, with ischemia-driven TVF rates of 7.6% and 9.7%, respectively. The rates of late stent thrombosis through 393 days for XIENCE V vs. TAXUS were 0.3% vs 0.6% by protocol definitions, and 1.1% vs. 0.6% by the Academic Research Consortium (ARC) definitions (definite plus probable).

The primary endpoint for the SPIRIT III 4.0 mm non- randomized arm was in-segment late loss at 240 days. The XIENCE V 4.0 mm non-randomized arm in-segment late loss was 0.17 mm and is non inferior (p-value <0.0001) to the TAXUS EXPRESS² in-segment late loss of 0.28 mm. The XIENCE V in-segment late loss in the 4.0 mm arm is comparable to the XIENCE V in-segment late loss in the SPIRIT III RCT.

Clinical pharmacokinetic substudies were conducted in three different geographies to demonstrate the elution of everolimus from the XIENCE V stent. SPIRIT II conducted outside the United States and SPIRIT III conducted in the United States (RCT) and Japan (registry) contained pharmacokinetic substudies. The pharmacokinetic profile for everolimus eluted from the XIENCE V stent is consistent across all geographies. The pharmacokinetic profile in clinical trials of the XIENCE V EECSS is consistent with the pre-clinical profile. The local arterial delivery and limited systemic exposure provide the opportunity for successful treatment of coronary lesions with limited risk associated with systemic exposure.

Taken together, these three studies have demonstrated superiority of XIENCE V in the following angiographic measures:

- In-stent late loss compared to VISION in SPIRIT FIRST
- In-stent late loss compared to TAXUS in SPIRIT II
- In-segment late loss compared to TAXUS in SPIRIT III

The studies also show consistent angiographic, clinical, and pharmacokinetic results for XIENCE V across all geographies. The observed lower MACE rates compared to TAXUS, and the low incidence of late stent thrombosis confirm the safety of XIENCE V.

Background

Abbott Vascular had originally proposed a primary endpoint of in-stent late loss for SPIRIT III, which was the primary endpoint for SPIRIT II. FDA agreed that in-stent late loss was an appropriate measure for effectiveness, however FDA requested that the primary endpoint be in-segment late loss to consider the edges of the stent.

To confirm the validity of in-segment late loss as a surrogate marker for clinical outcome, Abbott Vascular developed a model to predict ischemic-driven Target Vessel Failure (ID-TVF) from in-segment late loss. The model was based on Abbott Vascular's DELIVER I trial (which was also used in the development of Pocock's Model¹) which was the data set the most similar to SPIRIT III in terms of patient population and medical practice. The model was then used to define the delta (Figure 6-1).

The pooled CYPHER (from SIRIUS trial) and TAXUS (from the TAXUS IV trial) ID-TVF rates were 8.6%. Based on the model, a late loss of 0.44 mm would have predicted an ID-TVF rate of 8.6% for patients with single vessel treatment. Therefore, to assure that the event rate is no higher than 8.6% as predicted by the model, one would want to assure that the in-segment late loss was ≤ 0.44 mm. Based on the pooled results for in-segment late loss for CYPHER (from the SIRIUS trial) and TAXUS (from TAXUS IV), the assumed in-segment late loss was 0.24 mm for both arms in SPIRIT III. With an assumed in-segment late loss of 0.24 and a 0.195 mm delta, the trial assured that the in-segment late loss ≤ 0.435 which is less than the 0.44 mm, assuring that the ID-TVF rate would be less than 8.6%. Therefore, the delta is both statistically and clinically relevant.

¹ Pocock, S.; Stone, G. W.; Fahy, M., et al. Relationship between late loss, diameter stenosis and target lesion revascularization after stent implantation: An examination of surrogate endpoints from a pooled analysis of eight large randomized DES trials. *Journal of the American College of Cardiology* (2006) 47(4): 188A-188A

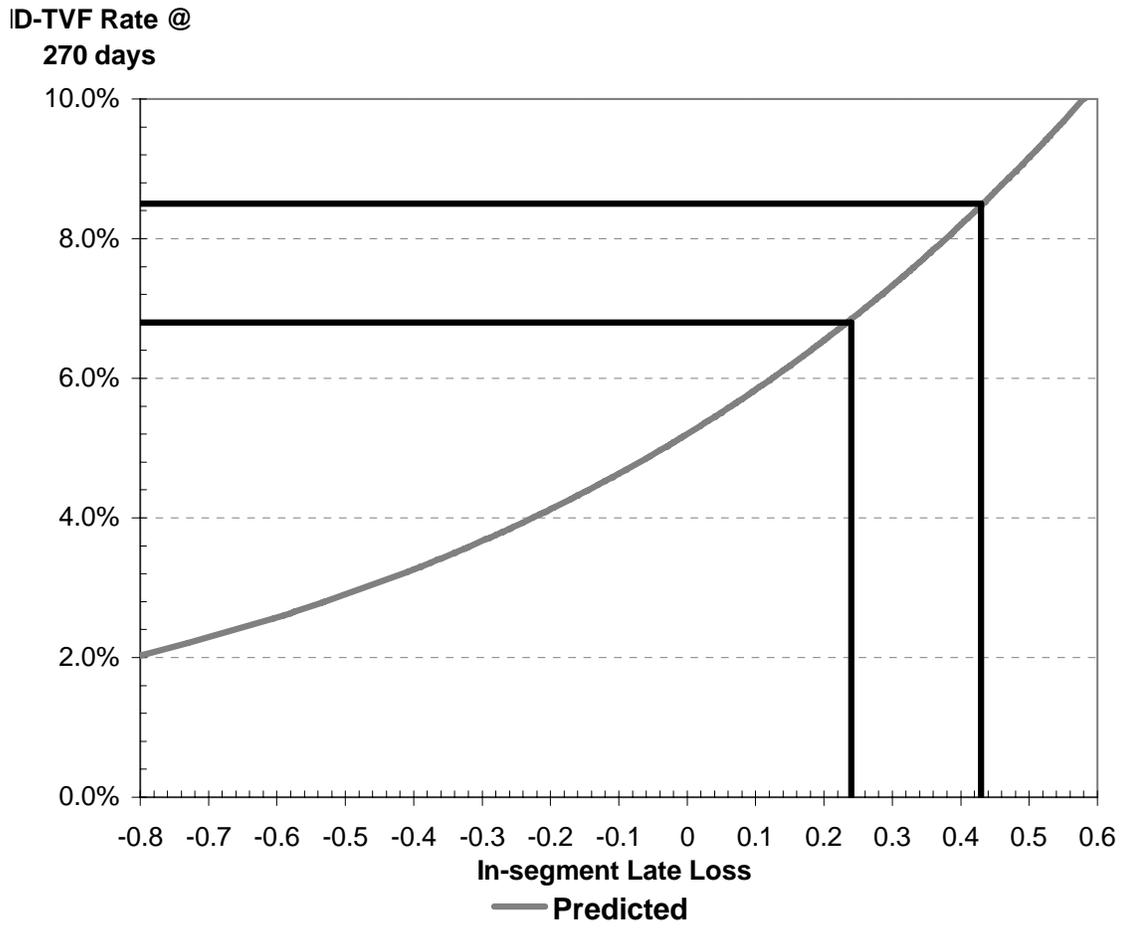


Figure 6-1 Relationship Between Late Loss Delta to TVF Delta

6.1 Descriptive Summary of SPIRIT FIRST

Introduction

This section summarizes the study design of the SPIRIT FIRST clinical trial and includes clinical results through the three years following the inception of the trial. The SPIRIT FIRST clinical trial was the first clinical trial conducted to assess feasibility and performance of the XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS). The nomenclature used to describe the XIENCE V EECSS in the SPIRIT FIRST clinical trial has changed over time. The SPIRIT FIRST clinical trial initially referred to the VISION stent coated with 100µg/cm² Everolimus in a PVDF-HFP durable coating as VISION-E; this design is synonymous with the XIENCE V EECSS.

Study Design

Objective

The objective of the SPIRIT FIRST clinical trial was to assess the feasibility and performance of the XIENCE V EECSS (named MULTI-LINK VISION-E RX Drug Eluting Stent System in this trial) in the treatment of subjects with a single *de novo* native coronary artery lesion. This study compared XIENCE V EECSS to a matched uncoated metallic stent control (MULTI-LINK VISION).

Study Type

The SPIRIT FIRST clinical trial was a prospective, single-blinded, randomized, controlled, parallel two-arm (1:1 randomization), multi-center, superiority trial designed to enroll 60 subjects.

Enrollment Criteria

Subjects were eligible if they were at least 18 years of age and had angina or a positive functional test identified for elective stenting. Additionally, female subjects had to provide a negative pregnancy test. Clinical exclusion criteria included:

- Patient must be at least 18 years of age.
- Patient is able to verbally acknowledge an understanding of the associated risks, benefits and treatment alternatives of receiving the Abbott Vascular MULTI-LINK VISION-E™ Stent and he or his legally authorized representative provides written informed consent prior to the stent procedure, as approved by the appropriate Ethics Committee.
- Patient must have evidence of myocardial ischemia (e.g., stable or unstable angina, silent ischemia, positive functional study).
- Patient must be an acceptable candidate for coronary artery bypass graft (CABG) surgery.
- Patient must agree to undergo all protocol-required follow-up examinations including angiographic and IVUS follow-up at two time points (180 days and 1 year).
- Female patients of childbearing potential must have had a negative pregnancy test within 7 days before treatment, and must not be nursing at the time of treatment.
- Female patients of childbearing potential must also agree at time of consent to use birth control up to and including the second angiographic follow-up at 1 year.

Subjects who met the general eligibility criteria were invited to participate in this study and were required to sign the consent form prior to enrollment. Final eligibility was confirmed based on pre-procedure angiography. Angiographic inclusion criteria included:

- Planned single, *de novo*, type A - B1, native coronary artery lesion treatment.
- Target lesion must be located in a native vessel with a diameter of 3.0 mm assessed by QCA on-line.
- Target lesion length \leq 12 mm., assessed by QCA on-line.
- The target lesion must be in a major artery or branch with a stenosis of \geq 50% and $<$

100% assessed by QCA on-line and with a TIMI flow of ≥ 1 .

Clinical exclusion criteria included:

- Patient has had a known acute myocardial infarction (greater than two times the upper limit of normal CK with presence of CK-MB) within 3 days preceding the index procedure and CK has not returned to normal limits at the time of the procedure.
- Patient has current or a history of unstable arrhythmias, regardless of whether cardiac rhythm management devices are used (e.g., pacemaker, Automatic Implantable Cardioverter Defibrillator).
- Patient has a known left ventricular ejection fraction $\leq 30\%$.
- Patient has received a heart transplant or any other organ transplant or is on a waiting list for any organ transplant.
- Patient is receiving or scheduled to receive chemotherapy or radiation therapy within 30 days prior to or after the procedure.
- Patient is receiving immunosuppression therapy or has known immunosuppressive disease.
- Patient is receiving chronic anticoagulation therapy (e.g., heparin, coumadin).
- Patient has a known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, cobalt, chromium, nickel, tungsten, everolimus, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated.
- Patient has a platelet count $<100,000$ cells/mm³ or $>700,000$ cells/mm³, a WBC of $<3,000$ cells/mm³, or documented or suspected liver disease (including laboratory evidence of hepatitis).
- Patient has known renal insufficiency (e.g., serum creatinine level of more than 2.5 mg/dL, patient on dialysis).
- Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
- Patient has had a cerebrovascular accident (CVA) or stroke or transient ischemic neurological attack (TIA) within the past six months.
- Patient has had a significant GI or urinary bleed within the past six months.
- Patient has extensive peripheral vascular disease that precludes safe 6 French sheath insertion or extreme anticoagulation.
- Patient has other medical illness (e.g., cancer or congestive heart failure) or recent history of substance abuse that may cause non-compliance with the protocol, confound the data interpretation or is associated with a limited life expectancy (i.e., less than one year).
- Patient is already participating in another investigational use device or drug study or has completed the follow-up phase of another trial within the last 30 days.
- Patient has received a drug eluting stent within the last 1 year.

Angiographic exclusion criteria included:

- The target lesion meets any of the following criteria:
 - Aorto-ostial location
 - Unprotected left main location

- Located within 2 mm of the origin of the LAD or LCX
- Located within or distal to an arterial or saphenous vein graft
- Located within 2 mm of a bifurcation
- Located distal to a previously implanted stent (same major epicardial vessel)
- Located in a major epicardial vessel that has been previously treated with brachytherapy
- Located in a major epicardial vessel that has been previously treated with any type of PCI (e.g., POBA, stent, cutting balloon, atherectomy), except if previous treatment occurred in a side branch distal to target lesion at least 180 days preceding the index procedure
- Involves jailing of side branches > 2.0 mm in diameter
- Total occlusion (TIMI flow 0)
- Excessive tortuosity proximal to or within the lesion
- Extreme angulation ($\geq 90\%$) proximal to or within the lesion
- Moderate to heavy calcification
- Restenotic from previous intervention
- The target vessel contains thrombus.
- Another significant lesion ($\geq 40\%$ DS) is located in the same major epicardial vessel as the target lesion.
- Patient has a high probability that a procedure other than pre-dilatation and stenting will be required for treatment of the target vessel (e.g. atherectomy, cutting balloon).
- Patient has additional lesion(s) for which an intervention within 180 days (prior to or after) of the index procedure would be required or has been performed.

General eligibility of the SPIRIT FIRST was similar to that of subsequent clinical trials, SPIRIT II and SPIRIT III.

Treatment Strategy

Prior to stent implantation, an interactive telephone randomization service (ICON Clinical Research, Sugar Land, Texas) was used to randomly assign subjects to receive either XIENCE V or MULTI-LINK VISION stent in a 1:1 ratio. Randomization was stratified by site and diabetic status to ensure a balanced distribution of subjects across treatment arms.

Eligible subjects underwent mandatory pre-dilatation of the target lesion by standard balloon angioplasty. Randomization could only take place after verification of the inclusion/exclusion criteria and successful pre-dilatation of the target lesion. Subjects were considered enrolled when the study stent was delivered beyond the guide catheter. A single 3.0 x 18 mm stent was used as a planned stent in both arms. The stent had to adequately cover the lesion such that a minimum of 3 mm of non-diseased vessel on either side of the lesion was covered by the stent. Post-dilatation was per investigators' decision and could only be done within the boundaries of the stent. If bailout stenting was deemed necessary during the procedure, either an 8 mm or an 18 mm length MULTI-LINK VISION stent was to be used in both study arms.

Subjects were required to receive a loading dose of clopidogrel bisulfate ≥ 300 mg within 24 hours prior to the index procedure, and were to maintain a regimen of 75 mg per day for at least three months following the procedure. Aspirin ≥ 80 mg was to be initiated within 24 hours of the procedure and to be continued at the same daily dose for a minimum of one year. If a subject developed sensitivity to clopidogrel bisulfate, they could be switched to ticlopidine hydrochloride at a dose according to hospital standard of care. All subjects were required to receive anticoagulation therapy during stent implantation according to the standard of care at the clinical site.

Data Collection and Assessment

All data were collected on electronic case report forms (InForm™, Phase-Foward, Waltham, MA).

Angiographic and IVUS data were assessed by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands) in a blinded manner. Serious adverse events were analyzed and adjudicated by a blinded Clinical Events Committee (Cardialysis, Rotterdam, The Netherlands).

Information on adverse events was reviewed by an unblinded Data Safety Monitoring Board (AMC-UVA, Amsterdam, The Netherlands) to evaluate subject safety on an ongoing basis. Safety analysis was performed by the Data Safety Monitoring Board during the subjects' enrollment and on completion of each follow-up time-point.

Key Endpoints

The primary endpoint of the SPIRIT FIRST clinical trial was in-stent late loss at 180 days. In-stent late loss was measured as the difference between the in-stent minimal lumen diameter (MLD) at post procedure and that at the 180-day follow-up. The in-stent MLD was determined by QCA. The major secondary endpoint was percent volume obstruction (%VO) at 180 days that was measured by 3D IVUS analysis ((stent volume-lumen volume)/stent volume). Other secondary endpoints included target vessel failure (TVF)², major adverse cardiac event (MACE)³ and stent thrombosis⁴ at each follow-up time-point.

² TVF: Comprised of Cardiac Death, QMI, NQMI, TLR (clinically-driven Target Lesion Revascularization by CABG/PCI and TVR (Clinically-driven Target Vessel Revascularization by CABG/PCI).

³ MACE: Comprised of Cardiac Death, QMI, NQMI and TLR by (CABG/PCI).

⁴ Stent Thrombosis: Total occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers and ECG changes consistent with an MI.

Statistics

Analysis of the follow-up data was performed in the per-treatment evaluable population. Subjects who had no bailout stents and no major protocol deviations were considered per-treatment evaluable. The trial had a 95% statistical power based on the primary endpoint to detect a 0.48 mm difference in in-stent late loss (0.35 ± 0.38 mm and 0.83 ± 0.56 mm, 58% reduction) with a 5% false positive rate (single-sided), assuming 70% of the follow-up angiographies were available.

Number of Subjects and Investigators

A total of 60 subjects were randomized and enrolled consecutively in this trial at nine (9) European investigational sites (six (6) sites in Germany, two (2) sites in The Netherlands, and one (1) site in Denmark). Twenty eight (28) subjects were enrolled in the XIENCE V arm and 32 subjects were enrolled in the MULTI-LINK VISION arm, as presented in Table 6-1. Four (4) subjects were excluded from the per-treatment population; three (3) subjects (one from the test arm and two from the control arm) received bailout stents and one (1) subject in the control arm had several major protocol deviations. Hence, the per-treatment population consisted of 56 subjects (test = 27, control = 29) at baseline. Two (2) subjects (one in each arm) withdrew consent after the completion of 30-day follow-up. There were no other drop-outs in the following two years. Therefore, 54 of 56 per-treatment evaluable subjects (96%) completed follow-up evaluations at the two-year time-point.

Table 6-1 Number of Patient Treated By Investigator

Principal Investigator	Center, Location	XIENCE V	VISION	Total
Prof. Piek	Academisch Medisch Centrum, Amsterdam, The Netherlands	9	9	18
Prof. Neumann	Herzzentrum Bad Krozingen, Bad Krozingen, Germany	7	7	14
Dr. Wiemer	HZ Bad Oeynhausen, Bad Oeynhausen, Germany	3	2	5
Prof. Serruys	ThoraxCentre, Erasmus Medical Center, Rotterdam, The Netherlands	2	3	5
Prof. Zieher	Uni. Klinikum Frankfurt, Frankfurt, Germany	1	3	4
Prof. Grube	Heart Center Siegburg, Siegburg, Germany	1	3	4
Dr. Haase	Red Cross Hospital, Frankfurt, Germany	2	2	4
Dr. Thuesen	Skejby Sygehus, Aarhus, Denmark	2	2	4
Prof. Hamm	Kerckhoff Klinik Bad Nauheim, Bad Nauheim, Germany	1	1	2
Total		28	32	60

Study Period

The first subject was enrolled on December 16, 2003 and the last subject was enrolled on April 1, 2004. Subjects were clinically evaluated at 30, 180 and 270 days and at 1, 2 and 3 years following the index procedure. Further clinical observations will be performed at 4 and 5 years. Angiography and IVUS follow-up were to be performed in all subjects at 180 days and at 1 year.

Summary of Study Population**Demographics**

Per-treatment subjects were similar for baseline demographics and lesion morphologies (Table 6-2). Demographics observed included age (62.74 ± 9.45 years), male gender (73.2%), current cigarette use (29.6%), any diabetes (10.7%), hyperlipidemia requiring medication (73.2%) and prior MI (18.5%). Hypertension requiring medication was higher in the XIENCE V arm (70.4%) than in the MULTI-LINK VISION arm (41.4%). Target lesions were located in LAD (46.4%), in LCX (21.4%) and in RCA (32.1%). Lesion morphologies were similar for eccentric lesions (94.6%) and ACC/AHA lesion class B2/C (60.7%), however, higher calcification was observed in the VISION arm (22.2% vs. 48.3%). Baseline QCA of both arms were similar and included lesion length (10.50 ± 2.98 mm), RVD (2.66 ± 0.34 mm), MLD (1.00 ± 0.30 mm) and %DS ($62.62 \pm 9.92\%$).

Table 6-2 Summary of Subject Demography and Lesion Morphology

	XIENCE V (N=27)	VISION (N=29)	TOTAL (N=56)	95% CI of Difference
Subject Demography				
Age (yrs)	64.21± 9.56 (27)	61.36± 9.31 (29)	62.74± 9.45 (56)	[-2.21, 7.91]
Number of Men	70.4% (19/27)	75.9% (22/29)	73.2% (41/56)	[-28.71%, 17.73%]
Current Cigarette Use	28.0% (7/25)	31.0% (9/29)	29.6% (16/54)	[-27.39%, 21.32%]
Any Diabetes	11.1% (3/27)	10.3% (3/29)	10.7% (6/56)	NC
Hypertension Req. Medication	70.4% (19/27)	41.4% (12/29)	55.4% (31/56)	[4.13%, 53.85%]
Hyperlipidemia Req. Medication	70.4% (19/27)	75.9% (22/29)	73.2% (41/56)	[-28.71%, 17.73%]
Prior Myocardial Infarction	24.0% (6/25)	13.8% (4/29)	18.5% (10/54)	NC
Target Vessel				
LAD	48.1% (13/27)	44.8% (13/29)	46.4% (26/56)	[-22.81%, 29.45%]
LCX	22.2% (6/27)	20.7% (6/29)	21.4% (12/56)	[-19.99%, 23.06%]
RCA	29.6% (8/27)	34.5% (10/29)	32.1% (18/56)	[-29.27%, 19.56%]
Lesion Morphology				
Calcification (moderate/severe)	22.2% (6/27)	48.3% (14/29)	35.7% (20/56)	[-50.07%, -2.04%]
Thrombus	3.7% (1/27)	0.0% (0/29)	1.8% (1/56)	NC
Eccentric Lesion	100.0% (27/27)	89.7% (26/29)	94.6% (53/56)	NC
Lesion Angulation > 45 ⁰	14.8% (4/27)	0.0% (0/29)	7.1% (4/56)	NC
ACC-AHA Lesion Class				
A	0.0% (0/27)	10.3% (3/29)	5.4% (3/56)	NC
B1	40.7% (11/27)	27.6% (8/29)	33.9% (19/56)	[-11.51%, 37.81%]
B2	59.3% (16/27)	62.1% (18/29)	60.7% (34/56)	[-28.41%, 22.79%]
C	0.0% (0/27)	0.0% (0/29)	0.0% (0/56)	NC

Abbreviations:

CI: Confidence Interval, **LAD:** Left Anterior Descending, **LCX:** Left Circumflex, **RCA:** Right Coronary Artery, **ACC:** American College of Cardiology, **AHA:** American Heart Association, **NC:** Not calculated (sample/event numbers are too small).

Notes:

- Analysis was performed in per-treatment evaluable population.
- Continuous numbers are shown in (mean ± standard deviation). Standard deviation calculated assuming a normal distribution
- 95% Confidence Interval is calculated by normal approximation
- The normality assumption may not be valid given the small sample size

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only.

Summary of Safety and Effectiveness Data

Primary and Major Secondary Endpoints

The primary endpoint, 180-day in-stent late loss, was 0.10 ± 0.23 mm in the XIENCE V arm (n = 23) and 0.85 ± 0.36 mm in the MULTI-LINK VISION arm (n = 27), an

88% reduction. The difference was found to be statistically significant ($p < 0.0001$) and the primary endpoint was met. The major secondary endpoint, 180-day in-stent % VO, was $7.95 \pm 10.44\%$ in the XIENCE V arm ($n = 21$) and $28.11 \pm 13.98\%$ in the MULTI-LINK VISION arm ($n = 24$), a 72% reduction. The difference was found to be statistically significant ($p < 0.0001$) and the major secondary endpoint was met. According to these criteria, superiority of the XIENCE V stent with respect to the MULTI-LINK VISION stent was proven (Table 6-3).

Table 6-3 Results of the Primary and Major Secondary Endpoint

	XIENCE V (N=27)	VISION (N=29)	Difference (Test-Control)	P-Value
Primary Endpoint 180-day In-stent Late Loss, mm	0.10 ± 0.23 (23) [0.00, 0.20]	0.85 ± 0.36 (27) [0.71, 1.00]	-0.76 [-0.93, -0.59]	< 0.0001
Major Secondary Endpoint 180-day %Volume Obstruction	7.95 ± 10.44 (21) [3.20, 12.70]	28.11 ± 13.98 (24) [22.21, 34.01]	-20.16 [-27.53, -12.79]	< 0.0001

Notes:

- Analysis was performed in per-treatment evaluable population.
- Numbers are shown in (mean \pm standard deviation). Standard deviation calculated assuming a normal distribution
- Numbers in [] are 95% Confidence Interval. 95% Confidence Interval is calculated by normal approximation
- P-values for the primary endpoint, while the major secondary endpoints are the results from one-tailed tests performed at the 0.05 significance level.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Secondary Endpoints

Acute Success

The rates of device success were not notably different between the XIENCE V arm and the MULTI-LINK VISION arm in the intent-to-treat population (96.4% and 93.8%, respectively), due to bailout. The procedure success rate was 100% in both arms and clinical success was 96.4% in the XIENCE V arm and 100% in the MULTI-LINK VISION arm. (Table 6-4).

Table 6-4 Acute Success

	XIENCE V (N=28) ^[1]	VISION (N=32) ^[1]	TOTAL (N=60) ^[1]
Acute Success			
Device Success	96.4% (27/28)	93.8% (30/32)	95.0% (57/60)
Procedure Success	100.0% (28/28)	100.0% (32/32)	100.0% (60/60)
Clinical Success	96.4% (27/28)	100.0% (32/32)	98.3% (59/60)

Definitions

Device Success: Attainment of final in-stent residual diameter stenosis of $< 50\%$ (by QCA) using the first assigned device only

Procedure Success: Attainment of residual diameter stenosis of $< 50\%$ (by QCA), using any PCI method.

Clinical Success: Attainment of final residual diameter stenosis of $< 50\%$ (by QCA), using any PCI method, without the occurrence of death, Q-wave or non-Q-wave MI, emergency by-pass surgery or repeat revascularization of the target lesion during the hospital stay

1. Acute success rates are calculated based on intent-to-treat population.

Clinical Outcomes

TVF and MACE at each follow-up time-point (up through the 3 year time-point) are summarized in Table 6-5. A Kaplan-Meier TVF-Free survival curve is presented in Figure 6-2.

There was one (1) subject in the XIENCE V arm who had recurrent angina on day 1 due to dissection of the proximal edge, which was left untreated at the time of procedure. The subject received an additional stent 3 weeks later. This event was counted as an in-hospital event (TLR by PCI). There was one (1) Q wave myocardial infarction in the XIENCE V arm due to a lesion in the non-target vessel 30 days after the index procedure. Although these two (2) events were not related to the XIENCE V stent, they were included as TVF events per protocol. Hence, the 30 day TVF rate was 7.4% (2/27) in the test arm. In the control arm there was no TVF during the 30 days following the index procedure.

There were no additional TVF events in the XIENCE V arm before the 180 day follow-up. However, there were four (4) events that occurred in the MULTI-LINK VISION arm by 180 days. Therefore, the TVF rate at 180 days in the MULTI-LINK VISION arm was 14.3% (4/28). These events were all revascularizations to the target lesion, one (1) TLR by CABG and three (3) TLR by PCI. There were two (2) additional TLR by PCI identified in the MULTI-LINK VISION arm from day 181 to day 194 (follow-up window). Hence, the TVF rate by day 194 was 21.4% (6/28) in the MULTI-LINK VISION arm.

One (1) non-Q wave myocardial infarction (not study device-related, reported as IVUS catheter related) and one (1) TLR by PCI (study device-related) occurred between day 181 and 1 year post-procedure in the XIENCE V arm. Consequently, the 1 year TVF rate was 15.4% (4/26). Of four TVF events, only one was study device-related. There were no TVF events in the MULTI-LINK VISION arm during this follow-up period. There were no additional TVF events reported in the XIENCE V arm between 1 year and 2 years. One (1) TLR by PCI and one (1) TVR by PCI were performed on subjects in the MULTI-LINK VISION arm. Hence, the 2 year TVF rates were 15.4% (4/26) and 28.6% (8/28) in the XIENCE arm and the MULTI-LINK VISION arm, respectively.

There were no additional TVF events reported in the XIENCE V arm between 2 years and 3 years. One (1) TVR by CABG was performed on subject in the MULTI-LINK VISION arm. Hence, the 3 year TVF rates were 15.4% (4/26) and 32.1% (9/28) in the XIENCE V arm and the MULTI-LINK VISION arm, respectively.

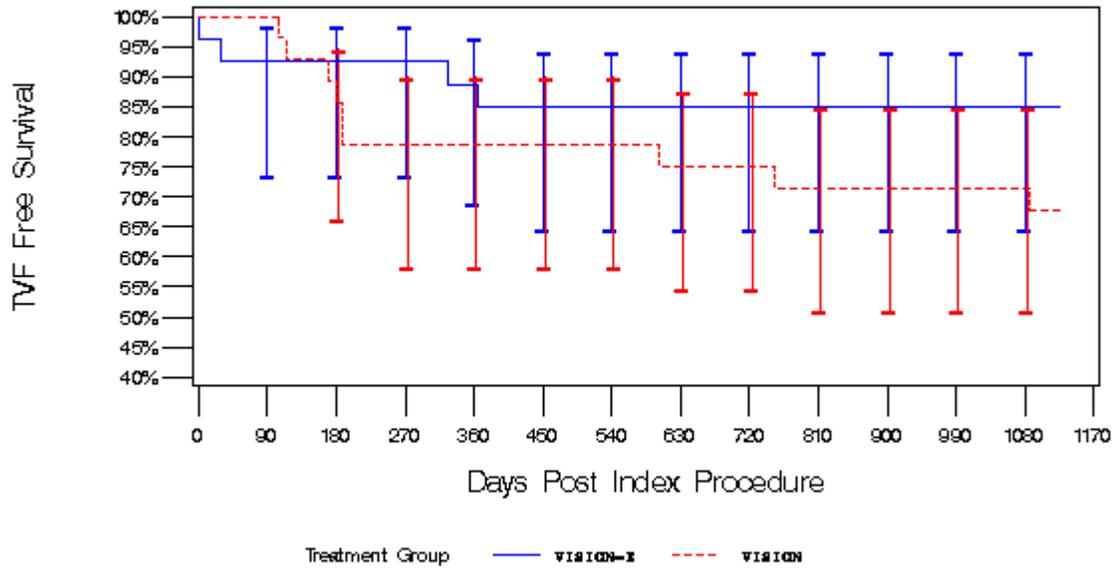


Figure 6-2 Kaplan-Meier TVF-Free Survival Through 3-Year Follow-Up

Table 6-5 Summary of Clinical Events Through 3 Years

		XIENCE V (N=27)^[1]	VISION (N=29)^[1]	TOTAL (N=56)^[1]
In- Hospital	TVF	3.7% (1/ 27)	0.0% (0/ 29)	1.8% (1/ 56)
	MACE	3.7% (1/ 27)	0.0% (0/ 29)	1.8% (1/ 56)
	Cardiac Death	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)
	QMI	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)
	NQMI	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)
	TLR by CABG	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)
	TLR by PCI	3.7% (1/ 27) ^[2]	0.0% (0/ 29)	1.8% (1/ 56)
TVR (CABG/PCI)	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)	
0 to day 30	TVF	7.4% (2/ 27)	0.0% (0/ 29)	3.6% (2/ 56)
	MACE	7.4% (2/ 27)	0.0% (0/ 29)	3.6% (2/ 56)
	Cardiac Death	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)
	QMI	3.7% (1/ 27)	0.0% (0/ 29)	1.8% (1/ 56)
	NQMI	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)
	TLR by CABG	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)
	TLR by PCI	3.7% (1/ 27)	0.0% (0/ 29)	1.8% (1/ 56)
TVR (CABG/PCI)	0.0% (0/ 27)	0.0% (0/ 29)	0.0% (0/ 56)	
0 to day 180	TVF	7.7% (2/ 26)^[3]	14.3% (4/ 28)^[3]	11.1% (6/ 54)^[3]
	MACE	7.7% (2/ 26)	14.3% (4/ 28)	11.1% (6/ 54)
	Cardiac Death	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
	QMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	NQMI	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
	TLR by CABG	0.0% (0/ 26)	3.6% (1/ 28)	1.9% (1/ 54)
	TLR by PCI	3.8% (1/ 26)	10.7% (3/ 28)	7.4% (4/ 54)
TVR (CABG/PCI)	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)	
0 to day 194 (F/U window)	TVF	7.7% (2/ 26)	21.4% (6/ 28)	14.8% (8/ 54)
	MACE	7.7% (2/ 26)	21.4% (6/ 28)	14.8% (8/ 54)
	Cardiac Death	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
	QMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	NQMI	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
	TLR by CABG	0.0% (0/ 26)	3.6% (1/ 28)	1.9% (1/ 54)
	TLR by PCI	3.8% (1/ 26)	17.9% (5/ 28)	11.1% (6/ 54)
TVR (CABG/PCI)	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)	
0 to 1 year	TVF	15.4% (4/ 26)	21.4% (6/ 28)	18.5% (10/ 54)
	MACE	15.4% (4/ 26)	21.4% (6/ 28)	18.5% (10/ 54)
	Cardiac Death	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
	QMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	NQMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	TLR by CABG	0.0% (0/ 26)	3.6% (1/ 28)	1.9% (1/ 54)
	TLR by PCI	7.7% (2/ 26)	17.9% (5/ 28)	13.0% (7/ 54)
TVR (CABG/PCI)	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)	
0 to 2 years	TVF	15.4% (4/ 26)	28.6% (8/ 28)	22.2% (12/ 54)
	MACE	15.4% (4/ 26)	25.0% (7/ 28)	20.4% (11/ 54)
	Cardiac Death	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
	QMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	NQMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	TLR by CABG	0.0% (0/ 26)	3.6% (1/ 28)	1.9% (1/ 54)
	TLR by PCI	7.7% (2/ 26)	21.4% (6/ 28)	14.8% (8/ 54)
TVR (CABG/PCI)	0.0% (0/ 26)	3.6% (1/ 28) ^[4]	1.9% (1/ 54)	

Table 6-5 Summary of Clinical Events Through 3 Years (cont'd)

0 to 3 years	TVF	15.4% (4/ 26)	32.1% (9/ 28)	24.1% (13/ 54)
	MACE	15.4% (4/ 26)	25.0% (7/ 28)	20.4% (11/ 54)
	Cardiac Death	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
	QMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	NQMI	3.8% (1/ 26)	0.0% (0/ 28)	1.9% (1/ 54)
	TLR by CABG	0.0% (0/ 26)	3.6% (1/ 28)	1.9% (1/ 54)
	TLR by PCI	7.7% (2/ 26)	21.4% (6/ 28)	14.8% (8/ 54)
	TVR (CABG/PCI)	0.0% (0/ 26)	7.1% (2/ 28) ^[5]	3.7% (2/ 54)

Abbreviations

TVF: Target Vessel Failure, **MACE:** Major Adverse Cardiac Events, **QMI:** Q-wave Myocardial Infarction, **NQMI:** Non Q-wave Myocardial Infarction, **TLR:** Clinically-Driven Target Lesion Revascularization, **TVR:** Clinically-Driven Target Vessel Revascularization, **CABG:** Coronary Artery Bypass Graft, **PCI:** Percutaneous Coronary Intervention

Definitions

TVF: Comprised of Cardiac Death, QMI, NQMI, TLR (by CABG/PCI) and TVR (by CABG/PCI).

MACE: Comprised of Cardiac Death, QMI, NQMI and TLR (by CABG/PCI)

QMI: The development of pathological Q-waves on the ECG

NQMI: Elevation of post-procedure CK levels to greater than or equal to two times the upper normal limit with elevated CK-MB in the absence of new pathological Q-waves.

TLR: Revascularization at the target lesion associated with positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis $\geq 50\%$ by quantitative coronary angiography (QCA), or revascularization of a target lesion with diameter stenosis $\geq 70\%$ by QCA without either angina or a positive functional study.

TVR: Revascularization in the target vessel associated with positive functional ischemia study or ischemic symptoms.

1. Analysis other than acute success was performed in per-treatment evaluable population.
2. TLR PCI in the XIENCE™ V arm happened 3 weeks after the index procedure; however, the subject had an ischemic symptom at day 1. Thus the event was counted as an in-hospital event.
3. Among 56 per-treatment subjects, one subject in the XIENCE V arm and one subject in the MULTI-LINK VISION arm had withdrawn consents. Hence, denominators were changed from 30-day results to 180-day results. All other per-treatment patients (54) completed the 2-year follow-up.
4. TVR by PCI
5. One (1) TVR by CABG and one (1) TVR by PCI

Note: Table presents hierarchical counts

Table 6-6 Stent Thrombosis (According to Protocol Definitions) Through 3 Years

	XIENCE V (N=27)	VISION (N=29)	TOTAL (N=56)
Stent Thrombosis through 3 Years			
Acute	0.0% (0/ 27)	0.0% (0/ 28)	0.0% (0/ 55)
Sub-acute	0.0% (0/ 27)	0.0% (0/ 28)	0.0% (0/ 55)
Late	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)
Very Late	0.0% (0/ 26)	0.0% (0/ 28)	0.0% (0/ 54)

Note: Per-Treatment Evaluable Population

Note: Subjects are only counted once for each endpoint.

Note: Patients without 3-year follow-up contact and who did not experience the corresponding event are not included in the denominator. For acute stent thrombosis, all patients available the day after the procedure are included in the denominator. For subacute stent thrombosis, all patients available for 30-day follow-up are included in the denominator.

QCA Analysis

Angiographic data at 180 days was analyzable for 50 of the 56 per-treatment subjects (89%). The primary endpoint, 180 day in-stent late loss, was 0.10 ± 0.23 mm in the XIENCE V arm (n = 23) and was 0.85 ± 0.36 mm in the MULTI-LINK VISION arm (n = 27), an 88% reduction. Angiographic effectiveness was also confirmed at 1 year. In-stent late loss remained 72% lower in the XIENCE V arm (0.23 ± 0.29 mm, n = 22) compared to that of the MULTI-LINK VISION arm (0.81 ± 0.44 mm, n = 25) (Table 6-7).

IVUS Analysis

The major secondary endpoint, 180 day in-stent % VO, was $7.95 \pm 10.44\%$ in the XIENCE V arm (n = 21) and was $28.11 \pm 13.98\%$ in the MULTI-LINK VISION arm (n = 24), a 72% reduction. At 1 year, the in-stent % VO was $10.71 \pm 6.92\%$ (n = 18) in the XIENCE V arm and $26.92 \pm 12.78\%$ (n = 23) in the MULTI-LINK VISION arm, reaching a 60% reduction (Table 6-7).

Table 6-7 Summary of Angiographic and IVUS Results

	XIENCE V (N=27)	VISION (N=29)	TOTAL (N=56)	95% CI of Difference
QCA Data				
Pre-Procedure				
Lesion Length, mm	10.08±2.56 (26)	10.88±3.31 (29)	10.50±2.98 (55)	[-2.40, 0.79]
RVD, mm	2.61±0.40 (26)	2.71±0.28 (29)	2.66±0.34 (55)	[-0.28, 0.09]
MLD, mm	0.92±0.23 (26)	1.06±0.34 (29)	1.00±0.30 (55)	[-0.29, 0.02]
%DS	64.25±9.32 (26)	61.17±10.38 (29)	62.62±9.92 (55)	[-2.24, 8.41]
Post-Procedure, In-stent				
RVD, mm	2.56±0.32 (27)	2.72±0.40 (29)	2.64±0.37 (56)	[-0.35, 0.03]
MLD, mm	2.34±0.26 (27)	2.43±0.30 (29)	2.39±0.28 (56)	[-0.24, 0.06]
%DS	12.34±4.02 (27)	14.85±4.76 (29)	13.64±4.56 (56)	[-4.87, -0.16]
180-day Follow-up, In-stent				
RVD, mm	2.61± 0.40 (23)	2.58± 0.36 (27)	2.59± 0.37 (50)	[-0.19, 0.24]
MLD, mm	2.28± 0.33 (23)	1.58± 0.41 (27)	1.90± 0.51 (50)	[0.49, 0.91]
%DS	15.57± 7.64 (23)	38.61± 14.25 (27)	28.01± 16.39 (50)	[-29.45, -16.64]
ABR	0.0% (0/23)	25.9% (7/27)	14.0% (7/50)	NC
Late Loss, mm	0.10± 0.23 (23)	0.85± 0.36 (27)	0.51± 0.49 (50)	[-0.93, -0.59]
1-Year Follow-up, In-Stent				
RVD, mm	2.63± 0.33 (22)	2.53± 0.36 (25)	2.58± 0.35 (47)	[-0.11, 0.30]
MLD, mm	2.15± 0.38 (22)	1.58± 0.44 (25)	1.85± 0.50 (47)	[0.33, 0.81]
%DS	18.02± 12.15 (22)	37.31± 16.90 (25)	28.28±17.64 (47)	[-27.88, -10.70]
ABR	4.5% (1/22)	28.0% (7/25)	17.0% (8/47)	NC
Late Loss, mm	0.23± 0.29 (22)	0.81± 0.44 (25)	0.54± 0.47 (47)	[-0.80, -0.36]
IVUS Data				
180-day Follow-up				
Plaque volume, mm ³	10.29±13.32 (21)	38.29±19.08 (24)	25.23±21.69 (45)	[-37.82, -18.19]
%VO	7.95±10.44 (21)	28.11±13.98 (24)	18.70±15.97 (45)	[-27.53, -12.79]
1-Year Follow-up				
Plaque volume, mm ³	13.26±8.46 (18)	36.40±17.69 (23)	26.24±18.38 (41)	[-31.68, -14.61]
%VO	10.71±6.92 (18)	26.92±12.78 (23)	19.80±13.29 (41)	[-22.55, -9.86]

Abbreviations

IVUS: Intravascular Ultrasound, **CI:** Confidence Interval, **QCA:** Quantitative Coronary Angiography, **RVD:** Reference Vessel Diameter, **MLD:** Minimal Lumen Diameter, **%DS:** Percent Diameter Stenosis, **ABR:** Angiographic Binary Restenosis Rate, **%VO:** Percent Volume Obstruction, **NC:** Not calculated (sample/event numbers are too small).

Definitions:

RVD: An approximation of the diameter of the vessel at the location of the target lesion (Interpolated method)

MLD: The average of two orthogonal views (when possible) of the narrowest point within the area of assessment.

%DS: The value calculated as $100 * (1 - \text{MLD}/\text{RVD})$, using the mean values from two orthogonal views

In-stent: Located within the margins of the stent

ABR: Percent of patients with a follow-up %DS of $\geq 50\%$.

Late Loss: Calculated as MLD post-procedure – MLD at follow-up

%VO: Defined as stent intimal hyperplasia and calculated as $100 * (\text{Stent Volume} - \text{Lumen Volume}) / \text{Stent Volume}$

Notes

-
- Analysis was performed in per-treatment evaluable population.
 - Continuous numbers are shown in (mean ± standard deviation). Standard deviation calculated assuming a normal distribution
 - 95% Confidence Interval is calculated by normal approximation
 - The normality assumption may not be valid given the small sample size

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Adverse Reactions and Complications

Death Summary

No deaths were reported in the per-treatment population in either the XIENCE V arm or the MULTI-LINK VISION arm. One death was reported with MULTI-LINK VISION; however, this subject had several major protocol deviations and was excluded from analysis. This 60 year old male subject was enrolled into the SPIRIT FIRST Clinical Trial where a MULTI-LINK VISION stent was implanted into his Right Coronary Artery to treat a *de novo* B2 lesion. At time of enrollment, patient was a heart transplant candidate, had heavy lesion calcification and an ejection fraction < 30%. On day 33, he experienced late stent thrombosis leading to QMI, TLR-PCI and death.

Study Conclusions

In the SPIRIT FIRST clinical trial, the XIENCE V EECSS demonstrated superiority to the MULTI-LINK VISION stent in in-stent late loss and % volume obstruction at 180 days. These observed rates were substained through 1 year follow-up. Additionally, the XIENCE V EECSS has observed favorable clinical outcomes up to the 3 year time-point. No stent thromboses have been reported through the 3 years following the index procedure. The XIENCE V EECSS demonstrated feasibility and performance in the SPIRIT FIRST clinical trial. The results of this trial provided evidence of safety for further evaluation of XIENCE V in larger clinical trials (SPIRIT II and SPIRIT III clinical trials).

Matched pairs of 6-month angiographic analysis results have been published⁵ and 1 year results for subjects who underwent angiography at 6 months and 1 year have been published⁶ as well.

⁵ Serruys PW, O.A., Piek JJ, Neumann FJ, van der Giessen WJ, Wiemer M, Zeiher A, Grube E, Haase J, Thuesen L, et al., *A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT FIRST trial*. Eurointervention 2005; 1: 58-65., 2005.

⁶ Tsuchida K, P.J., Neumann FJ, Giessen WJ, Wiemer M, Zeiher AM, Grube E, Haase J, Thuesen L, Hamm CW, Veldhof S, Dorange C, Serruys PW, *One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial)*. Eurointervention 2005; 1: 266-272., 2005.

6.2 Descriptive Summary of SPIRIT II 6 Month and 12 Month Endpoints

Introduction

This section summarizes the study design of the SPIRIT II clinical study and includes clinical, angiographic, and Intra-Vascular Ultrasound (IVUS) results through 6 months following the inception of the trial and clinical results through 1 year following the inception of the trial.

The SPIRIT II clinical study was designed to demonstrate the non-inferiority of the XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V EECSS) to the TAXUS EXPRESS² Paclitaxel Eluting Coronary Stent System (TAXUS PECSS).

Study Design

Objective

The objective of the SPIRIT II clinical study was to continue the assessment of safety and performance of the XIENCE V EECSS in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel.

Study Type

The SPIRIT II clinical study was a prospective, randomized, active controlled, single blinded, parallel two-group, multi-center, non-inferiority study designed to enroll 300 subjects (randomized 3:1; XIENCE V EECSS : TAXUS PECSS).

Enrollment Criteria

Subjects who met the clinical eligibility criteria were invited to participate in this study and were required to provide a signed informed consent prior to enrollment. General inclusion criteria included:

- Patient must be at least 18 years of age
- Patient is able to verbally confirm understanding of risks, benefits and treatment alternatives of receiving the XIENCE™ V EECSS and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure, as approved by the appropriate Medical Ethics Committee of the respective clinical site
- Patient must have evident of myocardial ischemia (e.g., stable or unstable angina, silent ischemia, positive functional study or a reversible change in the electrocardiogram (ECG) consistent with ischemia)
- Patient must be an acceptable candidate for coronary artery bypass graft (CABG) surgery
- Patient must agree to undergo all protocol-required follow-up examinations
- Female patients of childbearing potential must have had a negative pregnancy test within 7 days before treatment, and must not be nursing at the time of treatment. They must also agree at time of consent to use birth control up to and including the last angiographic follow-up

The final eligibility was confirmed based on the angiogram just before the intended procedure (i.e., the pre-procedure angiography). Angiographic inclusion criteria included:

- *De novo* target lesion(s) must be located in a native epicardial vessel with a Reference Vessel Diameter (RVD) between 2.5 mm and 4.25* mm by visual estimation. * between 2.5 mm and 3.75 mm until 4.0 mm TAXUS™ EPECSS is commercially available.
- If two target lesions meet the inclusion criteria they must be located in different major epicardial vessels (LAD with septal and diagonal branches, LCX with obtuse marginal and/or ramus intermedius branches and RCA and any of its branches)
- Target lesion(s) must be ≤ 28 mm in length by visual estimation (≥ 3 mm of non-diseased tissue on either side of the target lesion should be covered by XIENCE™ V EECSS)
- If two target lesions are being treated, each of these lesions must meet all angiographic inclusion/exclusion criteria listed under 6.5.2 and 6.5.4
- The target lesion(s) must be in a major artery or branch with a visually estimated diameter stenosis of ≥ 50% and < 100% and a TIMI flow of ≥ 1
- Non-study, percutaneous intervention for lesions in a non-target vessel is allowed if done ≥ 90 days prior to or if planned to be done > 9 months after the index procedure (Patients receiving brachytherapy in a non-target epicardial vessel will however, be excluded from the study).

General exclusion criteria included:

- Patient has had a known diagnosis of acute myocardial infarction (AMI) within 3 days preceding the index procedure (non-procedural/spontaneous MI, CK-MB ≥ 2 times upper limit of normal) and CK and CK-MB have not returned within normal limits at the time of procedure
- The patient is currently experiencing clinical symptoms consistent with AMI
- Patient has current unstable arrhythmias
- Patient has a known left ventricular ejection fraction (LVEF) < 30%
- Patient has received a heart transplant or any other organ transplant or is on a waiting list for any organ transplant
- Patient is receiving or scheduled to receive chemotherapy or radiation therapy within 30 days prior to or after the procedure.
- Patient is receiving immunosuppression therapy or has known immunosuppressive or autoimmune disease (e.g. human immunodeficiency virus, systemic lupus erythematosus etc.)
- Patient is receiving chronic anticoagulation therapy (e.g., heparin, coumadin).
- Patient has a known hypersensitivity or contraindication to aspirin, either heparin or bivalirudin, clopidogrel or ticlopidine, everolimus, paclitaxel, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated
- Elective surgery is planned within the first 9 months (± 14 days) after the procedure that will require discontinuing either aspirin or clopidogrel
- Patient has a platelet count <100,000 cells/mm³ or >700,000 cells/mm³, a WBC of

<3,000 cells/mm³, or documented or suspected liver disease (including laboratory evidence of hepatitis)

- Patient has known renal insufficiency (e.g., serum creatinine level of more than 2.5 mg/dl, patient on dialysis)
- Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions
- Patient has had a cerebrovascular accident (CVA) or transient ischemic neurological attack (TIA) within the past six months
- Patient has had a significant GI or urinary bleed within the past six months
- Patient has extensive peripheral vascular disease that precludes safe 6 French sheath insertion
- Patient has other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc.) that may cause non-compliance with the protocol, confound the data interpretation or is associated with a limited life expectancy (i.e. less than one year)
- Patient is already participating in another investigational use device or drug study or has completed the follow-up phase of another study within the last 30 days.

Key angiographic exclusion criteria included:

- Target lesion(s) meets any of the following criteria:
 - Aorto-ostial location (within 3 mm)
 - Left main location
 - Located within 2 mm of the origin of the LAD or LCX
 - Located within an arterial or saphenous vein graft or distal to a diseased arterial or saphenous vein graft (defined as vessel irregularity per angiogram and > 20% stenosed lesion by visual estimation)
 - Lesion involving a side branch \geq 2 mm in diameter or ostial lesion of the side branch > 50% stenosed by visual estimation or side branch requiring predilatation
 - Located in a major epicardial vessel that has been previously treated with brachytherapy
 - Located in a major epicardial vessel or a side branch that has been previously treated with any type of percutaneous intervention (e.g., balloon angioplasty, stent, cutting balloon, atherectomy), < 9 months prior to the index procedure
 - Total occlusion (TIMI flow 0), prior to wire crossing
 - Excessive tortuosity proximal to or within the lesion
 - Extreme angulation (\geq 90%) proximal to or within the lesion
 - Heavy calcification
 - Restenotic from previous intervention
- The target vessel contains visible thrombus
- Patient has a high probability that a procedure other than pre-dilatation, stenting and (if necessary) post-dilatation will be required at the time of index procedure for treatment of the target vessel (e.g. atherectomy, cutting balloon or brachytherapy)
- Patient has additional clinically significant lesion(s) (> 50% diameter stenosis) in a target vessel or side branch for which an intervention within 9 months after the index procedure may be required

Treatment Strategy

Prior to the stent implantation, an interactive telephone randomization service (ICON Clinical Research, Sugar Land, Texas) was used to randomly assign subjects to a treatment group (randomized 3:1; XIENCE V EECSS : TAXUS PECSS). Subjects were stratified by diabetes mellitus (diabetic vs. non-diabetic), dual vessel treatment (single vessel vs. dual vessel), and IVUS pre-selected sites (IVUS site vs. non-IVUS site).

Eligible subjects underwent mandatory pre-dilatation of the target lesion by standard balloon angioplasty. Randomization could only take place after verification of the inclusion/exclusion criteria and successful pre-dilatation of the target lesion.

Subjects were considered enrolled in the study at the moment the subject had been randomized. The XIENCE V EECSS used in the study included stents 2.5, 3.0, 3.5⁷ and 4.0 mm in diameter, and 8, 18 and 28 mm in length. The XIENCE V EECSS had to adequately cover the lesion such that a minimum of 3 mm of healthy vessel on either side of the lesion was covered by the stent. Therefore in the XIENCE V group, treatment of target lesions > 22 mm and ≤ 28 mm in length was accomplished by overlapping either two 18 mm stents, or a 28 mm and an 8 mm stent. Post-dilatation was left to the discretion of the investigator. However, if performed, it should only have been done with balloons sized to fit within the boundaries of the stent. If an additional stent was needed for bailout purposes it was to be from the same treatment group as the first implanted stent.

Subjects who were not on chronic antiplatelet or aspirin therapy were required to receive a loading dose of clopidogrel bisulfate ≥ 300 mg and aspirin ≥ 75 mg at least 6 hours prior to the implant procedure if possible, but no later than 1 hour after the procedure (in any case). All subjects were required to receive anticoagulation and other therapy during stent implantation according to the standard of care at the clinical site. All subjects were to be maintained on 75 mg clopidogrel bisulfate daily for a minimum of 6 months and ≥ 75 mg of aspirin daily for a minimum of one year following the index procedure. Subjects who developed hypersensitivity to clopidogrel bisulfate were to be switched to ticlopidine hydrochloride at a dose in accordance with standard hospital practice.

Data Collection and Assessment

All data were collected on electronic case report forms (InForm™, PhaseForward, Waltham, MA).

Angiographic and IVUS data were assessed by an independent core laboratory (Cardialysis, Rotterdam B.V. The Netherlands) in a blinded manner. Endpoint events, bleeding and vascular complications were analyzed and adjudicated by a blinded Clinical Events Committee (CEC).

Information on adverse events was reviewed by a blinded Data Safety Monitoring Board (blinded through 180 days) to evaluate subject safety on an on-going basis.

All Sponsor personnel remained blinded except the biostatisticians producing the

⁷ Stent sizes used were 2.5 to 3.5 mm until the 4.0 mm TAXUS PECSS was commercially available.

randomization schedule, site monitors, clinical data architect (CDA), inventory management staff and information system (IS) personnel until 180 day primary endpoint was reached for each subject.

Key Endpoints

The primary endpoint of the SPIRIT II Clinical Trial was in-stent late loss (LL) at 180 days. Key secondary endpoints included: in-segment LL at 180 days and 2 years; percent diameter stenosis (% DS) at 180 days and two years; in-stent percent volume obstruction (% VO) at 180 days and 2 years; ischemia-driven target vessel failure (ischemia-driven-TVF); ischemia-driven major adverse cardiac event (ischemia-driven-MACE), and stent thrombosis at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years follow-up time points.

Statistics

The overall sample size for the study was based on the primary endpoint of in-stent LL at 180 days. The study had a 91% statistical power based on the primary endpoint to prove non-inferiority of XIENCE V EECSS to TAXUS PECSS with a non-inferiority delta of 0.16 mm, true in-stent LL of 0.32 mm in the XIENCE V group and 0.39 mm in the TAXUS group with an overall 5% alpha (one-tailed), assuming a 20% subject dropout rate. The primary, as well as all secondary analyses were performed for the intent-to-treat (ITT) as well as the per-treatment evaluable (PTE) population. Due to the inclusion of two vessel/lesion treatment groups, primary endpoint hypothesis testing was based on the ITT population using the ‘analysis lesion’ (target lesion in single vessel subjects and a randomly selected lesion in dual vessel subjects). A repeated measures analysis for the primary endpoint using all target lesions was also performed and compared with the analysis using ‘analysis lesion’. Additionally, if non-inferiority was shown and smaller in-stent late loss was observed in the XIENCE V arm, superiority analysis will be performed using a two-sided t-test at the 5% alpha level.

Number of Subjects and Investigators

A total of 300 subjects were randomized and enrolled into the SPIRIT II clinical study at 28 sites. Of the 300 subjects who were enrolled, 223 were randomized to receive XIENCE V EECSS and 77 were randomized to receive the TAXUS® PECSS (Table 6-8). A total of 298 subjects completed the protocol required follow-up visit at 180 days. Of these, 275 subjects completed the protocol required angiography at 180 days (202 in the XIENCE V group and 73 in the TAXUS group). In addition, a total of 295 subjects completed the protocol required follow-up visit at 270 days and 1 year (220 in the XIENCE V group and 75 in the TAXUS group).

Table 6-8 Number of Subjects Enrolled by Investigational Site (Intent-to-treat population)

Primary Investigator	Center, Location	XIENCE V	TAXUS	Total*
Prof. Piek	Academisch Medisch Centrum, Amsterdam, Netherlands	20	5	25
Dr. Ruygrok	Auckland City Hospital, Auckland, New Zealand	19	6	25
Dr. Neuzner	Klinikum Kassel, Kassel, Germany	14	11	25
Dr. Seth	Max Devki Devi Heart & Vascular Institute, New Delhi, India	16	6	22
Prof. Schofer	Universitäres Herz- und Gefäßzentrum Hamburg, Hamburg, Germany	17	4	21
Dr. Wiemer	Herzzentrum Bad Oeynhausen, Bad Oeynhausen, Germany	17	0	17
Prof. Richardt	Segeberger Kliniken GmbH, Bad Segeberg, Germany	11	6	17
Prof. Carrie	Hôpital de Rangueil CHU, Toulouse, France	9	5	14
Prof. Thuesen	Skejby Sygehus, Aarhus, Denmark	9	2	11
Dr. Camenzind	R.V. Hôpital Cantonal Universitaire de Geneve, Geneva, Switzerland	8	2	10
Dr. Kelbaek	Rigshospitalet, Copenhagen, Denmark	8	2	10
Prof. Serruys	Erasmus Medical Center, Rotterdam, Netherlands	8	1	9
Dr. Macaya	Hospital Clinico San Carlos, Madrid, Spain	7	2	9
Prof. Berland	Clinique Saint Hilaire, Rouen, France	7	2	9
Dr. Desaga	Amper Kliniken AG- Klinikum Dachau, Dachau, Germany	6	3	9
Dr. Van den Branden	A.Z. Middelheim, Antwerpen, Belgium	5	4	9
Dr. Rasmussen	Aalborg Sygehus Syd, Aalborg, Denmark	5	3	8
Dr. Suryapranata	Isala Klinieken - Locatie Weezenlanden, Zwolle, Netherlands	5	2	7
Prof. Legrand	C.H.U. de Liège Sart Tilman, Liège, Belgium	4	3	7
Dr. Ruzylo	National Institute of Cardiology in Warsaw, Warsaw, Poland	5	1	6
Dr. Manari	Azienda Ospedaliera Santa Maria Nuova, Reggio Emilia, Italy	4	1	5
Prof. Spaulding	Hôpital Cochin, Paris, France	4	1	5
Dr. Suttorp	St. Antonius Ziekenhuis Nieuwegein, Nieuwegein, Netherlands	3	2	5
Dr. Boland	C.H.R. La Citadelle, Liège, Belgium	4	0	4
Prof. Huber	Wilhelminenspital der Stadt Wien, Vienna, Austria	3	1	4
Dr. Garcia	University Hospital Gregorio Maranon, Madrid, Spain	2	1	3
Dr. te Riele	Amphia Hospital, Breda, Netherlands	2	0	2
Dr. Ruygrok	The Mercy Hospital, Auckland, New Zealand	1	1	2

Table 6-8 Number of Subjects Enrolled by Investigational Site (Intent-to-treat population) (cont'd)

Total		223	77	300
* Sorted by the total number of subjects enrolled per site.				

Study Period

The first subject was enrolled on July 5, 2005 and the last subject was enrolled on November 10, 2005. Subjects were evaluated at 30, 180, 270 days, and 1 year following the index procedure. Further clinical observations were to be performed at 2 years. Angiography in all subjects and IVUS on a pre-specified subset of subjects (N=152) were performed at 180 days post index procedure. Additionally, 2 year angiography and IVUS will be performed in a subset of subjects (N=152).

Summary of Study Population**Demographics**

Key baseline demographics and risk factors were comparable between treatment groups (Table 6-9). The mean age of the overall population was 61.94 ± 10.06 years, 73.0% (219 subjects) were men, and 31.2% (86) of all subjects were tobacco users. Twenty point four percent (61 subjects) subjects were treated with medication for diabetes, 66.7% (200 subjects) were hypertensive requiring medication, and 70.3% (206 subjects) were hypercholesterolemic requiring medication. Thirty two point two percent (96 subjects) had a prior myocardial infarction while 3.7% (11 subjects) had prior cardiac intervention on the target vessel. Most of the key baseline lesion morphology and QCA data for the XIENCE V and TAXUS groups were comparable. Forty two and-a-half percent of target lesions were located in the left anterior descending (LAD) coronary artery, of those, 40.8% were in the XIENCE V group and 47.3 % in the TAXUS group. Twenty six and-a-half percent of target lesions were located in the circumflex/ramus, of those, 29.2% were in the XIENCE V group and 18.7% in the TAXUS group. Thirty one point one percent of target lesions were located in the right coronary artery (RCA), of those, 30.0% were in the XIENCE V and 34.1% in the TAXUS group. Twenty nine point two percent of the treated lesions had moderate/severe calcification, of those, 30.4% were in the XIENCE V group and 25.8% in the TAXUS group. Ninety nine point one percent of treated lesions were eccentric. Seventy eight point eight percent of the treated lesions were considered class B2 or C according to the American College of Cardiology-American Heart Association classification. Lesion characteristics included a mean lesion length of 13.04 ± 5.90 mm, a mean reference vessel diameter of 2.73 ± 0.54 mm, a mean minimum luminal diameter (MLD) of 1.08 ± 0.41 mm, and a mean % diameter stenosis (%DS) of $60.46 \pm 11.47\%$. Pre-procedure MLD was smaller in the XIENCE V group (1.06 ± 0.42 mm) than in the TAXUS group (1.14 ± 0.36 mm) (Table 6-10).

Table 6-9 Summary of Subject Demography and Lesion Morphology

	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Total (N=300) (M=351)	95% CI of Difference
Subject Demography				
Age (yrs)	61.95±10.29 (223)	61.92±9.44 (77)	61.94±10.06 (300)	[-2.49, 2.56]
Number of Men	70.9% (158/223)	79.2% (61/77)	73.0% (219/300)	[-19.22%, 2.48%]
Current Cigarette Use	31.6% (66/209)	29.9% (20/67)	31.2% (86/276)	[-10.91%, 14.37%]
Diabetes Treated with Medication	20.2% (45/223)	21.1% (16/76)	20.4% (61/299)	[-11.44, 9.70%]
Hypertension Req. Medication	67.3% (150/223)	64.9% (50/77)	66.7% (200/300)	[-9.98%, 14.64%]
Hypercholesterolemic Req. Medication	68.7% (149/217)	75.0% (57/76)	70.3% (206/293)	[-17.86%, 5.19%]
Prior Cardiac Intervention on Target Vessel(s)	3.6% (8/221)	4.0% (3/75)	3.7% (11/296)	ANF
Prior MI	34.8% (77/221)	24.7% (19/77)	32.2% (96/298)	[-1.33%, 21.66%]
Target Vessel				
LAD	40.8% (106/260)	47.3% (43/91)	42.5% (149/351)	[-18.35%, 5.39%]
Circumflex/Ramus	29.2% (76/260)	18.7% (17/91)	26.5% (93/351)	[0.82%, 20.28%]
RCA	30.0% (78/260)	34.1% (31/91)	31.1% (109/351)	[-15.28%, 7.15%]
Lesion Morphology				
Calcification (moderate/severe)	30.4% (76/250)	25.8% (23/89)	29.2% (99/339)	[-6.18%, 15.29%]
Eccentric Lesion	98.8% (247/250)	100.0% (89/89)	99.1% (336/339)	ANF
ACC-AHA Lesion Class				
A	0.8% (2/249)	0.0% (0/90)	0.6% (2/339)	ANF
B1	20.9% (52/249)	20.0% (18/90)	20.6% (70/339)	[-8.80%, 10.57%]
B2	65.5% (163/249)	66.7% (60/90)	65.8% (223/339)	[-12.60%, 10.19%]
C	12.9% (32/249)	13.3% (12/90)	13.0% (44/339)	[-8.64%, 7.68%]
Lesion Characteristics				
Lesion Length (mm) Mean ± SD (n)	12.98 ± 5.72 (246)	13.20 ± 6.41 (87)	13.04 ± 5.90 (333)	[-1.76, 1.32]
RVD (mm) Mean ± SD (n)	2.70 ± 0.52 (246)	2.82 ± 0.58 (87)	2.73 ± 0.54 (333)	[-0.26, 0.02]
MLD (mm) Mean ± SD (n)	1.06 ± 0.42 (256)	1.14 ± 0.36 (89)	1.08 ± 0.41 (345)	[-0.18, 0.01]
%DS Mean ± SD (n)	60.88 ± 11.97 (256)	59.25 ± 9.83 (89)	60.46 ± 11.47 (345)	[-0.90, 4.16]

Abbreviations:

CI: Confidence Interval, **LAD:** Left Anterior Descending, **LCX:** Left Circumflex, **RCA:** Right Coronary Artery, **ACC:** American College of Cardiology, **AHA:** American Heart Association, **ANF:** Assumption of distribution not fulfilled.

Notes:

- Analysis was performed in the ITT population.
- Continuous numbers are shown in (mean ± standard deviation). Standard deviation calculated assuming a normal distribution.
- 95% Confidence Interval is calculated by normal approximation.
- The normality assumption may not be valid given the small sample size.
- N is the total number of subjects; M is the total number of lesions

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Summary of Safety and Effectiveness Data

Primary Endpoint

The primary endpoint, in-stent LL was 0.11 ± 0.27 mm (201) for the XIENCE V group and 0.36 ± 0.39 mm (73) for the TAXUS group (Table 6-10). The null hypothesis was rejected; therefore, the data indicate that XIENCE V EECSS was non-inferior to the TAXUS PECSS for in-stent LL at 180 days, considering a delta margin of 0.16 mm (non-inferiority $p < 0.0001$). The difference between the two stents (-0.24 mm) represents a 72% reduction in late loss and is highly statistically significant ($p < 0.0001$). Additionally, since non-inferiority was shown in this study, a superiority analysis of the primary endpoint was performed using a two-sided t-test at the 5% alpha level. The analysis showed the superiority of XIENCE V EECSS to TAXUS PECSS in terms of the primary

endpoint of in-stent LL at 180 days ($p < 0.0001$) (Table 6-11).

Table 6-10 Results of the SPIRIT II Primary Endpoint

	XIENCE V (N=223)	TAXUS (N=77)	Difference	P-Value
Primary Endpoint 180-day In-stent Late Loss, mm (n)	0.11 ± 0.27 (201) [0.08, 0.15]	0.36 ± 0.39 (73) [0.27, 0.45]	-0.24 [-0.34, -0.15]	< 0.0001

Notes:

- Analysis was performed in the ITT population.
- Numbers are shown in (mean ± standard deviation). Standard deviation calculated assuming a normal distribution.
- Numbers in [] are 95% Confidence Interval. 95% Confidence Interval is calculated by normal approximation.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Secondary Endpoints

Acute Success

The clinical device success in the XIENCE V and TAXUS groups was comparable at the rates of 98.8 % (256/259) and 98.9 % (89/90), respectively. The clinical procedure success was comparable between treatment groups with rates in the XIENCE V and TAXUS groups of 99.1% (221/223) and 97.4% (75/77), respectively; (Table 6-11).

Table 6-11 Acute Success

	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Total (N=300) (M=351)
Acute Success			
Clinical Device Success	98.8% (256/259)	98.9% (89/90)	98.9% (345/349)
Clinical Procedure Success	99.1% (221/223)	97.4% (75/77)	98.7% (296/300)

Note: Clinical device success is computed per lesion and clinical procedure success is computed per subject.

Note: N is the total number of subjects; M is the total number of lesions

QCA Analysis

Post procedure in-stent RVD was lower in the XIENCE V group than that in the TAXUS group; 2.86 ± 0.43 mm in the XIENCE V group, and 3.00 ± 0.48 mm in the TAXUS group. Post-procedure in-stent MLD was lower in the XIENCE V group than that in the TAXUS group; 2.49 ± 0.40 mm in the XIENCE V group and 2.62 ± 0.45 mm in the TAXUS group. Mean in-segment %DS at 180 days was lower in the XIENCE V group than that in the TAXUS group; 23.61 ± 11.65 % in the XIENCE V group and 27.05 ± 12.68 % in the TAXUS group. Mean in-stent %DS at 180 days was lower in the XIENCE V group than that in the TAXUS group; 15.70 ± 9.88 % in the XIENCE V group and 20.89 ± 11.59 % in the TAXUS group. The in-segment ABR rate at 180 days was 3.4 % in the XIENCE V group and 5.8 % in the TAXUS group. The in-stent ABR rate at 180 days was 1.3% in the XIENCE V group and 3.5% in the TAXUS group (difference -2.22 %). In-segment LL at 180 days was 0.07 ± 0.33 mm and 0.15 ± 0.38 mm in the XIENCE V and TAXUS groups, respectively. A single instance of thrombus was observed in the XIENCE V group. No aneurysms were observed in either treatment group. Table 6-12 presents the summary of QCA data at 180 days post-procedure.

IVUS Analysis

Mean in-stent %VO at 180 day follow-up in XIENCE V group was lower than in the

TAXUS group ($2.51 \pm 4.68\%$ and $7.36 \pm 7.05\%$ in the XIENCE V group and TAXUS group, respectively). This represents a 66% reduction in %VO in the XIENCE V group as compared to the TAXUS group. The mean neointimal hyperplasia (NIH) volume at 180 day follow-up was different between the XIENCE V group and the TAXUS group; $3.83 \pm 6.55 \text{ mm}^3$ and $14.42 \pm 16.03 \text{ mm}^3$ in the XIENCE V and TAXUS groups, respectively. This represents a 73% reduction in NIH in the XIENCE V group as compared to TAXUS group. Plaque behind the stent volume at 180-day follow-up was $176.30 \pm 84.54 \text{ mm}^3$ and $213.44 \pm 116.92 \text{ mm}^3$ in XIENCE V and TAXUS groups, respectively. Persisting incomplete apposition at 180 day follow-up was 2.5% (3/120) and 0.0% (0/42) in the XIENCE V and TAXUS groups, respectively. No late acquired incomplete apposition was reported in both groups. Table 6-12 presents the summary of IVUS data at 180 days post-procedure.

Table 6-12 Summary of Angiographic and IVUS Results

	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Total (N=300) (M=351)	95% CI of Difference
QCA Data				
Pre-Procedure				
Lesion Length, mm	12.98 \pm 5.72 (246)	13.20 \pm 6.41 (87)	13.04 \pm 5.90 (333)	[-1.76, 1.32]
RVD, mm	2.70 \pm 0.52 (246)	2.82 \pm 0.58 (87)	2.73 \pm 0.54 (333)	[-0.26, 0.02]
MLD, mm	1.06 \pm 0.42 (256)	1.14 \pm 0.36 (89)	1.08 \pm 0.41 (345)	[-0.18, 0.01]
%DS	60.88 \pm 11.97 (256)	59.25 \pm 9.83 (89)	60.46 \pm 11.47 (345)	[-0.90, 4.16]
Post-Procedure				
RVD ^[1] , mm	2.86 \pm 0.43 (260)	3.00 \pm 0.48 (91)	2.90 \pm 0.45 (351)	[-0.25, -0.03]
In-segment MLD, mm	2.15 \pm 0.44 (260)	2.22 \pm 0.53 (91)	2.17 \pm 0.46 (351)	[-0.19, 0.05]
In-stent MLD, mm	2.49 \pm 0.40 (260)	2.62 \pm 0.45 (91)	2.52 \pm 0.41 (351)	[-0.24, -0.03]
In-segment %DS	22.51 \pm 8.98 (260)	23.36 \pm 11.20 (91)	22.73 \pm 9.60 (351)	[-3.43, 1.72]
In-stent %DS	13.01 \pm 6.02 (260)	12.66 \pm 5.53 (91)	12.92 \pm 5.89 (351)	[-1.01, 1.71]
Thrombus	0.4% (1/260)	0.0% (0/91)	0.3% (1/351)	ANF
Aneurysm	0.0% (0/260)	0.0% (0/91)	0.0% (0/351)	ANF
180-day Follow-up				
RVD ^[1] , mm	2.75 \pm 0.49 (236)	2.85 \pm 0.53 (86)	2.78 \pm 0.50 (322)	[-0.23, 0.02]
In-segment MLD, mm	2.10 \pm 0.51 (237)	2.08 \pm 0.54 (86)	2.10 \pm 0.52 (323)	[-0.11, 0.15]
In-stent MLD, mm	2.38 \pm 0.50 (237)	2.27 \pm 0.54 (86)	2.35 \pm 0.51 (323)	[-0.03, 0.23]
In-segment %DS	23.61 \pm 11.65 (237)	27.05 \pm 12.68 (86)	24.53 \pm 12.01 (323)	[-6.53, -0.35]
In-stent %DS	15.70 \pm 9.88 (237)	20.89 \pm 11.59 (86)	17.09 \pm 10.60 (323)	[-7.96, -2.41]
In-segment ABR	3.4% (8/237)	5.8% (5/86)	4.0% (13/323)	[-7.89%, 3.02%]
In-stent ABR	1.3% (3/237)	3.5% (3/86)	1.9% (6/323)	ANF
In-segment LL, mm	0.07 \pm 0.33 (237)	0.15 \pm 0.38 (86)	0.09 \pm 0.34 (323)	[-0.17, 0.01]
In-stent LL, mm	0.12 \pm 0.29 (237)	0.37 \pm 0.38 (86)	0.19 \pm 0.33 (323)	[-0.34, -0.16]

Table 6-12 Summary of Angiographic and IVUS Results (cont'd)

IVUS Data				
180-day Follow-up				
NIH volume, mm ³	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	6.87 ± 11.24 (139)	[-15.87, -5.32]
%VO	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	3.91 ± 5.87 (139)	[-7.27, -2.42]
Plaque behind the stent volume (mm ³)	176.30 ± 84.54 (97)	213.44 ± 116.92 (39)	186.95 ± 95.99 (136)	-37.13 [-78.41, 4.15]
Persisting Incomplete Apposition	2.5% (3/120)	0.0% (0/42)	0.0% (0/143)	2.50% [Assump. not fulfilled]
Late Acquired Incomplete Apposition	0.0% (0/104)	0.0% (0/39)	1.9% (3/162)	0.00% [Assump. not fulfilled]

Abbreviations

IVUS: Intravascular Ultrasound, **CI:** Confidence Interval, **QCA:** Quantitative Coronary Angiography, **RVD:** Reference Vessel Diameter, **MLD:** Minimal Lumen Diameter, **%DS:** Percent Diameter Stenosis, **ABR:** Angiographic Binary Restenosis Rate, **%VO:** Percent Volume Obstruction, **ANF:** Assumption of distribution not fulfilled.

Definitions:

RVD: An approximation of the diameter of the vessel at the location of the target lesion (Interpolated method)

MLD: The average of two orthogonal views (when possible) of the narrowest point within the area of assessment.

%DS: The value calculated as $100 * (1 - \text{MLD}/\text{RVD})$, using the mean values from two orthogonal views.

In-stent: Located within the margins of the stent.

ABR: Percent of subjects with a follow-up %DS of $\geq 50\%$.

Late Loss: Calculated as MLD post-procedure – MLD at follow-up.

%VO: Defined as stent intimal hyperplasia and calculated as $100 * (\text{Stent Volume} - \text{Lumen Volume}) / \text{Stent Volume}$.

Notes:

- N is the total number of subjects; M is the total number of lesions.
- Analysis was performed in the ITT population.
- Continuous numbers are shown in (mean ± standard deviation). Standard deviation calculated assuming a normal distribution.
- 95% Confidence Interval is calculated by normal approximation.
- The normality assumption may not be valid given the small sample size.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

1. Calculated by interpolated method, i.e. an approximation of the diameter of the vessel at the in-segment MLD.

Safety Endpoints

Ischemia-driven-TVF rates in-hospital in the XIENCE V and TAXUS groups were 0.9% (2/223) and 2.6% (2/77) respectively. There were two NQMI events which occurred in-hospital, in each group. These events were resolved without intervention. The NQMI events were not related to the treatment and/or the device. No other adverse events occurred in-hospital, in either group.

There were no adverse events which occurred from the time of discharge to 30 days follow-up in the XIENCE V group. However, one NQMI occurred 8 days post-index procedure in the TAXUS group. Therefore, the ischemia-driven-TVF rate for the XIENCE V group remained unchanged at 0.9% (2/223), while the ischemia-driven-TVF rate for the TAXUS group was elevated to 3.9% (3/77) by the 30-day time point. The NQMI in the TAXUS group was treated by ischemia-driven Target Lesion Revascularization (ischemia-driven-TLR) and was subsequently resolved (this ischemia-driven-TLR event is not counted in the Table 6-13 as all events are counted hierarchically).

There were 4 ischemia-driven-TLR by PCI events and 2 ischemia-driven-Target Vessel Revascularization (ischemia-driven-TVR) by PCI events which occurred from 31 days

through 194 days² (180 day follow-up window) post-index procedure in the XIENCE V group. Among the 4 ischemia-driven-TLR by PCI events which occurred through 194 days in the XIENCE V group, one ischemia-driven-TLR by PCI was performed at 53 days post-index procedure due to the treatment of the late stent thrombosis.

Additionally, there was one ischemia-driven-TVR by PCI event and one ischemia-driven-TVR by CABG event that occurred from 195 days through 270 days in the XIENCE™ V group which brought the ischemia-driven-TVF rate at 270 days to 4.5% (10/220). The ischemia-driven-TVF rates through 365 days remained at 4.5%. The ischemia-driven-MACE rates through 270 days and 365 days remained at 2.7% (6/220).

There was one death at 56 days post-index procedure in the TAXUS group. This subject experienced 2 NQMI events at 8 days and 54 days post-index procedure. The NQMI event occurred at 54 days post-index procedure was due to the late stent thrombosis and the subject expired at 2 days after the NQMI event. Additionally, there were 2 ischemia-driven-TLR by PCI events which occurred between 31 days through 194 days post-index procedure in the TAXUS group. These events in the TAXUS group brought the ischemia-driven-TVF rate and ischemia-driven-MACE rate at 194 days to 6.5% (5/77). There were 2 ischemia-driven-TLR by PCI events that occurred between 271 days through 365 days which brought the ischemia-driven-TVF rate and ischemia-driven-MACE rate at 365 days to 9.2% (7/76).

There were no instances of acute or sub-acute stent thrombi in either group at 30 days while there was one instance of late stent thrombosis observed in each group of this study through 365 days. These subjects were receiving anti-platelet medication at the time of stent thrombosis. The ischemia-driven-TVF and ischemia-driven-MACE at each follow-up time-point (up through the 365 day time-point) are summarized in Table 6-13. A Kaplan-Meier ischemia-driven-TVF-Free survival curve is presented in Figure 6-3.

² Data through 194 days post-index procedure is commonly used as a 6-month data in the literature.

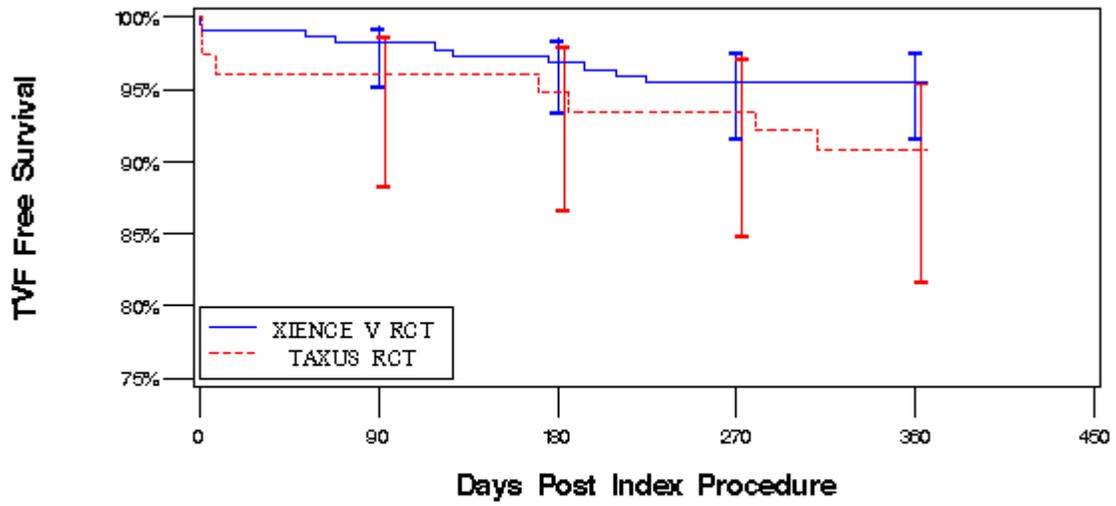


Figure 6-3 Kaplan-Meier Ischemia-Driven-TVF-Free Survival to 365-day Follow-Up

Table 6-13 Summary of Safety Endpoints

		XIENCE V (N=223)	TAXUS (N=77)	Total (N=300)
In-Hospital^[1]	ID-TVF	0.9% (2/223)	2.6% (2/77)	1.3% (4/300)
	ID-MACE	0.9% (2/223)	2.6% (2/77)	1.3% (4/300)
	Cardiac Death	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	QMI	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	NQMI	0.9% (2/223)	2.6% (2/77)	1.3% (4/300)
	ID-TLR by CABG	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	ID-TLR by PCI	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	ID-TVR (CABG/PCI)	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
0 to day 30	ID-TVF	0.9% (2/223)	3.9% (3/77)	1.7% (5/300)
	ID-MACE	0.9% (2/223)	3.9% (3/77)	1.7% (5/300)
	Cardiac Death	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	QMI	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	NQMI	0.9% (2/223)	3.9% (3/77)	1.7% (5/300)
	ID-TLR by CABG	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	ID-TLR by PCI	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
	ID-TVR (CABG/PCI)	0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
0 to day 180 (F/U window)	ID-TVF	3.6% (8/222)^[2]	6.5% (5/77)	4.3% (13/299)^[2]
	ID-MACE	2.7% (6/222)	6.5% (5/77)	3.7% (11/299)
	Cardiac Death	0.0% (0/222)	1.3% (1/77) ^[3]	0.3% (1/299)
	QMI	0.0% (0/222)	0.0% (0/77)	0.0% (0/299)
	NQMI	0.9% (2/222)	2.6% (2/77) ^[3]	1.3% (4/299)
	ID-TLR by CABG	0.0% (0/222)	0.0% (0/77)	0.0% (0/299)
	ID-TLR by PCI	1.8% (4/222)	2.6% (2/77)	2.0% (6/299)
	ID-TVR (CABG/PCI)	0.9% (2/222)	0.0% (0/77) ^[4]	0.7% (2/299)
0 to day 270	ID-TVF	4.5% (10/220)^[7]	6.6% (5/76)^[8]	5.1% (15/296)^[7,8]
	ID-MACE	2.7% (6/220)	6.6% (5/76)	3.7% (11/296)
	Cardiac Death	0.0% (0/220)	1.3% (1/76)	0.3% (1/296)
	QMI	0.0% (0/220)	0.0% (0/76)	0.0% (0/296)
	NQMI	0.9% (2/220)	2.6% (2/76)	1.4% (4/296)
	ID-TLR by CABG	0.0% (0/220)	0.0% (0/76)	0.0% (0/296)
	ID-TLR by PCI	1.8% (4/220)	2.6% (2/76)	2.0% (6/296)
	ID-TVR (CABG/PCI)	1.8% (4/220)	0.0% (0/76)	1.4% (4/296)
0 to day 365	ID-TVF	4.5% (10/220)	9.2% (7/76)	5.7% (17/296)
	ID-MACE	2.7% (6/220)	9.2% (7/76)	4.4% (13/296)
	Cardiac Death	0.0% (0/220)	1.3% (1/76)	0.3% (1/296)
	QMI	0.0% (0/220)	0.0% (0/76)	0.0% (0/296)
	NQMI	0.9% (2/220)	2.6% (2/76)	1.4% (4/296)
	ID-TLR by CABG	0.0% (0/220)	0.0% (0/76)	0.0% (0/296)
	ID-TLR by PCI	1.8% (4/220)	5.3% (4/76)	2.7% (8/296)
	ID-TVR (CABG/PCI)	1.8% (4/220)	0.0% (0/76)	1.4% (4/296)
Stent Thrombosis (per protocol) to 365 days				
Acute (<1 day)		0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
Sub-acute (1 to 30 day)		0.0% (0/223)	0.0% (0/77)	0.0% (0/300)
Late (>30 day)		0.5% (1/220) ^[5]	1.3% (1/76) ^[6]	0.7% (2/296)
Stent Thrombosis (Per ARC) at 365 days				
Definite + Probable, uncensored		0.0% (0/220)	1.3% (1/76)	0.3% (1/296)

Abbreviations

ID-TVF: Ischemia-Driven Target Vessel Failure, **ID-MACE:** Ischemia-Driven Major Adverse Cardiac Events, **QMI:** Q-wave Myocardial Infarction, **NQMI:** Non Q-wave Myocardial Infarction, **ID-TLR:** Ischemia-Driven Target Lesion Revascularization, **ID-**

TVR: Ischemia-Driven Target Vessel Revascularization, **CABG:** Coronary Artery Bypass Graft, **PCI:** Percutaneous Coronary Intervention.

Definitions

ID-TVf: Comprised of Cardiac Death, QMI, NQMI, ID-TLR (by CABG/PCI) and ID-TVR (by CABG/PCI).

ID-MACE: Comprised of Cardiac Death, QMI, NQMI and ID-TLR (by CABG/PCI).

QMI: The development of pathological Q-waves on the ECG.

NQMI: Elevation of post-procedure CK levels to greater than or equal to two times the upper normal limit with elevated CK-MB in the absence of new pathological Q-waves.

ID-TLR: Revascularization at the target lesion associated with any of the following: 1) non-invasive positive functional ischemia study (e.g. exercise testing or equivalent tests) or invasive positive functional ischemia study (e.g. Fractional Flow Reserve (FFR) or Coronary Flow Reserve (CFR)), 2) ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by on-line quantitative coronary angiography (QCA), 3) diameter stenosis $\geq 70\%$ by on-line QCA without either ischemic symptoms or a positive functional study.

ID-TVR: Revascularization in the target vessel associated with any of the following: 1) non-invasive positive functional ischemia study (e.g. exercise testing or equivalent tests) or invasive positive functional ischemia study (e.g. Fractional Flow Reserve (FFR) or Coronary Flow Reserve (CFR)), 2) ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by on-line quantitative coronary angiography (QCA), 3) diameter stenosis $\geq 70\%$ by on-line QCA without either ischemic symptoms or a positive functional study.

Notes:

- Analysis was performed in ITT population.
- This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

1. For subjects hospitalized greater than 7 days, in-hospital is out to a maximum of 7 days.
 2. One subject was excluded from the analysis due to subject withdrawal.
 3. There were 3 NQMI events at 30 days including one subject who died at 56 days, resulting in decreasing in the number of NQMI at 180 days (2 NQMI at 180 days). This subject also had another NQMI at 54 days that was not counted due to the hierarchical counting.
 4. One subject experienced both ID-TVR by PCI and ID-TLR by PCI through 180 days in the TAXUS® group. However, the ID-TVR by PCI was not counted due to the hierarchical counting.
 5. One stent thrombosis occurred at 53 days post-index procedure in the XIENCE V group and it was treated by ID-TLR by PCI without any further complications.
 6. One stent thrombosis occurred at 54 days post-index procedure in the TAXUS group. This subject also experienced NQMI at 54 days and expired at 56 days.
 7. Two subjects died from non-cardiac causes before the 9-month follow-up visit.
- One subject died from cardiac cause before the 6-month follow-up visit and excluded from the analysis after 270 days.

Adverse Reactions and Complications

Adverse Event Death Summaries

Three total deaths were reported for the SPIRIT II clinical study through 365 days post procedure. The death that occurred in the TAXUS group was adjudicated by the CEC as a cardiac death while the two deaths in the XIENCE V group were adjudicated as non cardiac deaths.

Conclusion

In the SPIRIT II clinical study, the XIENCE V EECSS has clearly demonstrated non-inferiority to the TAXUS PECSS in terms of primary endpoint of an in-stent late loss ($p < 0.0001$). As prespecified in the protocol, a superiority test of the primary endpoint was performed. The difference between the two stents ($0.11 \text{ mm} - 0.36 \text{ mm} = -0.25 \text{ mm}$) represents a 72% reduction in late loss and is highly statistically significant ($p < 0.0001$). Therefore, XIENCE V EECSS was superior to TAXUS PECSS for the primary endpoint. The IVUS results support the angiographic endpoint results. There was a 66% reduction in %VO in the XIENCE V group compared to the TAXUS group (2.5% vs. 7.4%) and a 73% reduction in NIH volume (3.8 mm^3 vs. 14.4 mm^3) in XIENCE V group, as compared to TAXUS group. Moreover, for other key clinical endpoints the XIENCE V group also had lower observed event rates than the TAXUS

group, e.g. ischemia-driven-TLR (1.8% vs. 3.9%), ischemia-driven-TVR (2.7% vs. 5.2%), ischemia-driven-MACE (2.7% vs. 6.5%), and stent thrombosis (0.5% vs. 1.3%). Therefore, 180 day angiographic, IVUS, and clinical endpoint results have demonstrated the safety and effectiveness of the XIENCE V EECSS. The clinical safety observed at 194 days was also sustained at 270 days and 365 days for the XIENCE V arm. The ischemia-driven-MACE rates through 270 days and 365 days remained at 2.7% in the XIENCE V arm while 6.6% and 9.2% through 270 days and 365 days, respectively in the TAXUS arm. In addition, no new instances of late stent thrombosis were observed in either group between the 195 days through 365 days.

The SPIRIT II protocol has been amended to extend the clinical follow-up period from 2 years to 5 years.

6.3 Descriptive Summary of SPIRIT III RCT

Introduction

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V EECSS to the TAXUS EXPRESS² Paclitaxel Eluting Coronary Stent System (TAXUS PECSS) and was conducted in the United States (US) and Japan.

The SPIRIT III clinical trial consists of five parts: a US randomized clinical trial (RCT), three non-randomized arms in the US (4.0 mm diameter stent, 2.25 mm diameter stent, and 38 mm length stent), and one non-randomized arm in Japan as shown in Figure 8.3-1. Enrollment is complete in the RCT and Japan arm, ongoing in the 4.0 mm arm, and has not yet been initiated in the 2.25 mm arm. Enrollment in the 38 mm arm is not planned.

The data from the 1,002 subjects enrolled in the RCT and the 69 subjects enrolled in the 4.0 mm non-randomized arm of the SPIRIT III clinical study support the claim of safety and effectiveness.

Study Design

The SPIRIT III RCT is a prospective, 2:1 randomized, active-controlled, single blinded, parallel, multi-center clinical evaluation of the XIENCE V EECSS compared to TAXUS PECSS in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

The primary endpoint of the SPIRIT III trial was 240 day in-segment Late Loss (LL). Additionally, the SPIRIT III RCT had a major secondary endpoint of ischemia driven Target Vessel Failure (TVF) at 270 days. Ischemia-driven TVF was defined as the composite endpoint comprised of the following:

- cardiac death
- myocardial infarction (Q-wave and non-Q-wave)
- ischemia-driven Target Lesion Revascularization (TLR) by Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI)
- ischemia-driven Target Vessel Revascularization, non-target lesion (TVR) by CABG or PCI

Both the primary (in-segment late loss) and the major secondary endpoint (ischemia driven TVF) had to be met for study success.

Other key secondary endpoints to examine the safety and effectiveness included the following:

- Ischemia-driven Target Vessel Failure (TVF) at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Ischemia-driven Target Lesion Revascularization (TLR) at 30, 180, 270 days,

- and 1, 2, 3, 4, and 5 years
- Ischemia-driven Target Vessel Revascularization (TVR) at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Ischemia-driven Major Adverse Cardiac Event (MACE) at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years,
- Persisting incomplete stent apposition, late-acquired incomplete stent apposition, aneurysm, thrombosis, and persisting dissection at 240 days
- Acute success (clinical device and clinical procedure)
- Proximal and distal LL at 240 days
- In-stent LL at 240 days
- In-stent and in-segment percent angiographic binary restenosis (% ABR) rate at 240 days
- In-stent and in-segment percent diameter stenosis (%DS) at 240 days
- In-stent percent volume obstruction (%VO) at 240 days

Statistics

The overall sample size for the SPIRIT III RCT was based on the major secondary endpoint of ischemia-driven TVF at 270 days. The sample size for the angiographic cohort of RCT was calculated based on the primary endpoint of in-segment LL at 240 days. Both the primary and major secondary endpoints had to be met in order to have a successful RCT study.

Primary Endpoint of RCT

The null hypothesis was that the XIENCE V arm would have a mean 8 month in-segment LL equal to or exceeding that of the control TAXUS arm by 0.195 mm or more. The alternative hypothesis was that XIENCE arm would have a mean in-segment LL less than that of TAXUS arm plus 0.195 mm. The assumptions for the sample size calculations were:

- one-tailed non-inferiority test
- $\alpha = 0.025$
- 2 (XIENCE V) : 1 (TAXUS) randomization ratio
- true mean in-segment LL was assumed to be 0.24 mm in both arms
- standard deviation was assumed to be 0.47 mm in both arms
- power = 99%
- non-inferiority margin = 0.195 mm

Based on the above assumptions, the sample size for the angiographic cohort of RCT was calculated to be 564 subjects, i.e. 376 in the XIENCE V arm and 188 in the TAXUS arm assuming 10% dropouts.

Due to the inclusion of two vessel/lesion treatment groups, primary endpoint hypothesis testing was based on the ITT population using the ‘analysis lesion’ (target lesion in single vessel subjects and a randomly selected lesion in dual vessel subjects). Additionally, a repeated measures analysis for the primary endpoint using all target lesions was also performed and compared with the analysis using ‘analysis lesion’.

If non-inferiority was shown and smaller in-segment late loss was observed in the XIENCE V arm, then superiority analysis would be performed using a two-sided t-test at the 5% alpha level.

Major Secondary Endpoint of RCT

The null hypothesis was that the XIENCE V arm would have a 9 month TVF rate equal to or exceeding that of the control TAXUS arm by 5.5% or more. The alternative hypothesis was that XIENCE V arm would have 9 month TVF rate less than that of TAXUS arm plus 5.5%. The assumptions for the sample size calculations were:

- one-tailed non-inferiority test
- alpha = 0.05
- 2 (XIENCE V) : 1 (TAXUS) randomization ratio
- true TVF rate of 9.4% for both arms
- non-inferiority margin = 5.5%
- power = 89%

Based on the above assumptions, the calculated sample size was 1002 subjects with 668 in the XIENCE V arm and 334 in the TAXUS arm assuming 1% dropouts.

If non-inferiority was shown and lower TVF rate was observed in the XIENCE V arm, then superiority analysis would be performed using a two-sided Fisher's exact test at the 5% alpha level.

Enrollment Criteria and Randomization

Subjects who met the eligibility criteria were required to provide a signed informed consent prior to enrollment in the SPIRIT III trial. Final eligibility was confirmed based on an angiogram prior to the index procedure (i.e., the pre-procedure angiography). Key inclusion and exclusion criteria included:

General Inclusion Criteria

- Subject must be at least 18 years of age.
- Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving the XIENCE V EECS and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.
- Subject must have evidence of myocardial ischemia (e.g., stable or unstable angina, silent ischemia, positive functional study or a reversible changes in the electrocardiogram (ECG) consistent with ischemia.
- Subject must be an acceptable candidate for Coronary Artery Bypass Graft (CABG) surgery.
- Subject must agree to undergo all protocol required follow up examinations.
- Subject must agree not to participate in any other clinical study for a period of one year following the index procedure.

Angiographic Inclusion Criteria

- Target lesion(s) must be located in a native coronary artery with visually estimated diameter of ≥ 2.25 mm and ≤ 4.25 mm. If two target lesions meet the

inclusion criteria, they must be in different epicardial vessels

- ≥ 2.5 mm and ≤ 3.75 mm for the RCT
- ≥ 3.75 and ≤ 4.25 mm for the 4.0 mm Arm
- If two target lesions are being treated, the RVD and lesion length of both target vessels must meet above criteria and belong to the same study.
- The target lesion(s) must be in a major artery or branch with a visually estimated stenosis of $\geq 50\%$ and $< 100\%$ with a TIMI flow of ≥ 1 .
- Non-study, percutaneous intervention for lesions in a non-target vessel is allowed if done ≥ 90 days prior to or if planned to be done 9 months after the index procedure (subjects receiving brachytherapy in a non-target epicardial vessel will, however, be excluded from the trial).
- Target lesion(s) must measure:
 ≤ 28 mm (RCT and 4.0 mm non-randomized arm) in length by visual estimation (≥ 3 mm of non-diseased tissue on either side of the target lesion should be covered by XIENCE V EECS)

General Exclusion Criteria

- Subject has had a known diagnosis of acute myocardial infarction (AMI) preceding the index procedure (CK-MB ≥ 2 times upper limit of normal) and CK and CK-MB have not returned within normal limits at the time of procedure.
- The subject is currently experiencing clinical symptoms consistent with AMI.
- Subject has current unstable arrhythmias.
- Subject has a known left ventricular ejection fraction (LVEF) $< 30\%$.
- Subject has received a heart transplant or any other organ transplant or is on a waiting list for any organ transplant.
- Subject is receiving or scheduled to receive chemotherapy for malignancy within 30 days prior to or after the procedure.
- Subject is receiving immunosuppression therapy or has known immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematosus etc.).
- Subject is receiving chronic anticoagulation therapy (e.g., heparin, coumadin).
- Subject has a known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, both clopidogrel and ticlopidine, everolimus, cobalt, chromium, nickel, tungsten, acrylic, or fluoropolymers or contrast sensitivity that cannot be adequately pre-medicated.
- Elective surgery is planned within the first 9 months after the procedure that will require discontinuing either aspirin or clopidogrel.
- Subject has a platelet count $< 100,000$ cells/mm³ or $> 700,000$ cells/mm³, a White Blood Count (WBC) $< 3,000$ cells/mm³, or documented or suspected liver disease (including laboratory evidence of hepatitis).
- Subject has known renal insufficiency (e.g., serum creatinine level of more than 2.5 mg/dL), or subject is on dialysis.
- Subject has a history of bleeding, diathesis, or coagulopathy or will refuse blood transfusions.
- Subject has had a cerebrovascular accident (CVA) or transient ischemic

neurological attack (TIA) within the past six months.

- Subject has had a significant gastro intestinal (GI) or urinary bleed within the past six months.
- Subject has extensive peripheral vascular disease that precludes safe 6 French sheath insertion.
- Subject has other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause non-compliance with the protocol, confound the data interpretation or is associated with a limited life expectancy (i.e., less than one year).
- Subject is already participating in another clinical study that has not yet reached its endpoint.
- Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential enrolled in the US sites must have a negative pregnancy test within 7 days prior to the index procedure.

Angiographic Exclusion Criteria

- The target lesion meets any of the following criteria:
 - Aorto-ostial location (within 3 mm)
 - Left main location
 - Located within 2 mm of the origin of the LAD or LCX
 - Located within an arterial or saphenous vein graft or distal to a diseased (vessel irregularity per angiogram and > 20% stenosed lesion by visual estimation) arterial or saphenous vein graft
 - Lesion involving a bifurcation ≥ 2 mm in diameter or ostial lesion > 50% stenosed by visual estimation or side branch requiring predilatation
 - Located in a major epicardial vessel that has been previously treated with brachytherapy
 - Located in a major epicardial vessel or a side branch that has been previously treated with any type of PCI (e.g., plain old balloon angioplasty (POBA), stent, cutting balloon, atherectomy) < 9 months prior to the index procedure
 - Total occlusion (TIMI flow 0), prior to wire crossing
 - Excessive tortuosity proximal to or within the lesion
 - Extreme angulation ($\geq 90^\circ$) proximal to or within the lesion
 - Heavy calcification
 - Restenotic from any previous intervention.
- The target vessel contains thrombus.
- Another clinically significant lesion (> 40%DS) is located in the same major epicardial vessel as the target lesion (including side branches).
- Subject has a high probability that a procedure other than predilatation and stenting will be required at the time of index procedure for treatment of the target vessel (e.g., atherectomy, cutting balloon or brachytherapy).
- Subject has additional clinically significant lesion(s) in a target vessel or side branch for which an intervention within 9 months after the index procedure may be required.

Treatment of a maximum of two *de novo* lesions, each in a different epicardial vessel, was allowed. Based on angiographic visual assessment of the target lesion(s) and reference vessel diameter(s), eligible US subjects were randomized into the RCT in a 2:1 ratio to receive XIENCE V or TAXUS respectively through ICON interactive voice response system (IVRS) central randomization service and registered in the 4.0 mm arm. The final eligibility was confirmed based on the pre-procedure angiography. Study subjects for the RCT were considered enrolled in the study from the moment they were randomized/registered by the ICON IVRS service.

Subjects were evaluated at 30, 180, 240, and 270 days following the index procedure. Further clinical observations will be performed at 1, 2, 3, 4 and 5 years. Angiography was to be performed on all subjects at 240-day follow-up. The screening and enrollment process is shown in Figure 6-4.

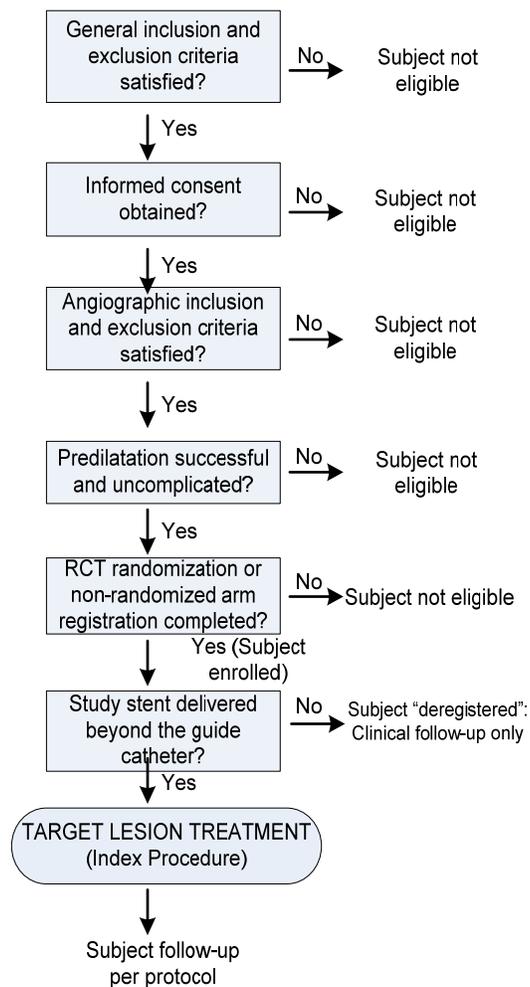


Figure 6-4 Screening and Enrollment Process

Treatment Strategy and Stenting Procedure

Subjects within each treatment group of the RCT were assigned to clinical, angiographic and IVUS follow-up (Group A), or clinical and angiographic follow-up (Group B), or only clinical follow-up (Group C), by the ICON IVRS service. Subjects were also stratified by diabetes mellitus (diabetes vs. non diabetes), dual vessel treatment (single vessel vs. dual vessel), and study sites. Approximately 564 of the 1,002 RCT subjects were scheduled for angiographic follow-up (Groups A and B), and approximately 240 of the 1,002 subjects were scheduled for IVUS follow-up (Group A).

All subjects enrolled into the 4.0 mm arm were required to have clinical and angiographic follow-up.

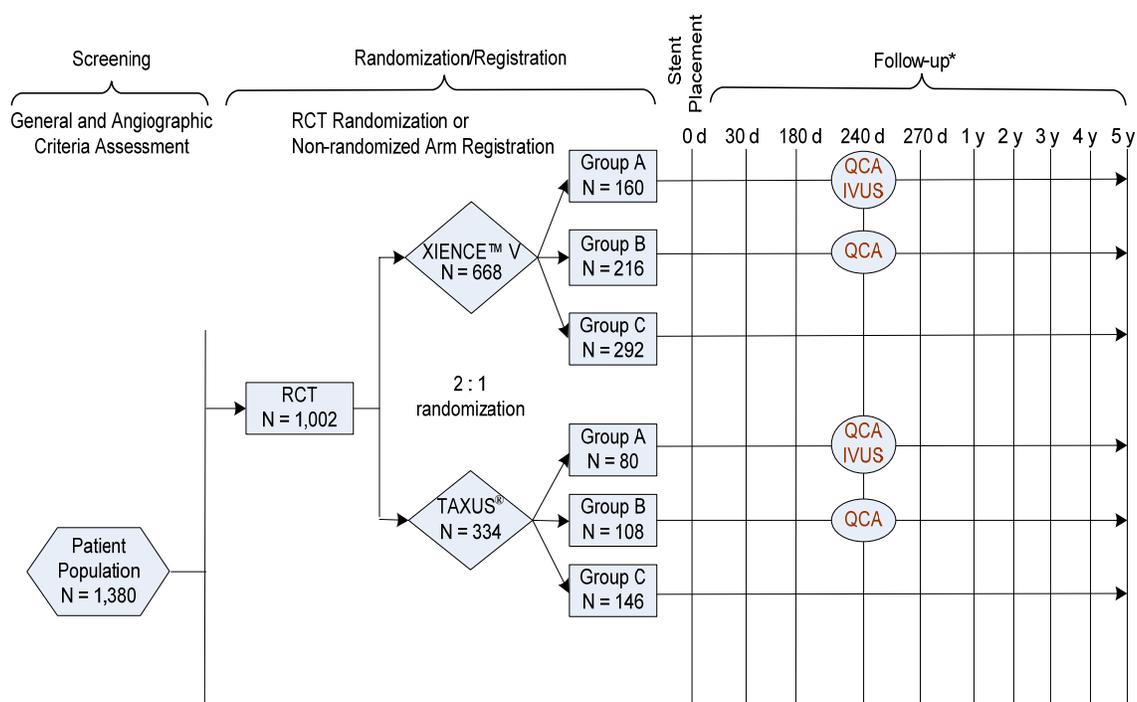
During the index procedure, bailout stenting was allowed if the subject experienced the following:

- Major dissection (type C or greater)
- Occlusive complication as evidenced by a decrease in target vessel flow
- Chest pain or ischemic ECG changes that did not respond to repeat balloon inflations, medical therapy or lytic agents
- Unplanned additional stent was required to cover the target lesion.

If an additional stent needed to be used for bailout purposes, it was to be from the same treatment arm as the first implanted stent. Also the bailout stent of an appropriate length was to be placed with a minimum of 1 mm to a maximum of 4 mm overlap to ensure that there was no gap between the stents. Additionally, a bailout procedure itself was not considered a major adverse cardiac event (MACE), unless the subject sustained cardiac death, emergent CABG procedure, or MI.

All subjects who received a bailout stent were scheduled to undergo clinical, angiographic, and IVUS (depending on site capability) follow up regardless of the group to which they were originally assigned at randomization. Group C subjects in the RCT who received a bailout stent and had follow-up angiography were not included in the primary endpoint analyses. Separate analyses for these bailout subjects were planned.

Figure 6-5 provides an overview of the study design identifying the RCT and 4.0 mm arm and the follow up schedule of events for the SPIRIT III clinical study.



*All subjects who receive a bailout stent will have QCA and at sites with IVUS capability, IVUS assessment at 240 days

Figure 6-5 Overview of SPIRIT III Clinical Study Design

The XIENCE V EECS used in the RCT arm included stent diameters of 2.5, 3.0, and 3.5 mm, and lengths of 8, 18 and 28 mm. The XIENCE V EECS used in the 4.0 arm included a stent diameter of 4.0 mm, and lengths of 8, 18 and 28 mm. The XIENCE V EECS had to adequately cover the lesion such that a minimum of 3 mm of healthy vessel on either side of the lesion was covered by the stent. Therefore, in the XIENCE V arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by overlapping either two 18 mm stents or a 28 mm and an 8 mm stent.

Predilatation was performed prior to stent deployment with an angioplasty balloon. Post-dilatation was left to the discretion of the investigator. However if post-dilatation was performed, then the balloon was sized to fit within the boundaries of the stent.

The clinical trial protocol required that IVUS be performed after optimal stent placement was obtained, for Group A follow-up subjects and bailout subjects, and be performed according to the IVUS core laboratory guidelines.

During the index procedure, medications administered included loading dose of clopidogrel bisulfate (≥ 300 mg) and aspirin (≥ 300 mg). Loading doses of antiplatelet medications were to be given at least six hours prior to the implant procedure if possible, but no later than one hour after the procedure in any case. All subjects in the US who received XIENCE V were to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of 6 months following the procedure. All subjects who received

the TAXUS PECSS were to be maintained on clopidogrel bisulfate for 6 months as instructed in the Instructions For Use (IFU) for TAXUS PECSS. For subjects allergic to clopidogrel bisulfate, ticlopidine hydrochloride was allowed at a dose according to standard hospital practice. Per guidance from the study principal investigators and agreement with the sponsor, sites were notified that the loading dose of clopidogrel bisulfate may be omitted in subjects who had been on a therapeutic dose (75 mg/day) for more than 7 days. All subjects were also required to receive ≥ 80 mg of aspirin daily to be taken throughout the length of the trial (5 years). An overview of the schedule of events through the study period is provided in Table 6-14.

Table 6-14 Schedule of Events (cont'd)

PROCEDURE/TEST	Prior to Procedure (Within 7 days)	Pre-Procedure (Within 24 hours)	Procedure	Post-Procedure	30 days (\pm 7 days) Office/hospital visit	180 days (\pm 14 days) Telephone call/office visit	240 days (\pm 28 days) Office /hospital visit	270 days (\pm 14 days) Telephone call/office visit	1 year (\pm 28 days) Office visit/ Telephone call)	2-5 years (\pm 28 days) Office visit/ Telephone call)
Concomitant medications	✓		✓	✓	✓	✓	✓	✓	✓	✓
Adverse events			✓	✓	✓	✓	✓	✓	✓	✓

¹ If CK-MB is elevated \geq 3 times upper limit of normal serial CK-MB must be done until a decline is noted

² Assess Troponin at pre-procedure for subjects with Acute Coronary Syndrome (ACS) only

³ Assess CRP level at pre-procedure only

⁴ HbA1c and glucose measurements not to be done at post-procedure

⁵ Between 12 hours post procedure or discharge before breakfast (fasting)

⁶ If missed at baseline

⁷ QCA for subjects in Group A and B, US non-randomized arms, Japanese non-randomized arm and all bailout subjects

⁸ IVUS for subjects in Group A, Japanese non-randomized arm and all bailout subjects at sites with IVUS capability ⁹ PK substudy to assess everolimus blood levels at selected predetermined sites (minimum of 5 sites in US and 5 sites in Japan) (Pre-procedure, Post-procedure 10, 30 minutes, 1,2,4,6,12,24,36, 48, 72, 168 hrs and at 30 days)

¹⁰ Clopidogrel bisulfate 75 mg must be given for a minimum of 6 months (ticlopidine hydrochloride will be given at Japanese sites at the dose of 200 mg/day) and aspirin \geq 80 mg to be taken throughout the length of the trial (5 years) post procedure. Complete blood count (CBC) must be done on all subjects every two weeks when on ticlopidine hydrochloride)

¹¹ If the blood draws are collected within 7 days prior to the procedure, per hospital standard of care, the data is acceptable

Blinding

The SPIRIT III RCT is a randomized single blinded clinical trial. The use of the commercially available TAXUS PECSS as the active control in the RCT required the physician performing the index procedure to be unblinded to the treatment assignment. The protocol required that blinded site personnel conduct clinical RCT follow-up assessments to avoid any opportunity for inadvertent unblinding of the subject. Core laboratory personnel assessing the angiographic and IVUS data were to remain blinded to the RCT subject's treatment assignment as were members of the CEC and DSMB.

Blinding is not applicable in the 4.0 mm arm

The SPIRIT III RCT blinded personnel include:

- Subjects
- Site personnel who conduct clinical follow-up
- All Sponsor personnel except those noted below under Non-Blinded personnel
- Data Safety Monitoring Board (DSMB) members
- Clinical Event Committee (CEC) members
- Angiographic and IVUS core laboratory personnel

The SPIRIT III RCT unblinded personnel included:

- Physician performing the index procedure
- Clinical trial site personnel assisting the implanting physician during the index procedure
- Physician performing follow-up angiogram or IVUS procedure, or revascularization procedures
- Statisticians of independent CRO who prepared blinded tables for DSMB
- Statistician who prepared the randomization codes for the independent CRO
- Independent consultant statistician who conducted the adaptive analysis
- Independent CRO who created IVRS system
- Sponsor personnel:
 - Biostatisticians involved in generating and verifying the randomization code (they did not have access to the clinical data nor were they involved in any aspect of the data analysis)
 - Clinical Data Architect (CDA)⁸
 - Information system personnel (IS)
 - Inventory management staff
 - Site monitors
 - Clinical safety monitor

During the clinical follow-up assessments, a follow-up worksheet/script was used to minimize the observer bias. Implanted subjects received generic study stent cards in order to maintain subject blinding and all subjects received subject information guides for both study stents. Subject blinding was to be maintained until all RCT subjects had completed the 270 day follow-up assessment.

Number of Subjects per Investigative Site and IRB

A total of 77 sites received IRB approval for the SPIRIT III study in the US of which 65 sites enrolled 1,002 subjects into the RCT. The primary investigator and the number of subjects enrolled at each approved site for each arm are presented in Table 6-15.

⁸ Clinical Data Architect position also known as Clinical Data Analyst

Table 6-15 Number of Subjects Enrolled by Investigational Site - RCT

Primary Investigator	Site	Investigational Site	XIENCE V	TAXUS	Total
Dr. Midei, M	27286	St. Joseph Medical Center, Towson, MD	71	36	107
Dr. Newman, W	28864	Wake Medical Center, Raleigh, NC	61	29	90
Dr. Sanz, M	27314	St. Patrick Hospital, Missoula, MT	38	22	60
Dr. Hermiller, J	87266	The Heart Center of IN, LLC, Indianapolis, IN	33	15	48
Dr. Williams, J	27310	Presbyterian Hospital, Charlotte, NC	27	14	41
Dr. Farhat, N	28930	EMH Regional Medical Center, Elyria, OH	26	13	39
Dr. Caputo, R	28500	St. Joseph's Hospital Health Center, Syracuse, NY	21	11	32
Dr. Xenopoulos, N	27303	Jewish Hospital, Louisville, KY	20	9	29
Dr. Applegate, R	27470	North Carolina Baptist Hospital, Winston-Salem ,NC	19	10	29
Dr. Gordon, P	29324	The Miriam Hospital, Providence, RI	18	11	29
Dr. Young, J	27731	The Christ Hospital, Cincinnati, OH	17	10	27
Dr. Carter, A	28807	Borgess Medical Center, Kalamazoo, MI	17	7	24
Dr. Williams, D	27626	Rhode Island Hospital, Providence, RI	16	7	23
Dr. Fortuna, R	27616	Scripps Memorial Hospital, La Jolla, CA	14	6	20
Dr. Collins, M ¹	82910	Columbia University, Medical Center, New York, NY	12	7	19

Table 6-15 Number of Subjects Enrolled by Investigational Site - RCT (cont'd)

Primary Investigator	Site	Investigational Site	XIENCE V	TAXUS	Total
Dr. Mauri, L	27113	Brigham & Women's Hospital, Boston, MA	12	6	18
Dr. Cannon, L	28489	Northern Michigan Hospital, Petoskey, MI	13	5	18
Dr. Matthews, R	27325	Good Samaritan Hospital, Los Angeles, CA	13	3	16
Dr. Dauerman, H	30677	Fletcher Allen Health Care, Burlington, VT	11	5	16
Dr. Netz, D	87867	Nebraska Heart Hospital, Lincoln, NE	10	4	14
Dr. Knapp, W Dr. Unterman, M	27053	Saint Joseph's Hospital of Atlanta, Atlanta, GA	9	4	13
Dr. Turco, M	27369	Washington Adventist Hospital, Takoma Park, MD	8	5	13
Dr. Grantham, A	27454	St. Luke's Hospital, Kansas City, MO	8	5	13
Dr. Nielsen, C	27611	Medical University of South Carolina, Charleston, SC	5	8	13
Dr. Singh, H Dr. Wohns, D	28376	Spectrum Health Hospital, Grand Rapids, MI	11	2	13
Dr. Liberman, H	28291	Emory Crawford Long Hospital, Atlanta, GA	7	5	12
Dr. Prabhu, S	27445	Integris Baptist Medical, Inc., Oklahoma City, OK	10	1	11
Dr. Feldman, R	27635	Alta Bates Summit Medical Center, Oakland, CA	5	5	10
Dr. Hirsch, C	28618	The Valley Hospital, Pomona, NY	7	3	10
Dr. Davis, T	27846	St. John Hospital & Medical Center, Detroit, MI	5	4	9

Table 6-15 Number of Subjects Enrolled by Investigational Site - RCT (cont'd)

Primary Investigator	Site	Investigational Site	XIENCE V	TAXUS	Total
Dr. Yakubov, S	27940	Riverside Methodist Hospital, Columbus, OH	8	1	9
Dr. Bertolet, B	28488	North Mississippi Medical Center, Tupelo, MS	3	6	9
Dr. Brown, C	28630	Piedmont Hospital, Atlanta, CA	8	1	9
Dr. Shadoff, N	27194	Presbyterian Hospital, Albuquerque, NM	5	3	8
Dr. Resar, J	27281	Johns Hopkins Hospital, Baltimore, MD	3	5	8
Dr. Chang, M	27328	Mercy General Hospital, Sacramento, CA	7	1	8
Dr. Saucedo, J	27488	The University of Oklahoma Health Sciences Center, Oklahoma City, OK	4	4	8
Dr. Doing, A	27620	Poudre Valley Hospital, Fort Collins, CO	8	0	8
Dr. Eagan, J	28019	Baptist Health System- Montclair, Birmingham, AL	6	2	8
Dr. Mooney, M	30244	Abbott Northwestern Hospital, Minneapolis, MN	5	3	8
Dr. Kaplan, A	30404	Dartmouth-Hitchcock Medical Center, Lebanon, NH	6	2	8
Dr. Wu, W	89964	Central Cardiovascular Research Foundation, San Antonio, TX	4	4	8
Dr. Lasala, J	27276	Barnes Jewish Hospital, St. Louis, MO	4	3	7
Dr. Sethi, V	28568	Hackensack Medical Center, Hackensack, NJ	4	3	7
Dr. Ramee, S	27102	Ochsner Clinic Foundation, New Orleans, LA	5	1	6
Dr. Bachinsky, W	27497	Pinnacle Health @ Harrisburg Hospital, Wormleysburg, PA	3	3	6

Table 6-15 Number of Subjects Enrolled by Investigational Site - RCT (cont'd)

Primary Investigator	Site	Investigational Site	XIENCE V	TAXUS	Total
Dr. Bernstein, P	27604	St. Luke's Medical Center, Milwaukee, WI	5	1	6
Dr. Satler, L	30145	Washington Hospital Center, Washington, DC	2	4	6
Dr. Brottman, M	27032	Elmhurst Memorial Hospital, Lombard, IL	4	1	5
Dr. Bouchard, A	28353	Baptist Medical Center Princeton, Birmingham, AL	3	2	5
Dr. Brown, D	27246	Medical City Dallas Hospital, Dallas, TX	4	0	4
Dr. Mishkel, G	27302	St. John's Hospital, Springfield, IL	2	2	4
Dr. Zidar, J	27474	Duke University Medical Center, Durham, NC	4	0	4
Dr. Caulfield, T	27488	Providence St. Vincent Medical Center, Portland, OR	3	1	4
Dr. Farah, T	27651	Allegheny General Hospital, Pittsburgh, PA	3	1	4
Dr. Niederman, A	27298	North Ridge Medical Center, Fort Lauderdale, FL	2	1	3
Dr. Chambers, J	29720	Sacred Heart Medical Center, Eugene, OR	2	1	3
Dr. Stumpf, R	47841	Arizona Heart Hospital, Phoenix, AZ	2	1	3
Dr. Schaer, G	27056	Rush University Medical Center, Chicago, IL	2	0	2
Dr. Quesada, R	27963	Baptist Hospital of Miami, Miami, FL	1	1	2
Dr. Gammon, R	43763	Austin Heart, PA, Austin, TX	1	1	2
Dr. Kaplan, B	27244	Long Island Jewish Medical Center, New Hyde Park, NY	0	1	1

Table 6-15 Number of Subjects Enrolled by Investigational Site - RCT (cont'd)

Dr. Kleiman, N	27512	The Methodist Hospital, Houston, TX	0	1	1
Dr. Reisman, M	27539	Swedish Medical Center, Seattle, WA	1	0	1
Dr. Carrozza, J	28212	Beth Israel Deaconess Medical Center, Boston, MA	1	0	1
Total			669	333	1002

¹ Previous Primary Investigator was Dr. Gregg Stone. Dr. Stone relinquished responsibility as Primary Investigator once he became SPIRIT III Study Principal Investigator.

Study Period

Enrollment in the RCT was initiated on June 22, 2005 and was completed on March 15, 2006, with 1,002 subjects enrolled at 65 sites.

Summary of Study Population

Subjects eligible for enrollment into the RCT were from the general interventional cardiology population with evidence of myocardial ischemia. These subjects were candidates for coronary artery bypass graft surgery who also satisfied the general and angiographic enrollment criteria. Subjects who met all the general inclusion/exclusion criteria were to be considered for study participation. Upon meeting all angiographic inclusion/exclusion criteria, and after calling the ICON IVRS service, the subjects were considered enrolled into the study.

Demographic and Risk Factors

Key baseline demographics and risk factors were similar between treatment arms in the RCT as shown in Table 6-16. The mean age of the overall population was 63.08 ± 10.43 years, 68.6 % (687 subjects) were men and 23.1% (227 subjects) were tobacco users. There were 25.4% (254 subjects) treated with medication for diabetes, and 75.5% (755 subjects) were hypertensive requiring medication. There were 10.8% (106 subjects) who had prior cardiac intervention on the target vessel and 2.7% (26 subjects) who had an MI within two months of the index procedure.

Table 6-16 Key Demographics and Risk Factors, RCT (ITT)

	XIENCE V (N=669)	TAXUS (N=333)	Total (N=1002)	Difference [95% CI]¹
Age (year) Mean ± SD (n)	63.23 ± 10.53 (669)	62.80 ± 10.24 (332)	63.08 ± 10.43 (1001)	0.43 [0.94, 1.79]
Male Subjects	70.1% (469/669)	65.7% (218/332)	68.6% (687/1001)	4.44% [-1.73%, 10.62%]
Current Tobacco Use	23.4% (154/659)	22.5% (73/324)	23.1% (227/983)	0.84% [-4.74%, 6.42%]
All Diabetes Mellitus	29.6% (198/669)	27.9% (92/330)	29.0% (290/999)	1.72% [-4.23%, 7.67%]
Diabetes Mellitus Requiring Medication	25.6% (171/669)	25.2% (83/330)	25.4% (254/999)	0.41% [-5.32%, 6.14%]
Hypertension Requiring Medication	76.2% (510/669)	74.0% (245/331)	75.5% (755/1000)	2.22% [-3.51%, 7.94%]
Hypercholesterolemia Requiring Medication	74.2% (489/659)	71.5% (233/326)	73.3% (722/985)	2.73% [-3.20%, 8.66%]
All Prior Cardiac Interventions	32.3% (215/666)	29.5% (98/332)	31.4% (313/998)	2.76% [-3.29%, 8.82%]
Prior Cardiac Intervention on Target Vessel(s)	11.0% (72/655)	10.4% (34/326)	10.8% (106/981)	0.56% [-3.53%, 4.66%]
MI within 2 Months	2.8% (18/652)	2.4% (8/327)	2.7% (26/979)	0.31% [-1.78%, 2.41%]

¹ By normal approximation.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Summary of Safety and Effectiveness Data

All SPIRIT III data were collected on electronic case report forms (InForm™, PhaseForward, Waltham, MA). Angiographic data were assessed by a blinded independent core laboratory (Cardiovascular Research Foundation, New York, NY). IVUS data were assessed by a blinded independent core laboratory (Center for Research in Cardiovascular Interventions, Stanford, CA). The endpoint events, bleeding and vascular complications were adjudicated by a blinded Clinical Events Committee (CEC). Information on adverse events was reviewed by a blinded Data Safety Monitoring Board (DSMB) to evaluate subject safety on an on-going basis.

Two analysis populations were defined in this study: Intent-To-Treat (ITT) population and Per-Treatment Evaluable (PTE) population.

ITT Population

The ITT population for RCT consisted of all subjects randomized / registered to the study,

regardless of the treatment actually received. Deregistered subjects (subjects for whom the study stent was not delivered beyond the guide catheter) are included in the ITT population. Subjects were analyzed in the treatment group to which they were randomized.

Per-Treatment Evaluable (PTE) Population

The PTE population for the RCT consisted of subjects who received a study stent at the target lesion(s), who had no major procedural protocol deviations, other than those relating to randomization assignment versus study stent actually received, and for whom follow-up data was available. Analyses based on the PTE population were “as treated”; that is, subjects were included in the treatment group corresponding to the study stent actually received. Subject treated with a non-study stent were excluded.

Primary Endpoint

The primary endpoint for the RCT is in-segment late loss (LL) at 240 days. In-segment LL is defined as: in-segment MLD post-procedure minus in-segment MLD at 240 day follow-up. In-segment LL at 240 days in the 4.0 mm XIENCE™ V arm was compared with that of the TAXUS arm of the RCT.

In-segment LL at 240 days was $0.14 \text{ mm} \pm 0.41 \text{ mm}$ for the XIENCE V arm and $0.28 \pm 0.48 \text{ mm}$ for the TAXUS arm. XIENCE V was shown to be non-inferior to TAXUS for in-segment LL at 240 days (non-inferiority p-value < 0.0001), with XIENCE V EECSS showing a 50% reduction as compared to TAXUS PECSS as shown in Table 6-17. Primary hypothesis testing for the primary endpoint was conducted on the per subject analysis of the ITT angiographic subpopulation.

Furthermore, as pre-specified in the statistical analysis plan, since non-inferiority of XIENCE V relative to TAXUS was established and a smaller in-segment LL at 240 days was observed in the XIENCE V arm, a superiority analysis was performed using a two-sided t-test at the 5% alpha level based on the analysis lesion. XIENCE V EECSS was shown to be superior to TAXUS PECSS in in-segment LL at 240 days (p-value = 0.0037) as shown in the Table 6-17.

Using all target lesions in the same ITT angiographic subpopulation, in-segment LL at 240 days was $0.14 \pm 0.39 \text{ mm}$ for the XIENCE V arm and $0.26 \pm 0.46 \text{ mm}$ for the TAXUS arm as shown in Table 6-17.

Applying the Generalized Estimating Equation (GEE) method to all the lesions, the least square mean of in-segment LL was $0.14 \pm 0.02 \text{ mm}$ for the XIENCE V arm and $0.26 \pm 0.04 \text{ mm}$ for the TAXUS arm. The all lesion analysis and the GEE approach are both similar to the primary analysis as shown in Table 6-17.

Table 6-17 Primary Endpoint Analysis, RCT (ITT)

Measurements	XIENCE V (N=376) (M=427)	TAXUS (N=188) (M=220)	Difference [95% CI]	Non- Inferiority P-Value ³	Superiority P-Value ⁴
240-Day In-Segment Late Loss (mm) Analysis Lesion Mean ± SD (n)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	-0.14 [-0.23, -0.05] ²	<0.0001	0.0037
All Lesions Mean ± SD (m)	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04] ²	--	--
Generalized Estimating Equations Least-Square Mean ± SE (m) ¹	0.14 ± 0.02 (343)	0.26 ± 0.04 (158)	-0.13 [-0.21, -0.04]	--	--

¹Estimates from Generalized Estimating Equations (GEE) model using all lesions.

²By normal approximation.

³One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.

⁴Two-sided p-value by superiority test using two-sample T-test is to be compared at a 0.05 significance level.

Note: N is the total number of subjects; M is the total number of lesions.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Major Secondary Endpoint

The major secondary endpoint for the RCT was ischemia- driven target vessel failure (TVF) through 284 days post procedure. Ischemia-driven TVF is a composite endpoint comprised of cardiac death, myocardial infarction, ischemia-driven target lesion revascularization (TLR) by CABG or PCI, and ischemia-driven target vessel revascularization (TVR).

Ischemia- driven TVF rate through 284 days was 7.6% for the XIENCE V arm and 9.7% for the TAXUS arm. XIENCE V was shown to be non-inferior to TAXUS fo through 284 days (non-inferiority p-value < 0.0001) as shown in Table 6-18.

The ischemia- driven TVF rate continued to be lower in the XIENCE V arm through 393 days with a rate of 8.6% in the XIENCE V arm and 11.3% in the TAXUS arm, as shown in Table 6-19.

Table 6-18 Major Secondary Endpoint Analysis – Per Subject Analysis, RCT (ITT)

Measurements	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI] ¹	Non- Inferiority P-Value ²
Major Secondary Endpoint 9-Month TVF (Cardiac Death, MI, TLR, TVR, non-target lesion)	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]	<0.0001

¹ By normal approximation.

² One sided p- value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

Note: Includes ischemia-driven TVF events through 284 days

Note: TLR and TVR are ischemia-driven.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Secondary Endpoints

Clinical device and procedure success were similar between the XIENCE V and TAXUS arm with 98.3% vs. 98.7% and 98.5% vs. 97.3%, respectively. The per-subject analysis ischemia-driven TLR-free rate to 284 days was higher in the XIENCE V arm compared to the TAXUS arm, 97.3 % and 95.0%, respectively. The ischemia-driven TLR-free rate continued to be higher in the XIENCE V arm through 393 days with a rate of 96.7% in the XIENCE V arm and 94.4% in the TAXUS arm. The ischemia-driven MACE rate through 284 days was lower in the XIENCE V arm compared to the TAXUS arm, 5.0% and 8.8%, respectively. The ischemia-driven MACE rate continued to be lower in the XIENCE V arm through 393 days with a rate of 6.0% in the XIENCE V arm and 10.3% in the TAXUS arm. The late stent thrombosis rates through 284 days were low and similar between XIENCE V and TAXUS arms, 0.2% and 0.0%, respectively. The late stent thrombosis rates through 393 days continued to be low and similar between the two arms with rates of 0.3% in the XIENCE V arm and 0.6% in the TAXUS arm. A summary of the key clinical



Table 6-19 Summary of Clinical Endpoints, RCT (ITT)

Measurements	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI] ⁴
Acute Success			
Clinical Device Success	98.3% (750/763)	98.7% (374/379)	-0.38% [-1.86%, 1.09%]
Clinical Procedure Success	98.5% (651/661)	97.3% (322/331)	1.21% [-0.78%, 3.19%]
Per-Subject Analysis Clinical Endpoints to 284 Days¹			
TVF-free	92.4%	90.5%	1.98% [-1.80%, 5.76%]
TLR-free	97.3%	95.0%	2.24% [-0.44%, 4.92%]
Revascularization ² -free	94.7%	93.5%	1.21% [-1.98%, 4.41%]
Cardiac Death-free	99.4%	99.4%	0.01% [-1.04%, 1.05%]
MACE-free	95.0%	91.4%	3.62% [0.15%, 7.09%]
Per-Subject Analysis Clinical Endpoints to 393 Days⁵			
TVF-free	91.5%	88.9%	2.62% [-1.41%, 6.65%]
TLR-free	96.7%	94.4%	2.26% [-0.61%, 5.12%]
Revascularization ² -free	93.9%	92.5%	1.39% [-2.02%, 4.79%]
Cardiac Death-free	99.2%	99.1%	0.17% [-1.08%, 1.41%]
MACE-free	94.1%	89.8%	4.27% [0.51%, 8.02%]
Safety Measures-Per Subject Analysis			
TVF in-hospital ³	0.9% (6/669)	2.4% (8/330)	-1.53% [-3.33%, 0.28%]
TVF through 37 days	1.6% (11/667)	3.3% (11/330)	-1.68% [-3.85%, 0.48%]
TVF through 194 days	4.1% (27/663)	5.5% (18/326)	-1.45% [-4.35%, 1.45%]
TVF through 284 days	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]
TVF through 393 days	8.6% (56/653)	11.3% (36/320)	-2.67% [-6.75%, 1.40%]
MACE in-hospital ³	0.9% (6/669)	2.4% (8/330)	-1.53% [-3.33%, 0.28%]
MACE through 37 days	1.3% (9/667)	3.0% (10/330)	-1.68% [-3.73%, 0.37%]
MACE through 194 days	2.9% (19/663)	5.2% (17/326)	-2.35% [-5.08%, 0.38%]
MACE through 284 days	5.0% (33/657)	8.8% (28/320)	-3.73% [-7.24%, -0.21%]
MACE through 393 days	6.0% (39/653)	10.3% (33/320)	-4.34% [-8.14%, -0.54%]
Stent Thrombosis			
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 to 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (31 to 284 days)	0.2% (1/653)	0.0% (0/319)	0.15% [Assump. not met]
Late (31 to 393 days)	0.3% (2/646)	0.6% (3/317)	-0.32% [Assump. not met]
Stent Thrombosis (per ARC) Definite + Probable, uncensored (at 393 days)	1.1% (7/648)	0.6% (2/317)	0.45% [Assump. not met]

Table 6-19 Summary of Clinical Endpoints, RCT (ITT) (cont'd)

Bleeding Complication to 284 days	3.1% (20/653)	5.0% (16/319)	-1.95% [-4.69%, 0.78%]
Bleeding Complication to 393 days	3.3% (21/646)	5.4% (17/316)	-2.3% [-4.97%, 0.71%]
Vascular Complication to 284 days	0.9% (6/654)	0.9% (3/319)	-0.02% [Assump. not met]
Vascular Complication to 393 days	0.9% (6/647)	1.6% (5/316)	-0.65% [-2.22%, 0.91%]
CVA to 284 days	0.8% (5/653)	0.6% (2/319)	0.14% [Assump. not met]
CVA to 393 days	1.1% (7/646)	0.6% (2/316)	0.45% [Assump. not met]

¹ Kaplan-Meier estimates for analysis to 284 days.

² Revascularization includes both TLR and TVR, non-target lesion.

³ In-hospital is defined as hospitalization less than or equal to 7 days post index procedure.

⁴ By normal approximation.

⁵ Kaplan-Meier estimates for analysis to 393 days.

Note: N is the total number of subjects; M is the total number of lesions.

Note: Clinical device success is computed per lesion and clinical procedure success is computed per subject.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study; Data from this subject is excluded from all data analyses.

Note: All events are ischemia-driven.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Angiographic Secondary Endpoint

Key secondary angiographic analysis at 240 days showed that in-stent LL was 0.16 ± 0.41 mm (301) for the XIENCE V arm and 0.31 ± 0.55 mm (134) for the TAXUS arm, representing an observed 50% reduction in in-stent LL. In-stent % DS at 240 days was $6.26 \pm 16.55\%$ (302) for the XIENCE V arm and $10.61 \pm 22.07\%$ (134) for the TAXUS arm, representing an observed 41% reduction in in-stent %DS in the XIENCE V arm compared to the TAXUS arm as shown in Table 6-20.

Table 6-20 Summary of Angiographic Endpoints, RCT (ITT)

Measurements	XIENCE V (N=302)	TAXUS (N=134)	Difference [95% CI] ¹
240-Day In-Stent Late Loss (mm) Mean ± SD (n) Median (Q1, Q3) Range (min, max) [95% Confidence Interval] ¹	0.16 ± 0.41 (301) 0.09 (-0.05, 0.25) (-0.70, 2.60) [0.11, 0.20]	0.31 ± 0.55 (134) 0.18 (-0.04, 0.42) (-0.45, 3.04) [0.21, 0.40]	-0.15 [-0.25, -0.04]
240-Day In-Segment %DS Mean ± SD (n) Median (Q1, Q3) Range (min, max) [95% Confidence Interval] ¹	18.82 ± 14.71 (302) 14.77 (10.63, 22.49) (-33.71, 100.00) [17.16, 20.49]	23.22 ± 16.49 (134) 18.06 (11.92, 29.27) (-5.56, 88.86) [20.41, 26.04]	-4.40 [-7.67, -1.14]
240-Day In-Stent %DS Mean ± SD (n) Median (Q1, Q3) Range (min, max) [95% Confidence Interval] ¹	6.26 ± 16.55 (302) 5.40 (-2.14, 11.19) (-44.94, 100.00) [4.38, 8.13]	10.61 ± 22.07 (134) 6.37 (-2.46, 20.00) (-41.82, 88.86) [6.84, 14.38]	-4.35 [-8.55, -0.15]

¹By normal approximation. Confidence intervals are unadjusted for multiple comparisons and are meant for descriptive purposes only

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

Proximal and distal in-stent LL were similar for both arms. In-stent ABR was lower in the XIENCE V arm, 2.3%, compared to the TAXUS RCT arm, 5.7%. In-segment %ABR was lower in the XIENCE V arm, 4.7%, compared to the TAXUS RCT arm, 8.9%. No aneurysm and dissections were reported through 240 day. A summary of key angiographic data at 240 days is presented in Table 6-21.

Table 6-21 Summary of Angiographic Endpoints, RCT (ITT)

Measurement	XIENCE V (N=376) (M=427)	TAXUS (N=188) (M=222)	Difference [95% CI]
240-Day Angiographic Endpoints- All-Lesions Analysis			
In-Segment Late Loss Mean ± SD (m)	0.14 ± 0.39 (343)	0.26 ± 0.46(158)	-0.13 [-0.21, -0.04]
In- Stent Late Loss Mean ± SD (m)	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
Proximal Late Loss Mean ± SD (m)	0.12 ± 0.40 (293)	0.20 ± 0.41 (134)	-0.07 [-0.16, 0.01]
Distal Late Loss Mean ± SD (m)	0.09 ± 0.36 (327)	0.10 ± 0.37 (154)	-0.01 [-0.08, 0.06]
In-Stent % DS Mean ± SD (m)	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment % DS Mean ± SD (m)	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Proximal %DS Mean ± SD (m)	10.17 ± 13.11 (315)	11.04 ± 13.21 (143)	-0.87 [-3.49, 1.75]
Distal %DS Mean ± SD (m)	10.44 ± 11.45 (334)	10.24 ± 11.37 (155)	0.20 [-1.98, 2.38]
In-Stent ABR	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment ABR	4.7% (16/344)	8.9% (14/158)	-4.21%[-9.17%, 0.75%]
Proximal ABR	2.9% (9/315)	2.8 % (4/143)	0.06% [Assump. not met]
Distal ABR	0.9% (3/334)	1.3% (2/155)	-0.39% [Assump. not met]
In-Stent MLD Mean ± SD (m)	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD Mean ± SD (m)	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
Proximal MLD Mean ± SD (m)	2.69 ± 0.58 (316)	2.70 ± 0.57 (143)	-0.00 [-0.12, 0.11]
Distal MLD Mean ± SD (m)	2.37 ± 0.52 (334)	2.39 ± 0.54 (155)	-0.02 [-0.12, 0.08]
Aneurysm	0.0% (0/343)	0.0% (0/158)	0.00% [Assump. not met]
Persisting Dissection	0.0% (0/343)	0.0% (0/157)	0.00% [Assump. not met]

Note: N is the total number of subjects; M is the total number of lesions.

Note: Angiographic results at 240 day only include subjects who were assigned to Group A and Group B at randomization with analyzable follow-up angiograms.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study; Data from this subject is excluded from all data analyses

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

IVUS Secondary Endpoint

IVUS analysis showed %VO was $6.91 \pm 6.35\%$ for the XIENCE V arm and $11.21 \pm 9.86\%$ for the TAXUS arm at 240 day follow up, representing a 38.4 % reduction in %VO in the XIENCE V arm. The mean neointimal hyperplasia (NIH) volume for XIENCE V and TAXUS arm was $10.13 \pm 11.46 \text{ mm}^3$ and $20.87 \pm 31.51 \text{ mm}^3$ respectively, representing a 51.5% reduction in the XIENCE V arm as shown in Table 6-22.

Table 6-22 Summary of IVUS Endpoints, RCT (ITT)

	XIENCE V (N=90) (M=101)	TAXUS (N=43) (M=40)	Total (N=133) (M=142)	Difference [95% CI] ³
240-Day Neo-Intimal Hyperplasia (NIH) Volume (mm³)¹				
Mean ± SD (m)	10.13 ± 11.46	20.87 ± 31.51	13.23 ± 19.97	-10.74
Median	(101)	(41)	(142)	[-20.92, -0.56]
(Q1,Q3)	7.84	9.94	7.99	
Range (min, max)	(1.97, 13.61)	(5.06, 23.67)	(2.25, 15.65)	
[95% Confidence Interval] ³	(0.00, 63.35) [7.87, 12.39]	(0.00, 144.95) [10.93, 30.82]	(0.00, 144.95) [9.92, 16.55]	
% Volume Obstruction²				
Mean ± SD (m)	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)	8.13 ± 7.73 (137)	-4.30 [-7.72, -0.88]
Median	5.45	7.84	6.07	
(Q1,Q3)	(1.72, 10.62)	(4.14, 15.52)	(2.22, 11.42)	
Range (min, max)	(0.00, 30.40)	(0.51, 42.25)	(0.00, 42.25)	
[95% Confidence Interval] ³	[5.63, 8.18]	[8.01, 14.40]	[6.83, 9.44]	

¹ Only measured at 240-day follow-up. All available data for this variable are presented in this table.

² % Volume Obstruction=100*(NIH stent volume / stent volume). Only measured at 240-day follow-up. All available data for this variable are presented in this table.

³ By normal approximation.

Note: N is the total number of subjects; M is the total number of lesions.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Matched pair IVUS analysis for total treated lesions (274) showed that incomplete stent apposition post-procedure was 34.4% in the XIENCE V arm and 25.6% in the TAXUS arm. Late acquired incomplete stent apposition at 240 days was comparable between the two arms 1.1% for the XIENCE V arm and 2.3% for the TAXUS arm. Persisting incomplete stent apposition at 240 days was 24.4% for the XIENCE V and 14.0% for the TAXUS arm as shown in Table 6-23.

Table 6-23 Summary of IVUS Endpoints, RCT (ITT)

	XIENCE V (N=160) (M=181)	TAXUS (N=80) (M=93)	Total (N=240) (M=274)	Difference [95% CI]
Post-Procedure Incomplete Apposition [95% Confidence Interval]	34.4% (31/90) [24.74%, 45.20%]	25.6% (11/43) [13.52%, 41.17%]	31.6% (42/133) [23.80%, 40.20%]	8.86% [-7.46%, 25.19%]
240-Day Incomplete Apposition [95% Confidence Interval] ¹	25.6% (23/90) [16.94%, 35.84%]	16.3% (7/43) [6.81%, 30.70%]	22.6% (30/133) [15.77%, 30.61%]	9.28% [-4.97%, 23.52%]
Persisting Incomplete Apposition [95% Confidence Interval] ¹	24.4% (22/90) [16.00%, 34.64%]	14.0% (6/43) [5.30%, 27.93%]	21.1% (28/133) [14.47%, 28.97%]	10.49% [-3.15%, 24.13%]
Late-acquired Incomplete Apposition [95% Confidence Interval] ¹	1.1% (1/90) [0.03%, 6.04%]	2.3% (1/43) [0.06%, 12.29%]	1.5% (2/133) [0.18%, 5.33%]	-1.21% [Assump. not met]

¹ By normal approximation

Note: N is the total number of subjects; M is the total number of lesions.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Subgroup Analysis

Key clinical endpoint analysis was performed on the following pre-specified subgroups: diabetes mellitus status, single vessel, dual vessel, and planned overlap. Additionally, a post hoc analysis was performed on the gender subgroup upon request by FDA.

All Diabetes Mellitus

The TVF rate through 393 days for the XIENCE V All Diabetes Mellitus subgroup is higher compared to the XIENCE V No Diabetes Mellitus subgroup, with rates of 11.3% and 7.4%, respectively. The TVF rate through 393 days for the TAXUS All Diabetes Mellitus subgroup is lower compared to the TAXUS No Diabetes Mellitus subgroup, with rates of 7.0% and 12.9%, respectively. The MACE rate through 393 days for the XIENCE V All Diabetes Mellitus subgroup is higher compared to the XIENCE V No Diabetes Mellitus subgroup, with rates of 8.8% and 4.8%, respectively. The MACE rate through 393 days for the TAXUS All Diabetes Mellitus subgroup is lower compared to the TAXUS No Diabetes Mellitus subgroup, with rates of 4.7% and 12.5%, respectively. Key clinical events through 393 days are presented in Table 6-24 below. The sample size is low for TAXUS All Diabetes Mellitus Subgroup (N=92). Caution should be used in the interpretation of these results. Therefore, any clinical event rates based on these subgroups are not powered.

Table 6-24 Key Clinical Events Through 393 Days for All Diabetes Mellitus

	XIENCE V All Diabetes Mellitus (N=198)	XIENCE V No Diabetes Mellitus (N=471)	TAXUS All Diabetes Mellitus (N=92)	TAXUS No Diabetes Mellitus (N=238)
Hierarchical Count				
TVF (Cardiac Death, MI, TLR, TVR, non-target lesion)	11.3% (22/194)	7.4% (34/459)	7.0% (6/86)	12.9% (30/232)
MACE (Cardiac Death, MI, TLR)	8.8% (17/194)	4.8% (22/459)	4.7% (4/86)	12.5% (29/232)
Non- Hierarchical Count				
Cardiac Death	1.5% (3/194)	0.4% (2/459)	0.0% (0/86)	1.3% (3/232)
Myocardial Infraction (MI)	4.6% (9/194)	2.0% (9/459)	3.5% (3/86)	4.3% (10/232)
QMI	1.0% (2/194)	0.0% (0/459)	0.0% (0/86)	0.4% (1/232)
NQMI	3.6% (7/194)	2.0% (9/459)	3.5% (3/86)	3.9% (9/232)
TLR	4.6% (9/194)	2.8% (13/459)	1.2% (1/86)	7.3% (17/232)
TVR, non- target Lesion	3.6% (7/194)	2.8% (13/459)	3.5% (3/86)	4.7% (11/232)

Note: Subjects are only counted once for each type of event.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: All counts presented in this table are subject counts.

Single Vessel Treatment

The TVF rate through 393 days for the XIENCE V Single Vessel subgroup is lower compared to the TAXUS Single Vessel subgroup, with rates of 7.8%, and 9.3%, respectively. The MACE through 393 days for the XIENCE V Single Vessel subgroup is lower compared to the TAXUS Single Vessel subgroup, with rates of 5.6%, and 8.1%, respectively. Key clinical events through 393 days are presented in Table 6-25 below.

Table 6-25 Key Clinical Events Through 393 Days for Single Vessel Treatment

	XIENCE V (N=566)	TAXUS (N=281)
Hierarchical Count		
TVF (Cardiac Death, MI, TLR, TVR, non-target lesion)	7.8% (43/552)	9.3% (25/270)
MACE (Cardiac Death, MI, TLR)	5.6% (31/552)	8.1% (22/270)
Cardiac Death	0.9% (5/552)	0.4% (1/270)
QMI	0.2% (1/552)	0.0% (0/270)
NQMI	2.0% (11/552)	3.0% (8/270)
TLR CABG	0.0% (0/552)	0.0% (0/270)
TLR PCI	2.5% (14/552)	4.8% (13/270)
TVR CABG, non-target Lesion	0.5% (3/552)	0.4% (1/270)
TVR PCI, non-target Lesion	1.6% (9/552)	0.7% (2/270)

Note: Subjects are only counted once for each type of event.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: There are 5 subjects included in this table who were randomized to 1 lesion, but were treated with 2 lesions in the same vessel. The randomized lesion is considered as the target lesion, and the other is considered as a non-target lesion.

Note: All counts presented in this table are subject counts

Dual Vessel Treatment

The TVF rate through 393 days for the XIENCE V Dual Vessel subgroup is lower compared to the TAXUS Dual Vessel subgroup, with rates of 12.9%, and 22.0%, respectively. The MACE through 393 days for the XIENCE V Dual Vessel subgroup is lower compared to the TAXUS Dual Vessel subgroup, with rates of 7.9%, and 22.0%, respectively. Key clinical events through 393 days are presented in Table 6-26 below. The sample size is low for the Dual Vessel subgroup (103 for XIENCE V and 51 for TAXUS). Caution should be used in the interpretation of these results. Therefore, any clinical event rates based on these subgroups are not powered.

Table 6-26 Key Clinical Events Through 393 Days for Dual Vessel Treatment

	XIENCE V (N=103)	TAXUS (N=51)
Hierarchical Count		
TVF (Cardiac Death, MI, TLR, TVR, non-target lesion)	12.9% (13/101)	22.0% (11/50)
MACE (Cardiac Death, MI, TLR)	7.9% (8/101)	22.0% (11/50)
Cardiac Death	0.0% (0/101)	4.0% (2/50)
QMI	1.0% (1/101)	0.0% (0/50)
NQMI	4.0% (4/101)	8.0% (4/50)
TLR CABG	1.0% (1/101)	0.0% (0/50)
TLR PCI	2.0% (2/101)	10.0% (5/50)
TVR CABG, non-target Lesion	0.0% (0/101)	0.0% (0/50)
TVR PCI, non-target Lesion	5.0% (5/101)	0.0% (0/50)

Note: Subjects are only counted once for each type of event.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: There are 4 subjects included in this table who were randomized to 2 vessels/lesions, but were treated with 2 lesions in the same vessel. Both lesions are considered as target lesion

Note: All counts presented in this table are subject counts

Gender

The TVF rate through 393 days for the XIENCE V Male subgroup is lower compared to the TAXUS Male subgroup, with rates of 7.4%, and 7.7%, respectively. The TVF rate through 393 days for the XIENCE V Female subgroup is lower compared to the TAXUS Female subgroup, with rates of 11.3%, and 17.9%, respectively. The MACE rate through 393 days for the XIENCE V Male subgroup is lower compared to the TAXUS Male subgroup, with rates of 5.0%, and 7.2%, respectively. The MACE rate through 393 days for the XIENCE V Female subgroup is lower compared to the TAXUS Female subgroup, with rates of 8.2%, and 16.1%, respectively. Key clinical events through 393 days are presented in Table 6-27 below.

Table 6-27 Key Clinical Events Through 393 Days for Gender

	XIENCE V Male (N=469)	TAXUS Male (N=218)	XIENCE V Female (N=200)	TAXUS Female (N=114)
Hierarchical Count				
TVF (Cardiac Death, MI, TLR, TVR, non-target lesion)	7.4% (34/459)	7.7% (16/208)	11.3% (22/194)	17.9% (20/112)
MACE (Cardiac Death, MI, TLR)	5.0% (23/459)	7.2% (15/208)	8.2% (16/194)	16.1% (18/112)
Non-Hierarchical Count				
Cardiac Death	0.9% (4/459)	1.4% (3/208)	0.5% (1/194)	0.0% (0/112)
Myocardial Infraction (MI)	2.6% (12/459)	2.4% (5/208)	3.1% (6/194)	7.1% (8/112)
QMI	0.2% (1/459)	0.5% (1/208)	0.5% (1/194)	0.0% (0/112)
NQMI	2.4% (11/459)	1.9% (4/208)	2.6% (5/194)	7.1% (8/112)
TLR	2.2% (10/459)	3.8% (8/208)	6.2% (12/194)	8.9% (10/112)
TVR, non-target Lesion	3.1% (14/459)	1.9% (4/208)	3.1% (6/194)	8.9% (10/112)

Note: Subjects are only counted once for each type of event.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: All counts presented in this table are subject counts.

Adverse Reactions and Complications

All adverse events (AEs) reported by the subject, observed by the Investigator, or documented in medical records were listed on the adverse event or serious adverse event case report forms. All pre-existing medical conditions were recorded on baseline case report forms. Starting with device implant, any new event/experience that was not present at baseline, or worsening of an event present at baseline, was considered an adverse event.

Myocardial Infarction (MI)

Myocardial infarctions were categorized as Q-wave (development of new, pathological Q-wave on the ECG) and non-Q-wave (elevation of CK levels to greater than two times the upper limit of normal and elevated CK-MB in the absence of new pathological Q-waves). All myocardial infarctions, including the relationship of the event to the target lesion, were adjudicated by the CEC. Culprit lesion information from the angiographic core lab was provided to the CEC if an angiogram was available; all infarcts that could not be clearly attributed to a vessel other than the target vessel were considered related to the target

vessel.

Upon adjudication of the events, a total of 21 myocardial infarctions occurred through 284 days post-procedure, with thirteen events (61.9%) occurring in XIENCE V RCT arm and eight events (38.1%) occurring in TAXUS RCT arm. An additional six (6) myocardial infarctions occurred between 285 and 393 days post-procedure, with three (3) events occurring in the XIENCE V RCT arm and three (3) events occurring in the TAXUS RCT arm.

Stent Thrombosis

The CEC adjudicated all cases of stent thrombosis for confirmation and outcome. For those cases where an angiogram was available, the angiographic core laboratory provided information to the CEC regarding the culprit lesion containing the thrombus.

Stent thrombosis was defined as clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (thrombus within or adjacent to the treated target lesion), or in the absence of angiography, any unexplained death or acute MI in the distribution of the target lesion within 30 days of the index procedure. Stent thrombosis was categorized as acute (≤ 1 day), subacute (> 1 day to ≤ 30 days), or late (> 30 days) relative to the index procedure. Six (6) stent thromboses were reported through 393 days post-procedure.

Ischemia Driven Target Lesion Revascularization (TLR)

The angiographic core laboratory reviewed all angiograms (protocol required and symptom-driven) and assessed the relationship of any revascularizations to the target lesion, target vessel/non-target lesion, or non-target vessel. The CEC determined whether the revascularization was ischemia-driven or non-ischemia driven. Ischemia-driven TLR was defined as revascularization at the target lesion associated with:

- A) a positive functional ischemia study, or
- B) ischemic symptoms and $\geq 50\%$ stenosis by QCA, or
- C) $\geq 70\%$ stenosis by QCA without either ischemic symptoms or a positive functional study.

A total of 35 revascularizations in 33 subjects were adjudicated to be TLR through 284 days post procedure; 19 TLR in 17 XIENCE V arm subjects and 16 TLR in 16 TAXUS arm subjects. All of the revascularizations except one CABG in the XIENCE V arm were performed by PCI. An additional six (6) revascularizations in six (6) subjects occurred between 285 days and 393 days following post procedure; four TLR in the XIENCE V arm and 2 TLR in the TAXUS arm.

Ischemia Driven Target Vessel Revascularization (TVR), Non-Target Lesion

The angiographic core laboratory reviewed all angiograms (protocol required and symptom-driven indicated) and assessed the relationship of any revascularizations to the target lesion, target vessel/non-target lesion, or non-target vessel. The CEC determined whether the revascularization was ischemia driven or non-ischemia driven. Ischemia driven TVR was defined as revascularization at the target vessel associated with:

- A) a positive functional ischemia study, or
- B) ischemic symptoms and $\geq 50\%$ stenosis by QCA, or
- C) $\geq 70\%$ stenosis by QCA without either ischemic symptoms or a positive functional study.

A total of 41 revascularizations in 33 subjects were adjudicated to be TVR/NTL through 284 days post procedure; 23 TVR/NTL in 20 XIENCE™ V arm subjects and 18 TVR/NTL in 13 TAXUS arm. All of the revascularizations except three CABGs in the XIENCE V arm and two CABG in the TAXUS arm were performed by PCI. An additional two TVR/NTL occurred between 285 days and 393 days post procedure; one (1) in the XIENCE V arm and one (1) in the TAXUS arm.

Vascular and Bleeding Complications

Cerebrovascular Accident or Stroke (CVA)

Cerebrovascular events include cerebral infarction (ischemic stroke), intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). All cerebrovascular accidents were adjudicated by the CEC to confirm occurrence and to evaluate the outcome of the event.

A total of five cerebrovascular events were reported in five subjects, four events in the XIENCE V arm and one event in the TAXUS arm. There were two transient ischemic attack (TIA) events reported within 0-284 days, one (1) TIA event in the XIENCE V arm and one (1) TIA event in the TAXUS. An additional two (2) cerebrovascular events occurred between 285 day and 393 days post procedure; both events occurred in the XIENCE V arm.

Vascular Events

Vascular complications include pseudoaneurysm, arteriovenous fistula, peripheral ischemia or nerve injury. All vascular events were adjudicated by the CEC to confirm occurrence and to evaluate the outcome of the event

All of the reported vascular events were pseudoaneurysms noted at the PCI access site. A total of nine vascular events were reported; six vascular events reported in the XIENCE V arm, and three vascular events reported in the TAXUS arm. All of the events occurred within two weeks of the index procedure or a revascularization procedure, and all were resolved within days of occurrence. Of the nine vascular events, three required either surgical repair or transfusion. An additional two (2) vascular events occurred between 285 days and 393 days post procedure; both events occurred in the TAXUS arm.

Bleeding Events

A bleeding event (e.g., hematoma, access site, GI, or retroperitoneal bleed) was defined as a bleed that required transfusion or surgical repair, or was associated with a hemoglobin drop of more than 5 g/dL. All bleeding events were adjudicated by the CEC to confirm occurrence and to evaluate the outcome of the event.

Ten (10) subjects had events that met the protocol definition of bleeding events. Six (6) of these subjects were in the XIENCE V arm and four (4) subjects were in the TAXUS arm. An additional three bleeding events occurred between 285 days and 393 days post procedure; two (2) events in the XIENCE V arm and one (1) event in the TAXUS arm.

Deaths

Cardiac death was defined as any death for which a cardiac cause could not be excluded. The event included, but was not limited to AMI, cardiac perforation/pericardial tamponade, arrhythmia, or conduction abnormality, CVA within 30 days of the procedure or CVA suspected of being related to the procedure, death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery. All deaths were adjudicated by the CEC. Deaths that could not be clearly attributed to another cause were considered cardiac deaths.

A total of nine deaths were reported through 284 days post procedure, five of which were adjudicated as cardiac deaths. Of the five cardiac deaths, three were XIENCE V arm subjects and two were TAXUS arm subjects. There were no autopsies performed for any of these subjects.

An additional two (2) deaths occurred between 285 days and 393 days post procedure. Both deaths were adjudicated as cardiac deaths; one (1) occurred in the XIENCE V arm and one occurred in the TAXUS arm.

Subject Discontinuation

The reasons for discontinuation were similar for the RCT arm and the 4.0 mm arms. They were categorized based on input from the sites as follows:

- Subject withdrawal of consent
- Subject termination by Investigator (deemed medically necessary)
- Subject lost to follow-up
- Subject follow-up terminated by sponsor
- Subject follow-up terminated by regulatory agency
- Other reason to be specified

Withdrawn/ Lost to Follow-Up

There were 1,002 subjects randomized to the RCT. Of these total subjects, 669 subjects were randomized to the XIENCE V arm and 333 subjects to the TAXUS arm. Twelve of 669 XIENCE V arm subjects and 10 of 333 of TAXUS arm terminated prior to 270 day follow up as shown in Table 6-28.

Table 6-28 Early Termination – (RCT) (Intent-To-Treat Population)

	XIENCE V (N=669)	TAXUS (N=333)	Total (N=1002)
Early Termination at 30-Day Visit ¹			
Subject Withdrawal	0	2	2
Subject Lost to Follow-up	2	0	2
Early Termination at 180-Day Visit ²			
Subject Withdrawal	2	1	3
Subject Lost to Follow-up	2	3	5
Early Termination at 270-Day Visit ³			
Subject Withdrawal	1	1	2
Subject Lost to Follow-up	5	3	8
Total	12	10	22

¹ Early Termination at 30-Day Visit is defined as the termination of study occurred before 23 days after index procedure.

² Early Termination at 180-Day Visit is defined as the termination of study occurred on or after 23 days and before 166 days after index procedure.

³ Early Termination at 270-Day Visit is defined as the termination of study occurred on or after 166 days and before 256 days after index procedure.

Protocol Deviations

Protocol deviations were recorded in the clinical trial database and classified as major or minor by the sponsor. A major deviation is a deviation which may potentially compromise subject health, welfare or safety or which may potentially significantly affect data. Major deviations were those involving subject unblinding, or follow-up visits within 270 days conducted by non-blinded personnel (with subject blind maintained), eligibility criteria deviations, treatment rule deviations, and omission of informed consent. A minor deviation was any protocol deviation not classified as major. Minor protocol deviations were primarily those involving protocol required medications, follow up and assessments not done, not done per protocol or done outside the protocol required window.

The protocol deviation management committee met regularly to evaluate each deviation reported and corrective actions were implemented to address the deviations as per the sponsor's protocol deviation procedures and documents in the protocol deviation committee meeting minutes.

Study Conclusion

In the SPIRIT III RCT clinical study, the XIENCE V EECSS has shown non-inferiority to

the TAXUS PECSS in terms of the primary endpoint of in-segment LL at 240 days ($p < 0.0001$). The difference between the in-segment LL for the XIENCE V arm and the TAXUS arm ($0.14 \text{ mm} - 0.28 \text{ mm} = -0.14 \text{ mm}$) represents a 50% reduction in LL and is highly statistically significant. Therefore the null hypothesis was rejected proving that XIENCE V EECSS was non-inferior to TAXUS PECSS for in-segment LL at 240 days ($p < 0.0001$). As previously specified in the statistical analysis plan, a superiority test of the primary endpoint was performed. Since non-inferiority was demonstrated in this study, a superiority test was performed. This test demonstrated the superiority of XIENCE V vs. TAXUS in terms of the primary endpoint ($p = 0.0037$).

Additionally, there was a 50% reduction in-stent LL and 41% reduction in stent %DS at observed at 240 days in XIENCE V as compared to TAXUS. Furthermore, XIENCE V also not only showed non-inferiority to TAXUS in terms of ischemic-driven TVF rate (7.2% versus 9.0%, $p < 0.0001$) but also an observed 43% reduction ischemic- driven MACE rate (4.6% versus 8.1%) through 284 days.

The IVUS results support the angiographic endpoint results. At 240 days, there was a 38.4% reduction in %VO and a 51.5% reduction in NIH volume in the XIENCE V arm as compared to the TAXUS arm. The per-subject analysis ischemia-driven TLR-free rate to 284 days was higher in the XIENCE V arm compared to the TAXUS arm, 97.4 % and 95.0% respectively. The late stent thrombosis rates were low and similar between XIENCE V and TAXUS arms, 0.2% and 0.0% respectively. Therefore, 240 day angiographic, IVUS, and clinical endpoints through 284 days have demonstrated the safety and effectiveness of the XIENCE V EECSS.

6.4 Descriptive Summary of SPIRIT III 4.0 mm Arm Study Design

The SPIRIT III 4.0 mm arm is a non-randomized, prospective, multi-center, single arm evaluation of XIENCE V EECSS compared to TAXUS PECSS in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD > 3.75 mm to ≤ 4.25 mm. The 4.0 mm arm was designed to enroll up to 80 subjects at up to 80 sites in the US

The primary endpoint of the SPIRIT III trial was 240-day in-segment Late Loss (LL). Key secondary endpoints to examine the safety and effectiveness included the following:

- Ischemia-driven Target Vessel Failure (TVF) at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Ischemia-driven Target Lesion Revascularization (TLR) at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Ischemia-driven Target Vessel Revascularization (TVR) at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Ischemia-driven Major Adverse Cardiac Event (MACE) at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years,
- Persisting incomplete stent apposition, late-acquired incomplete stent apposition, aneurysm, thrombosis, and persisting dissection at 240 days
- Acute success (clinical device and clinical procedure)
- Proximal and distal LL at 240 days
- In-stent LL at 240 days
- In-stent and in-segment percent angiographic binary restenosis (% ABR) rate at 240 days
- In-stent and in-segment percent diameter stenosis (%DS) at 240 days
- In-stent percent volume obstruction (%VO) at 240 days

Enrollment Criteria

Enrollment criteria information is provided in Section 6.3.

Treatment Strategy and Stenting Procedure

Treatment strategy and stenting procedure information is provided in Section 6.3.

Number of Subjects per Investigative Site and IRB

A total of 77 sites received IRB approval for the SPIRIT III study in the US of which 30 sites enrolled 69 subjects into the 4.0 mm arm. The primary investigator and the number of subjects enrolled at each approved site are presented in Table 6-29.

Table 6-29 Number of Subjects Enrolled by Investigational Site- 4.0 mm Arm

Primary Investigator	Site	Investigational Site	XIENCE V 4.0 mm Arm
Dr. Gordon, P	29324	The Miriam Hospital, Providence, RI	8
Dr. Sanz, M	27314	St. Patrick Hospital, Missoula, MT	5
Dr. Williams, D	27626	Rhode Island Hospital, Providence, RI	5
Dr. Newman, W	28864	Wake Medical Center, Raleigh, NC	5
Dr. Carter, A	28807	Borgess Medical Center, Kalamazoo, MI	4
Dr. Shadoff, N	27194	Presbyterian Hospital, Albuquerque, NM	3
Dr. Midei, M	27286	St. Joseph Medical Center, Towson, MD	3
Dr. Grantham, A	27454	St. Luke's Hospital, Kansas City, MO	3
Dr. Fortuna, R	27616	Scripps Memorial Hospital, La Jolla, CA	3
Dr. Hermiller, J	87266	The Heart Center, of IN, LLC, Indianapolis, IN	3
Dr. Xenopoulos, N	27303	Jewish Hospital, Louisville, KY	2
Dr. Williams, J	27310	Presbyterian Hospital, Charlotte, NC	2
Dr. Saucedo, J	27448	The University of Oklahoma Health Sciences Center, Oklahoma City, OK	2
Dr. Bernstein, P	27604	St. Luke's Medical Center, Milwaukee, WI	2
Dr. Cannon, L	28489	Northern Michigan Hospital, Petoskey, MI	2
Dr. Chambers, J	29720	Sacred Heart Medical Center, Eugene, OR	2
Dr. Kaplan, A	30404	Dartmouth-Hitchcock Medical Center, Lebanon, NH	2
Dr. Knapp, W Dr. Unterman, M	27053	Saint Joseph's Hospital of Atlanta, Atlanta, GA	1
Dr. Matthews, R	27325	Good Samaritan Hospital, Los Angeles, CA	1

**Table 6-29 Number of Subjects Enrolled by Investigational Site- 4.0 mm Arm
(cont'd)**

Primary Investigator	Site	Investigational Site	XIENCE V 4.0 mm Arm
Dr. Turco, M	27369	Washington Adventist Hospital, Takoma Park, MD	1
Dr. Doing, A	27620	Poudre Valley Hospital, Fort Collins, CO	1
Dr. Young, J	27731	The Christ Hospital, Cincinnati, OH	1
Dr. Yakubov, S	27940	Riverside Methodist Hospital, Columbus, OH	1
Dr. Quesada, R	27963	Baptist Hospital of Miami, Miami, FL	1
Dr. Singh, H Dr. Wohns, D	28376	Spectrum Health Hospital, Grand Rapids, MI	1
Dr. Hirsch, C	28618	The Valley Hospital, Pomona, NY	1
Dr. Satler, L	30145	Washington Hospital Center, Washington, DC	1
Dr. Mooney, M	30244	Abbott Northwestern Hospital, Minneapolis, MN	1
Dr. Dauerman, H	30677	Fletcher Allen Health Care, Burlington, VT	1
Dr. Netz, D	87867	Nebraska Heart Hospital, Lincoln, NE	1
Total			69

Study Period

Enrollment commenced in the 4.0 mm arm on September 10, 2005. At the time enrollment in the RCT was completed, 69 of the planned 80 subjects were enrolled in the 4.0 mm arm at 30 sites. Interim analysis was performed to determine if enrollment could be discontinued based upon the results of the 69 patients.

Summary of Study Population

Subjects eligible for enrollment into the 4.0 mm arm were from the general interventional cardiology population with evidence of myocardial ischemia. These subjects were

candidates for coronary artery bypass graft surgery who also satisfied the general and angiographic enrollment criteria. Subjects who met all the general inclusion/exclusion criteria were to be considered for study participation. Upon meeting all angiographic inclusion/exclusion criteria, and after calling the ICON IVRS service, the subjects were considered enrolled into the study.

Demographic and Risk Factors

Key baseline demographics and risk factors were similar between the 4.0 mm XIENCE V arm and the angiographic groups of the TAXUS and XIENCE V arms of the RCT as shown in Table 6-30. However, in the XIENCE V 4.0 mm arm, 65.2% (45 subjects) were hypertensive requiring medication compared to 74.2% (138 subjects) and 74.7% (281 subjects) in the TAXUS and XIENCE V arms of the RCT, respectively. Subjects with MI within 2 months was slightly higher in the XIENCE V 4.0 arm with 5.8% (4 subjects) compared to 2.7% (5 subjects) and 2.5% (9 subjects) in the TAXUS and XIENCE V arms of the RCT, respectively.

**Table 6-30 Baseline Demographics – Per-Subject Analysis (ITT)
XIENCE V 4.0 mm Arm vs. Angiographic Group of TAXUS vs.
XIENCE V RCT**

	XIENCE V 4.0 mm Arm (N=69)	TAXUS RCT (N=188)	XIENCE V RCT (N=376)
Age (year) Mean ± SD (n)	61.93 ± 11.20 (69)	63.45 ± 10.67 (187)	63.26 ± 10.33 (376)
Male Subjects	72.5 % (50/69)	65.8% (123/187)	70.2% (264/376)
Current Tobacco Use	27.9 % (19/68)	24.4% (44/180)	20.8% (77/370)
All Diabetes Mellitus	30.4% (21/69)	26.9% (50/186)	29.3% (110/376)
Diabetes Mellitus Requiring Medication	23.2 % (16/69)	23.7% (44/186)	24.7% (93/376)
Hypertension Requiring Medication	65.2 % (45/69)	74.2% (138/186)	74.7% (281/376)
Hypercholesterolemia Requiring Medication	77.9 % (53/68)	69.0% (127/184)	73.5% (272/370)
All Prior Cardiac Interventions	21.7% (15/69)	26.2% (49/187)	31.9% (120/376)
Prior Cardiac Intervention On Target Vessel (s)	8.7 % (6/69)	10.8% (20/185)	13.0% (48/368)
MI within 2 Months	5.8% (4/69)	2.7% (5/187)	2.5% (9/365)

Summary of Safety and Effectiveness Data

All SPIRIT III data were collected on electronic case report forms (InForm™,

PhaseForward, Waltham, MA). Angiographic data were assessed by a blinded independent core laboratory (Cardiovascular Research Foundation, New York, NY). The endpoint events, bleeding and vascular complications were adjudicated by a blinded Clinical Events Committee (CEC). Information on adverse events was reviewed by a blinded Data Safety Monitoring Board (DSMB) to evaluate subject safety on an on-going basis.

Two analysis populations were defined in this study: Intent-To-Treat (ITT) population and Per-Treatment Evaluable (PTE) population.

ITT Population

The ITT population for the 4.0 mm arm consisted of all subjects randomized / registered to the study, regardless of the treatment actually received. Deregistered subjects (subjects for whom the study stent was not delivered beyond the guide catheter) are included in the ITT population. Subjects were analyzed in the treatment group to which they were randomized.

Per-Treatment Evaluable (PTE) Population

The PTE population for the 4.0 mm arm consisted of subjects who received a study stent at the target lesion(s), who had no major procedural protocol deviations, other than those relating to randomization assignment versus study stent actually received, and for whom follow-up data was available. Analyses based on the PTE population were “as treated”; that is, subjects were included in the treatment group corresponding to the study stent actually received. Subjects treated with a non-study stent were excluded.

Primary Endpoint

The primary endpoint for the 4.0 mm arm is in-segment late loss (LL) at 240 days. In-segment LL is defined as: in-segment MLD post-procedure minus in-segment MLD at 240 day follow-up. In-segment LL at 240 days in the 4.0 mm XIENCE V arm was compared with that of the TAXUS arm of the RCT.

For the primary endpoint, in-segment LL at 240 days within the XIENCE V 4.0 mm arm was compared to angiographic group subjects from the TAXUS RCT arm. Analysis was conducted on the analysis lesion. In-segment LL at 240 days was 0.17 ± 0.38 mm for the XIENCE V 4.0 mm arm and 0.28 ± 0.48 mm for the TAXUS arm as shown in the Table 6-31. The XIENCE V 4.0 mm arm was shown to be non-inferior to TAXUS RCT arm for in-segment LL at 240 days (non-inferiority p-value <0.0001), with the XIENCE V 4.0 mm diameter stent showing a 39% reduction in in-segment LL as compared to TAXUS PECSS as shown in Table 6-31.

**Table 6-31 Primary Endpoint Analysis (ITT)
(XIENCE V 4.0 mm Arm vs. TAXUS Arm of RCT) – Analysis Lesion**

	XIENCE V 4.0 mm Arm (N=69)	TAXUS RCT (N=188)	Non-Inferiority P-Value¹
240 Day In-Segment LL Mean ± SD (n)	0.17 ± 0.38 (49)	0.28 ± 0.48 (134)	< 0.0001

¹One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.038 significance level.

Note: TAXUS RCT includes subjects in angiographic group only.

Major Secondary Endpoint

The 4.0 mm arm did not have a major secondary endpoint.

Secondary Endpoints

The clinical endpoints in the XIENCE V 4.0 mm arm were compared to the TAXUS RCT arm. Clinical device success in the two treatment arms were similar, with rates in the XIENCE V 4.0 mm arm and TAXUS RCT arm of 98.5% and 98.7% respectively. The clinical procedure success in the two treatment arms were similar, with a rate in the XIENCE V 4.0 mm arm of 94.2% and a rate in the TAXUS RCT arm of 97.3%. The ischemia driven TVF rate, through 284 days, was lower in the XIENCE V 4.0 mm, 5.9%, compared to the TAXUS RCT arm, 9.0%. The ischemia driven TVR rate continued to be lower in the XIENCE V 4.0 mm arm through 393 days with a rate of 5.9% in the XIENCE V 4.0 mm arm and a rate of 11.3% in the TAXUS RCT arm. The per subject analysis ischemia driven TLR-free rate, to 284 days, was higher in the XIENCE V 4.0 mm arm, 98.5%, compared to the TAXUS RCT arm, 95.0%. The ischemia driven TLR-free rate continues to be higher in the XIENCE V 4.0 mm arm through 393 days with a rate of 98.5% in the XIENCE V 4.0 mm arm and a rate of 95% in the TAXUS RCT arm. The ischemia driven MACE rate, through 284 days, was lower for the XIENCE V 4.0 mm arm, 5.9% compared to the TAXUS RCT arm, 8.1%. The ischemia driven MACE rate continues to be lower in the XIENCE V 4.0 mm arm through 393 days with a rate of 5.9% in the XIENCE V 4.0 mm arm and a rate of 10.3% in the TAXUS RCT arm. Acute stent thrombosis in the XIENCE™ V 4.0 mm arm and the TAXUS RCT arm were 1.4% and 0.0% respectively. The late stent thrombosis rates in the two treatment arms were low and similar with rates in the XIENCE V 4.0 mm arm and TAXUS RCT arm, of 0.0% and 0.0%, respectively. The late stent thrombosis rates continue to be low and similar in both arms with rates in the XIENCE V 4.0 mm arm and TAXUS RCT arm, of 0.0% and 0.6%, respectively. A summary of the key clinical endpoint events are presented in Table 6-32.



Table 6-32 Summary of Clinical Endpoints (ITT) (XIENCE V 4.0 mm Arm vs. TAXUS RCT) through 284 days

Measurements	XIENCE V 4.0 mm Arm (N=69) (M=69)	TAXUS RCT (N=333) (M=383)	Difference [95% CI] ⁴
Acute Success			
Clinical Device Success	98.5% (67/68)	98.7% (374/379)	-0.15% [Assump. not met]
Clinical Procedure Success	94.2% (65/69)	97.3% (322/331)	-3.08% [Assump. not met]
Per-Subject Analysis Clinical Endpoints to 284 Days¹			
TVF-free	94.2%	90.5%	3.72% [-2.67%, 10.11%]
TLR-free	98.5%	95.0%	3.48% [-0.27%, 7.23%]
Revascularization ² -free	98.5%	93.5%	5.03% [1.06%, 8.99%]
Cardiac Death-free	98.5%	99.4%	-0.85% [-3.84%, 2.13%]
MACE-free	94.2%	91.4%	2.79% [-3.53%, 9.11%]
Per-Subject Analysis Clinical Endpoints to 393 Days⁵			
TVF-free	94.2%	88.9%	5.29% [-1.22%, 11.80%]
TLR-free	98.5%	94.4%	4.11% [0.27%, 7.95%]
Revascularization ² -free	98.5%	92.5%	5.97% [1.89%, 10.05%]
Cardiac Death-free	98.5%	99.1%	-0.54% [-3.59%, 2.51%]
MACE-free	94.2%	89.8%	4.36% [-2.08%, 10.80%]
Safety Measure- Per Subject Analysis			
TVF in-hospital ³	4.3% (3/69)	2.4% (8/330)	1.92% [Assump. not met]
TVF through 37 days	4.3% (3/69)	3.3% (11/330)	1.01% [Assump. not met]
TVF through 194 days	5.9% (4/68)	5.5% (18/326)	0.36% [Assump. not met]
TVF through 284 days	5.9% (4/68)	9.7% (31/320)	-3.81% [Assump. not met]
TVF through 393 days	5.9% (4/68)	11.3% (36/320)	-5.37% [Assump. not met]
MACE in-hospital ³	4.3% (3/69)	2.4% (8/330)	1.92% [Assump. not met]
MACE through 37 days	4.3% (3/69)	3.0% (10/330)	1.32% [Assump. not met]
MACE through 194 days	5.9% (4/68)	5.2% (17/326)	0.67% [Assump. not met]
MACE through 284 days	5.9% (4/68)	8.8% (28/320)	-2.87% [Assump. not met]
MACE through 393 days	5.9% (4/68)	10.3% (33/320)	-4.43% [Assump. not met]

Table 6-32 Summary of Clinical Endpoints (ITT) (XIENCE V 4.0 mm Arm vs. TAXUS RCT) through 393 days (cont'd)

Stent Thrombosis Acute (< 1 day)	1.4% (1/69)	0.0% (0/330)	1.45% [Assump. not met]
Subacute (1 to 30 days)	0.0% (0/69)	0.0% (0/330)	0.00% [Assump. not met]
Late (30 to 284 days)	0.0% (0/67)	0.0% (0/319)	0.00% [Assump. not met]
Late (30 to 393 days)	0.0% (0/67)	0.6% (2/317)	-0.63% [Assump. not met]
Stent Thrombosis (per ARC) Definite + Probable, uncensored (at 393 days)	0.0% (0/68)	0.6% (2/317)	NC
Bleeding Complication to 284 days	6.0% (4/67)	5.0% (16/319)	0.95% [Assump. not met]
Bleeding Complication to 393 days	6.0% (4/67)	5.4% (17/316)	0.59% [Assump. not met]
Vascular Complication to 284 days	0.0% (0/67)	0.9% (3/319)	-0.94% [Assump. not met]
Vascular Complication to 393 days	0.0% (0/67)	1.6% (5/316)	-1.58% [Assump. not met]
CVA to 284 days	0.0% (0/67)	0.6% (2/319)	-0.63% [Assump. not met]
CVA to 393 days	0.0% (0/67)	0.6% (2/316)	-0.63% [Assump. not met]

¹ Kaplan-Meier estimates for analysis to 284 days.

² Revascularization includes both TLR and TVR, non-target lesion.

³ In-hospital is defined as hospitalization less than or equal to 7 days post index procedure.

⁴ By normal approximation.

⁵ Kaplan-Meier estimates for analysis to 393 days.

Note: N is the total number of subjects; M is the total number of lesions.

Note: Clinical device success is computed per lesion and clinical procedure success is computed per subject.

Note: Angiographic results at 240 days only include subjects who were assigned to Group A and Group B at randomization with analyzable follow-up angiograms.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study; Data from this subject is excluded from all data analyses.

Note: NC is Not Calculated.

Note: All events are ischemia-driven.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Angiographic Secondary Endpoint

In-stent LL at 240 days was lower in the XIENCE V 4.0 mm arm, 0.12 ± 0.34 mm, compared to the TAXUS RCT arm, 0.30 ± 0.53 mm, representing 60% reduction. In-stent %DS was lower in the XIENCE V 4.0 mm arm, $4.78 \pm 13.20\%$ compared to the TAXUS RCT arm $10.30 \pm 21.43\%$. Distal LL and Proximal LL were similar for both arms. In-segment %DS was lower in the XIENCE V 4.0 mm arm, $17.92 \pm 10.83\%$, compared to the TAXUS RCT arm, $22.82 \pm 16.35\%$. In-stent ABR was lower in the XIENCE™ V 4.0 mm arm, 0.0%, compared to the TAXUS RCT arm, 5.7%. In-segment ABR was lower in the XIENCE V 4.0 mm arm, 2.0%, compared to the TAXUS RCT arm, 8.9%. No aneurysm and persisting dissections were reported through 240 days. A summary of key angiographic data at 240 days is presented in Table 6-33.

Table 6-33 Summary of Angiographic Endpoints, 4.0 mm arm (ITT)

Measurement	XIENCE V 4.0 mm Arm (N=49) (M=49)	TAXUS RCT (N=134) (M=158)	Difference [95% CI]
240-Day Angiographic Endpoints- All-Lesions Analysis			
In-Segment Late Loss Mean ± SD (m)	0.17 ± 0.38 (49)	0.26 ± 0.46(158)	-0.09 [-0.22, 0.04]
In- Stent Late Loss Mean ± SD (m)	0.12 ± 0.34 (49)	0.30 ± 0.53 (158)	-0.18 [-0.31, -0.06]
Proximal Late Loss Mean ± SD (m)	0.19 ± 0.38 (46)	0.20 ± 0.41 (134)	-0.01 [-0.14, 0.12]
Distal Late Loss Mean ± SD (m)	0.10 ± 0.32 (46)	0.10 ± 0.37 (154)	-0.00 [-0.11, 0.11]
In-Stent % DS Mean ± SD (m)	4.78 ± 13.20 (49)	10.30 ± 21.43 (158)	-5.51 [-10.54, -0.49]
In-Segment % DS Mean ± SD (m)	17.92 ± 10.83 (49)	22.82 ± 16.35 (158)	-4.90 [-8.90, -0.90]
Proximal %DS Mean ± SD (m)	10.22 ± 10.98 (49)	11.04 ± 13.21 (143)	-0.81 [-4.62, 2.99]
Distal %DS Mean ± SD (m)	9.18 ± 6.99 (48)	10.24 ± 11.37 (155)	-1.05 [-3.75, 1.64]
In-Stent ABR	0.0 % (0/49)	5.7% (9/158)	-5.70% [Assump. not met]
In-Segment ABR	2.0% (1/49)	8.9% (14/158)	-6.82% [Assump. not met]
Proximal ABR	2.0 % (1/49)	2.8 % (4/143)	-0.76% [Assump. not met]
Distal ABR	0.0% (0/48)	1.3% (2/155)	-1.29% [Assump. not met]
In-Stent MLD Mean ± SD (m)	3.36 ± 0.46 (49)	2.45 ± 0.65 (158)	0.91 [0.74, 1.07]
In-Segment MLD Mean ± SD (m)	2.91 ± 0.51 (49)	2.12 ± 0.60 (158)	0.79 [0.62, 0.96]
Proximal MLD Mean ± SD (m)	3.42 ± 0.59 (49)	2.70 ± 0.57 (143)	0.73 [0.53, 0.92]
Distal MLD Mean ± SD (m)	3.20 ± 0.48 (48)	2.39 ± 0.54 (155)	0.80 [0.64, 0.97]
Aneurysm	0.0% (0/49)	0.0% (0/158)	0.00% [Assump. not met]
Persisting Dissection	0.0% (0/49)	0.0% (0/157)	0.00% [Assump. not met]

Note: N is the total number of subjects; M is the total number of lesions.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

IVUS Secondary Endpoint

The SPIRIT III protocol did not require subjects enrolled in the 4.0 mm arm to have an IVUS follow up.

Adverse Reactions and Complications

All adverse events (AEs) reported by the subject, observed by the Investigator, or documented in medical records were listed on the adverse event or serious adverse event case report forms. All pre-existing medical conditions were recorded on baseline case report forms. Starting with device implant, any new event/experience that was not present at baseline, or worsening of an event present at baseline, was considered an adverse event.

Myocardial Infarction (MI)

Myocardial infarctions were categorized as Q-wave (development of new, pathological Q-wave on the ECG) and non-Q-wave (elevation of CK levels to greater than two times the upper limit of normal and elevated CK-MB in the absence of new pathological Q-waves). All myocardial infarctions, including the relationship of the event to the target lesion, were adjudicated by the CEC. Culprit lesion information from the angiographic core lab was provided to the CEC if an angiogram was available; all infarcts that could not be clearly attributed to a vessel other than the target vessel were considered related to the target vessel.

A total of 3 myocardial infarctions were reported in 3 subjects through 284 days post-procedure in the XIENCE V 4.0 mm arm. No additional myocardial infarctions occurred between 285 days and 393 days post procedure.

Stent Thrombosis

The CEC adjudicated all cases of stent thrombosis for confirmation and outcome. For those cases where an angiogram was available, the angiographic core laboratory provided information to the CEC regarding the culprit lesion containing the thrombus.

Stent thrombosis was defined as clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (thrombus within or adjacent to the treated target lesion), or in the absence of angiography, any unexplained death or acute MI in the distribution of the target lesion within 30 days of the index procedure. Stent thrombosis was categorized as acute (≤ 1 day), subacute (> 1 day to ≤ 30 days), or late (> 30 days) relative to the index procedure.

A total of one acute stent thrombosis was reported through 284 days post-procedure in the XIENCE V 4.0 mm arm. No additional late stent thrombosis event occurred between 285 days and 393 days post procedure.

Ischemia Driven Target Lesion Revascularization (TLR)

The angiographic core laboratory reviewed all angiograms (protocol required and symptom-driven) and assessed the relationship of any revascularizations to the target lesion, target vessel/non-target lesion, or non-target vessel. The CEC determined whether the revascularization was ischemia-driven or non-ischemia driven. Ischemia-driven TLR was defined as revascularization at the target lesion associated with:

- A) a positive functional ischemia study, or
- B) ischemic symptoms and $\geq 50\%$ stenosis by QCA, or
- C) $\geq 70\%$ stenosis by QCA without either ischemic symptoms or a positive functional study.

A total of one (1) ischemia-driven TLR case done by PCI was reported through 284 days post-procedure in the XIENCE V 4.0 arm. There were no non-ischemia-driven TLR cases. No additional ischemia driven TLR events occurred between 285 days and 393 days post

procedure.

Ischemia Driven Target Vessel Revascularization (TVR), Non-Target Lesion

The angiographic core laboratory reviewed all angiograms (protocol required and symptom-driven indicated) and assessed the relationship of any revascularizations to the target lesion, target vessel/non-target lesion, or non-target vessel. The CEC determined whether the revascularization was ischemia driven or non-ischemia driven. Ischemia driven TVR was defined as revascularization at the target vessel associated with:

- A) a positive functional ischemia study, or
- B) ischemic symptoms and $\geq 50\%$ stenosis by QCA, or
- C) $\geq 70\%$ stenosis by QCA without either ischemic symptoms or a positive functional study.

There were no ischemia-driven, or non-ischemia-driven, non-target-lesion TVR reported in XIENCE V 4.0 mm subjects through the 284 days post-procedure. No additional ischemia driven TVR events occurred between 285 days and 393 days post procedure.

Vascular and Bleeding Complications

Cerebrovascular Accident or Stroke (CVA)

Cerebrovascular events include cerebral infarction (ischemic stroke), intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). All cerebrovascular accidents were adjudicated by the CEC to confirm occurrence and to evaluate the outcome of the event.

There were no cerebrovascular events in the XIENCE V 4.0 mm arm.

Vascular Events

Vascular complications include pseudoaneurysm, arteriovenous fistula, peripheral ischemia or nerve injury. All vascular events were adjudicated by the CEC to confirm occurrence and to evaluate the outcome of the event.

There were no vascular events in the XIENCE V 4.0 mm arm.

Bleeding Events

A bleeding event (e.g., hematoma, access site, GI, or retroperitoneal bleed) was defined as a bleed that required transfusion or surgical repair, or was associated with a hemoglobin drop of more than 5 g/dL. All bleeding events were adjudicated by the CEC to confirm occurrence and to evaluate the outcome of the event.

There was one (1) bleeding event through 284 days post-procedure in the XIENCE V 4.0 mm arm. No additional bleeding events occurred between 285 days and 393 days post procedure.

Deaths

Cardiac death was defined as any death for which a cardiac cause could not be excluded.

The event included, but was not limited to AMI, cardiac perforation/pericardial tamponade, arrhythmia, or conduction abnormality, CVA within 30 days of the procedure or CVA suspected of being related to the procedure, death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery. All deaths were adjudicated by the CEC. Deaths that could not be clearly attributed to another cause were considered cardiac deaths.

One death was reported in the XIENCE V 4.0 mm arm through 284 days post-procedure. This death was adjudicated by the CEC as a cardiac death. No additional deaths occurred between 284 days and 393 days post procedure.

Subject Discontinuation

The reasons for discontinuation for the 4.0 mm arm were categorized based on input from the sites as follows:

- Subject withdrawal of consent
- Subject termination by Investigator (deemed medically necessary)
- Subject lost to follow-up
- Subject follow-up terminated by sponsor
- Subject follow-up terminated by regulatory agency
- Other reason to be specified

Withdrawn/ Lost to Follow-Up

Of the 69 subjects enrolled into the 4.0 mm arm, 1 subject terminated prior to 270 days follow up as shown in Table 6-34.

Table 6-34 Early Termination (Intent-To-Treat Population)

	XIENCE V 4.0 mm Arm (N=69)
Early Termination at 30-Day Visit ¹	
Subject Withdrawal	0
Subject Lost to Follow-up	0
Early Termination at 180-Day Visit ²	
Subject Withdrawal	0
Subject Lost to Follow-up	1
Early Termination at 270-Day Visit ³	
Subject Withdrawal	0
Subject Lost to Follow-up	0
Total	1

¹Early Termination at 30-Day Visit is defined as the termination of study occurred before 23 days after index procedure.

²Early Termination at 180-Day Visit is defined as the termination of study occurred on or after 23 days and before 166 days after index procedure.

³ Early Termination at 270-Day Visit is defined as the termination of study occurred on or after 166 days and before 256 days after index procedure.

Protocol Deviations

Protocol deviations were recorded in the clinical trial database and classified as major or minor by the sponsor. A major deviation is a deviation which may potentially compromise subject health, welfare or safety or which may potentially significantly affect data. Major deviations were those involving subject unblinding, or follow-up visits within 270 days conducted by non-blinded personnel (with subject blind maintained), eligibility criteria deviations, treatment rule deviations, and omission of informed consent. A minor deviation was any protocol deviation not classified as major. Minor protocol deviations were primarily those involving protocol required medications, follow up and assessments not done, not done per protocol or done outside the protocol required window.

The protocol deviation management committee met regularly to evaluate each deviation reported and corrective actions were implemented to address the deviations as per the sponsor's protocol deviation procedures and documents in the protocol deviation committee meeting minutes.

Study Conclusion

In the SPIRIT III 4.0 mm clinical non-randomized arm, the XIENCE V EECSS has shown non-inferiority to TAXUS PECSS in terms of the primary endpoint, in-segment LL at 240 days ($p < 0.0001$) with a margin (delta) of 0.195 mm. In this interim analysis of 69 subjects, 49 subjects (71%) had angiographic follow up, slightly lower than the angiographic follow up rate in the SPIRIT III RCT (77%). In-segment LL at 240 days was 0.17 ± 0.38 mm for the XIENCE V 4.0 mm arm and 0.28 ± 0.48 mm for the TAXUS RCT arm ($p < 0.0001$). The difference between the two arms ($0.17 \text{ mm} - 0.28 \text{ mm} = -0.11 \text{ mm}$) represents a 39% reduction in in-segment LL in the XIENCE V 4.0 mm arm compared to the TAXUS RCT arm. Therefore, the null hypothesis was rejected proving that XIENCE V EECSS is non-inferior to TAXUS PECSS for in-segment LL at 240 days (p -value < 0.0001). These results are consistent with what was observed in the RCT for the primary endpoint of in-segment LL: 0.14 ± 0.41 for the XIENCE V group in the RCT, and 0.17 ± 0.38 for the 4.0 mm arm.

Furthermore, the XIENCE V 4.0 mm arm showed non-inferiority to the TAXUS RCT arm in terms of 284 day TVF rate (5.9% vs. 9.0%, p -value = 0.025) with a one-sided alpha of 0.05. The per subject analysis ischemia driven TLR-free rate, to 284 days, was higher in the XIENCE V 4.0 mm arm, 98.5%, compared to the TAXUS RCT arm, 95.0%. The MACE rate, through 284 days, was lower for the XIENCE V 4.0 mm arm, 5.9% compared to the TAXUS RCT arm, 8.1%. The late stent thrombosis rates in the two treatment arms were low and similar with rates in the XIENCE V 4.0 mm arm and TAXUS RCT arm, of 0.0% and 0.0%, respectively.

In this trial, the 4.0 mm arm had a mean vessel diameter of 3.53 ± 0.36 (69) for XIENCE V while the TAXUS arm had a mean vessel diameter of 2.77 ± 0.46 (382). The better outcome for the 4.0 group could have been associated with the treatment of larger diameter vessels; however, comparing the outcomes for the 4.0 group with the outcomes of the

XIENCE V RCT group does not reveal any effects associated with vessel diameter.

Therefore, 240 day angiographic endpoint results and clinical endpoint results through 284 days have demonstrated the safety and effectiveness of the 4.0 mm diameter XIENCE V EECSS.

6.5 Descriptive Summary of SPIRIT Clinical Pharmacology

Executive Summary

The pharmacokinetics (PK) of everolimus eluted from the XIENCE V Everolimus Eluting Coronary Stent (EECS) has been evaluated in three different substudies in three different geographies. Two of the substudies were conducted as part of the SPIRIT III trial (protocol 03-360). The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the US randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The SPIRIT III clinical trial arms/studies, including the stent diameters and lengths provided for the study and geographies is presented in Table 6-35.

Table 6-35 SPIRIT III Clinical Trial Arm/Studies

Trial Arm/Studies	Stent Diameters (mm)	Stent Lengths (mm)	Geography
Randomized	2.5, 3.0, 3.5	8, 18, 28	US
4.0 mm Non-Randomized	4.0	8, 18, 28	US
Pharmacokinetic Substudy*	2.5, 3.0, 3.5, 4.0	8, 18, 28	US
2.25 mm Non-Randomized**	2.25	8, 18, 28	US
38 mm Non-Randomized**	3.0, 3.5, 4.0	38	US
Japan, Non-Randomized	2.5, 3.0, 3.5, 4.0	8, 18, 28	Japan
Japan, Pharmacokinetic Substudy***	2.5, 3.0, 3.5, 4.0	8, 18, 28	Japan

*PK subjects were enrolled from either the randomized portion or 4.0 mm non-randomized arm.

** These non-randomized arms were not initiated.

*** Japanese PK subjects were enrolled from the Japan non-randomized arm.

The third PK substudy was conducted OUS as part of the SPIRIT II trial (protocol 03-364). The SPIRIT II clinical trial arms/studies, including the stent diameters and lengths provided for the study and geographies is presented in Table 6-36.

Table 6-36 SPIRIT II Clinical Trial Arm/Studies

Trial Arm/Studies	Stent Diameters (mm)	Stent Lengths (mm)	Geography
Randomized	2.5, 3.0, 3.5, 4.0	8, 18, 28	OUS
Pharmacokinetic Substudy	2.5, 3.0, 3.5, 4.0	8, 18, 28	OUS

Abbott Vascular is providing global pharmacokinetic data to support the PMA approval of the XIENCE V EECS. This proposal was presented to FDA in a meeting that occurred on November 3, 2005. The global pharmacokinetic data includes a total of 73 subjects. The pharmacokinetic enrollment by study is presented below:

- SPIRIT III US N=17
- SPIRIT III Japan N=17
- SPIRIT II OUS N=39

Abbott Vascular believes that the global pharmacokinetic studies have adequately

characterized the pharmacokinetic profile of everolimus in human whole blood. These studies demonstrated that whole blood concentrations of everolimus increase proportionally to the total stent dose (ranging from 53 to 588 μg). The findings were consistent across studies and geographies.

The pharmacokinetic parameters associated with the elution of everolimus from the XIENCE V EECS were consistent in all three substudies in all three geographies. The C_{max} values ranged from 2.2 ng/ml to 2.7 ng/ml and these values were all associated with the highest dose (total amount) of everolimus administered. These values are also consistent with the C_{max} values seen in preclinical studies.

Dose-normalized C_{max} values were evaluated in comparison to the total stent dose in all three substudies. Across the geographies the evaluation showed that the data were evenly distributed around the median value indicating that the pharmacokinetic parameter, C_{max} , increased proportionally to the total stent dose.

Statistical testing was also done to show consistency between the US and Japanese populations in SPIRIT III. For both populations, more than 50% of the individual values of $\text{AUC}_{0-\infty}$, λ_z , and $t_{1/2, \text{term}}$ could not be determined accurately due to the rapid disappearance of everolimus from blood in subjects. Therefore $\text{AUC}_{0-\infty}$ was rejected as a primary pharmacokinetic parameter in the overall statistical analysis and $\text{AUC}_{0-24\text{h}}$ was used instead.

Based on the ratios of the least square (LS) means from the US and Japanese populations, the C_{max} and $\text{AUC}_{0-24\text{h}}$ values of everolimus determined for the Japanese population were similar to the US population, respectively increased by approximately 17% and 8%. These differences were not statistically significant. The LS mean values of AUC_{0-t} were the same for the US and Japanese populations.

Because there were no statistically significant differences between the primary pharmacokinetic parameters of the US and Japanese populations, a linear regression analysis on the combined primary pharmacokinetic results from both populations against total stent dose was also performed. Taking into account the variability in relation to the sample size, observed for the populations in the US, R^2 values from the combined linear regression were $C_{\text{max}} = 0.582$, $\text{AUC}_{0-24\text{h}} = 0.7125$, $\text{AUC}_{0-t} = 0.5739$ and $\text{AUC}_{0-\infty} = 0.5081$. Although R^2 is influenced by inter-individual variability, the analysis shows that the pharmacokinetic parameters determined for whole blood everolimus in US and Japanese subjects increase proportionally to the total stent dose. These results are similar to the results observed with systemic administration of everolimus where no statistical differences were seen between the US and Japanese populations.

The maximum time to the disappearance of everolimus was 168 hours in all subjects with the exception of one subject in SPIRIT II that still had detectable levels at 720 hours (30 days). In all three geographies, the C_{max} value never reached the minimum therapeutic value of 3.0 ng/ml necessary to be maintained for effective systemic administration to prevent organ rejection. The pharmacokinetic parameters, $t_{1/2, \text{term}}$, AUC_{last} , AUC_{∞} , and CL

could also not be determined accurately because of the rapid disappearance of everolimus from blood in subjects. These types of results have been seen with other drug eluting stents.

The disappearance of everolimus from the circulation after implantation of the XIENCE V EECS should further limit the systemic extent of exposure. Therefore, subjects exposed to the XIENCE V EECS should have limited exposure to the adverse events associated with long term systemic administration of everolimus at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies. Successful local delivery has also been confirmed by in-stent late loss values in the SPIRIT II clinical study. The SPIRIT II study evaluated the pharmacokinetic profile of everolimus and demonstrated the safety and effectiveness of the XIENCE V EECS when compared to TAXUS PECSS.

The pharmacokinetic profile for everolimus eluted from the XIENCE V EECS is consistent across all geographies. The pharmacokinetic profile in clinical trials of the XIENCE V EECS is consistent with the pre-clinical profile. The local arterial delivery and limited systemic exposure provide the opportunity for successful treatment of coronary lesions with limited risk associated with systemic exposure.

Preclinical *In Vivo* Pharmacokinetic Studies

Preclinical pharmacokinetic studies were conducted in *in vivo* porcine models to determine: 1) the release rate of everolimus from the XIENCE V EECS; 2) the tissue concentrations of everolimus over time; and 3) the impact, if any, of systemic maximum dose everolimus on platelet function. The tissues that were evaluated include blood, the stented artery, the artery 5 mm proximal and 5 mm distal to the stented artery, myocardium subjacent to the stented artery, myocardium distal to the stented artery, spleen, lung, liver, and both kidneys.

The preclinical pharmacokinetic data using stents coated with 100 $\mu\text{g}/\text{cm}^2$ of everolimus demonstrate that everolimus is delivered to the arterial wall in a controlled reproducible manner. Approximately 80% of the drug is released during the first 28 days post stenting. Everolimus levels are maintained at approximately 0.5 – 2 ng/mg in the arterial wall for the first month following deployment of the stent with low levels of drug distributing to the myocardium and peripheral organs. The peak levels of everolimus detected (at 30 minutes post stenting) in blood in the systemic circulation ($C_{\text{max}} = 1.67 \text{ ng/mL}$) are low and should be considered safe since the level is far less than the minimum therapeutic concentration necessary to prevent organ transplant rejection when everolimus is delivered orally (see the Therapeutic Concentration Range section). No adverse effects on platelet function, as evaluated by performing two coagulation assays and platelet counts at baseline and at predetermined endpoints, were seen with exposure to maximum dose everolimus.

Systemic Administration to Subjects

The information in the General Clinical Pharmacokinetics and Therapeutic Concentration Range sections has been excerpted from the Certican® Investigators' Brochure, Edition 9, dated August 27, 2007. The information is presented as a reference for the pharmacokinetic behavior of everolimus as administered for therapeutic effect in the treatment of transplant rejection.

General Clinical Pharmacokinetics

Absorption: Following oral administration, everolimus is rapidly absorbed with a median time to peak concentration of 1 hour after single doses in healthy subjects and 2 hours after multiple doses in organ transplant subjects. Both C_{max} and AUC are dose-proportional over the range tested in organ transplantation of 0.5 to 2 mg bid.

Distribution: Whole blood everolimus concentrations are 76% to 83% partitioned into red blood cells. The mean apparent distribution volume after single doses in renal transplant subjects was 4.7 L/kg. Protein binding was 74% in human plasma.

Metabolism: Everolimus is a substrate for both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein. The main metabolic pathways identified in man are mono-hydroxylations and O-dealkylations. Two main metabolites are formed by hydrolysis of the cyclic lactone. Everolimus is the main circulating component in blood. None of the main metabolites contributes significantly to the immunosuppressive activity of everolimus.

Excretion: After a single dose of [^{14}C] everolimus in renal transplant subjects, the majority (80%) of radioactivity was recovered in the feces, and only a minor amount (5%) was excreted in the urine. Systemic half life values were approximately 30 hours depending on the population studied.

Ethnicity: The influence of ethnicity on everolimus disposition was assessed in a population PK analysis of 673 renal transplant subjects from the pooled Phase 3 studies. Additionally, single-dose escalation was performed in healthy Japanese subjects. No significant difference in CL/F was detected for Japanese subjects (n = 17) in the population analysis. In the study in Japanese subjects, the dose-AUC relationship was similar to that in Caucasians. In the population analysis, Blacks (n = 65) had an average 20% higher oral CL/F, and may therefore need a higher everolimus dose to achieve similar systemic exposure as non-Black subjects.

Therapeutic Concentration Range

In both renal and heart transplantation, everolimus trough concentrations ≥ 3 ng/mL were associated with a significantly lower *acute rejection rate* compared with trough levels < 3 ng/mL. There was a minor further reduction in the acute rejection rate at everolimus trough levels of > 8 ng/mL. Based on exposure-efficacy and exposure-safety analysis, the recommended therapeutic range is 3 to 8 ng/mL. Exposure to blood concentrations

greater than 12 ng/mL has not been studied.

With respect to systemic effects, orally administered everolimus has been evaluated in clinical trials in the US and Europe for use in conjunction with other medications to prevent transplant rejection. Everolimus (Certican) has received market approval in over 60 countries. Additionally, Everolimus (Certican) is under review for market approval in the United States. Novartis has received two approvable letters and is currently conducting additional clinical studies to support dose recommendations with eucopenia in kidney and heart transplantation. Per FDA's recommendations, Novartis intends to submit data from on-going clinical studies for FDA review. When used for prevention of transplant rejection, the following adverse events were noted in clinical trials and appear in the Certican[®] labeling: abdominal pain, acne, anemia, coagulopathy, diarrhea, edema, hemolysis, hypercholesterolemia, hyperlipidemia, hypertension, hypertriglyceridemia, hypogonadism male, eucopenia, liver function test abnormal, lymphocele, myalgia, nausea, pain, pneumonia, pyelonephritis, rash, renal tubular necrosis, sepsis, surgical wound complication, thrombocytopenia, urinary tract infection, viral, bacterial and fungal infections, vomiting, wound infection.⁹

The subjects that reported the adverse events were receiving Certican doses of either 1.5 mg/day or 3.0 mg/day for at least 12 months together with cyclosporine and corticosteroids. The total dose of everolimus on a single XIENCE V EECS as represented by the 3.0 x 18 mm is less than one tenth of the recommended starting oral dose in renal transplant subjects. Additionally, transplant subjects took everolimus for an extended period of time to maintain the minimum therapeutic blood concentration of 3 ng/mL.

Overview of Clinical Trials

The SPIRIT III clinical trial is designed to evaluate the safety and effectiveness of the XIENCE V EECS following the treatment of subjects with up to two *de novo* lesions in native coronary arteries. The SPIRIT III study consisted of a randomized clinical trial (RCT) in the US and two concurrent non-randomized arms, a 4.0 mm registry (N=80) and a Japanese registry (N=88). The RCT was a blinded, active controlled study that enrolled 1,002 subjects (2:1 randomization XIENCE V EECS : TAXUS EXPRESS² PECS) at 62 US sites. The SPIRIT II clinical trial is a randomized, blinded, active controlled, multi-center clinical trial. A total of 300 subjects (3:1 randomization, XIENCE V EECS : TAXUS EXPRESS² PECS) were enrolled in the study at 31 sites outside the United States (OUS). Table 6-37 summarizes the design features of the SPIRIT III and SPIRIT II Clinical Trials.

⁹ Summary of Product Characteristics. Novartis Pharmaceuticals Corporation. Release date: 13 June 2002 (internal document).

Table 6-37 Summary of SPIRIT Trials

	SPIRIT III (PIVOTAL US/Japan)		SPIRIT II (Supportive, OUS)
	RCT	Registries	
Study Type/Design	Multi-center Randomized Single-blinded Active Control	Multi-center Single-arm Open-label	Multi-center Randomized Single-blinded Active Control
Planned Number of Subjects	Total: 1,002 XIENCE™ V: 668 TAXUS®: 334	4.0 mm: 80 Japan: 88	Total: 300 XIENCE™ V: 225 TAXUS®: 75
Treatment	Up to two <i>de novo</i> lesions in different epicardial vessels	Up to two <i>de novo</i> lesions in different epicardial vessels	Up to two <i>de novo</i> lesions in different epicardial vessels
Lesion Size	RVD: $\geq 2.5 \leq 3.75$ mm Length: ≤ 28 mm	4.0 mm RVD: $> 3.75 \leq 4.25$ mm Length: ≤ 28 mm Japan RVD: $\geq 2.5 \leq 4.25$ mm Length: ≤ 28 mm	RVD: $\geq 2.5 \leq 4.25$ mm Length: ≤ 28 mm
XIENCE™ V EECS sizes	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm Planned overlapping allowed to cover lesions > 22 mm throughout SPIRIT III trial	4.0 mm Diameter: 4.0 mm Length: 8, 18, 28 mm Japan Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm Planned overlapping allowed to cover lesions > 22 mm
Post-procedure Antiplatelet Therapy	Clopidogrel 6 months (or ticlopidine per site standard) Aspirin 5 years	4.0 mm: same as RCT Japan: Ticlopidine 3 months and Aspirin 5 years	Clopidogrel 6 months (or ticlopidine per site standard) Aspirin 1 year
Primary Endpoint	In-segment late loss@240-day	In-segment late loss@240-day	In-stent late loss@180-day
Major Secondary Endpoint	ID-TVF @270-day	None	None
Clinical Follow-up	30, 180, 240, 270 days, 1 to 5 years	30, 180, 240, 270 days, 1 to 5 years	30, 180, 270 days, 1 -5 years
Angiographic Follow-up	240 days (N=564)	240 days (All registry)	180-day (all), 2-year (N=152)
IVUS Follow-up	240 days (N=240)	240 days (Japan only)	180-day, 2-year (N=152)
PK Study	US: Min 15 subjects with single lesion, max 20 with dual lesions Japan: Min 10 subjects with single lesion, max 20 with dual lesions		Min 15 subjects with single lesion, max 20 with dual
PK Sampling Times (Identical in SPIRIT III & II)	Prior to 1 st stent implant, 10, 30 minutes, 1, 2, 4, 6, 12, 24, 36, 48, 72, 168, and 720 hours (30 days)		

Design of the Pharmacokinetics Program

Pharmacokinetic substudies were designed to evaluate the elution of everolimus from the XIENCE V EECS in three different geographies. Subjects enrolled at pre-specified sites in the SPIRIT III and SPIRIT II studies were invited to participate in the pharmacokinetic substudy. Planned subject numbers in each region were as follows.

US (SPIRIT III RCT and 4.0 mm Registry)

- Minimum 15 subjects with single vessel/lesion treatment
- Up to 20 subjects with dual vessel/lesion treatment

Japan (SPIRIT III Japan Registry)

- Minimum 10 subjects with single vessel/lesion treatment
- Up to 20 subjects with dual vessel/lesion treatment

OUS (SPIRIT II)

- Minimum 15 subjects with single vessel/lesion treatment
- Up to 20 subjects with dual vessel/lesion treatment

Venous blood was scheduled to be drawn at baseline (prior to 1st stent implant), and at 10, 30 minutes, and at 1, 2, 4, 6, 12, 24, 36, 48, 72, 168 and 720 hours (30 days) post-stent implantation. Deployment time of the final stent was used for the 0 hour.

Whole blood samples were temporarily stored at -30°C or lower at investigational sites and were shipped to a Central Pharmacokinetic Core Laboratory (CRL Medinet, the Netherlands), regardless of the study region. The methodology for everolimus extraction from whole blood and LC-MS/MS analysis was prepared and provided by the Pharmacokinetic Core Laboratory. The pharmacokinetic analysis of the everolimus blood concentration-time data using non-compartmental methods was conducted by using WinNonlin Professional Version 4.1 (Pharsight Corporation, Mountain View, CA, USA) by Kinesis Pharma B. V., the Netherlands

SPIRIT III PK Substudy (US RCT)

The purpose of the pharmacokinetic substudy was to determine the pharmacokinetics of everolimus delivered from the XIENCE V EECS in the US RCT. All subjects were screened per the protocol inclusion and exclusion criteria. Enrolled subjects who volunteered to participate in the pharmacokinetic substudy had blood drawn prior to the first stent implant, and at 10, 30 minutes, and at 1, 2, 4, 6, 12, 24, 36, 48, 72, 168 and 720 hours (30 days) after completion of implantation of the last stent (14 sampling points).

The nominal doses of everolimus delivered by the XIENCE V EECS size are shown in Table 6-38.

Table 6-38 XIENCE V Sizes and Nominal Total Doses of Everolimus Per Stent

Stent Diameter (mm)	Stent Length (mm)	Drug Dose (µg)
2.5, 3.0	8	37
2.5, 3.0	18	88
2.5, 3.0	28	132
3.5, 4.0	8	53
3.5, 4.0	18	113
3.5, 4.0	28	181
3.0	38	183
3.5, 4.0	38	242

Subjects who satisfied all clinical and angiographic inclusion/exclusion criteria were eligible to participate in the pharmacokinetic substudy if they volunteered and were randomized to XIENCE V.

Follow-up and Data Assessment: Subjects enrolled in the pharmacokinetics substudy were scheduled to have blood drawn prior to the first stent implant, and at 10, 30 minutes,

and at 1, 2, 4, 6, 12, 24, 36, 48, 72, 168 and 720 hours (30 days) after completion of implantation of the last stent (14 sampling points) in addition to all protocol required follow-ups.

Study Endpoints: The pharmacokinetic parameters of everolimus were determined from subjects receiving XIENCE V in the US RCT. The pharmacokinetic analysis of the everolimus blood concentration-time data using non-compartmental methods was conducted by using WinNonlin Professional Version 4.1 (Pharsight Corporation, Mountain View, CA, USA). Actual blood pharmacokinetic sample collection times were used in the pharmacokinetic analysis.

Everolimus blood concentrations below the quantifiable limit (BQL) prior to the first measurable concentration were considered to be equal to zero when conducting the pharmacokinetic analysis. Concentrations BQL were excluded from pharmacokinetic analysis if the value followed the last measurable concentration during the sample collection period or if the value was embedded between two adjacent quantifiable values.

Values for the following everolimus pharmacokinetic parameters were calculated by a standard non-compartment analysis:

- The maximum observed blood concentration (C_{\max})
- The first time of occurrence of C_{\max} (t_{\max}) was the actual observed values
- The terminal phase rate constant (λ_z) was estimated from log-linear regression analysis of the terminal phase of the blood concentration-time profile. The associated apparent terminal phase half-life ($t_{1/2}$) was calculated as $t_{1/2} = \ln 2 / \lambda_z$
- The area under the blood concentration versus time curve from time zero to 24 hours ($AUC_{(0-24)}$), the area under the blood concentration versus time curve from time zero to the time of the last quantifiable concentration ($AUC_{(0-t)}$) and extrapolated to infinite time ($AUC_{(0-\infty)}$) were calculated by a combination of linear and logarithmic trapezoidal methods. The linear method was employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method was used for those arising from decreasing concentrations. The percentage of $AUC_{(0-\infty)}$ obtained by extrapolation ($\%AUC_{\text{ex}}$) was calculated as $(AUC_{(0-\infty)} - AUC_{(0-t)}) / AUC_{(0-\infty)} * 100$. $AUC_{(0-24\text{h})}$ was also calculated.
- The total blood clearance (CL)

Data was summarized by dose based upon the number and size of stents implanted (Table 6-40). The results were expressed as means and standard deviations determined for each dose group. Pharmacokinetic correlations were evaluated by linear regression analysis.

Results (SPIRIT III PK Substudy, US RCT)

Subject Enrollment and Disposition: A total of 17 subjects who provided signed informed consent were randomized and enrolled into the pharmacokinetic substudy at 5 US investigational sites between June 22, 2005 and March 15, 2006. Table 6-39 presents the demographic characteristics of the population involved in the sub-study in comparison

with the overall population in the RCT (Randomized Controlled Trial). As demonstrated in Table 6-39, the characteristics of the sub-study participants are similar to the characteristics of the entire population that participated in the RCT.

Table 6-39 Key Demographics, Physical Measurements and Risk Factors – Per-Subject Analysis (Intent-To-Treat Population) (SPIRIT III PK Subgroup vs. RCT)

	PK US (N=17)	RCT (N=1002)
Age (year)		
Mean ± SD (n)	62.44 ± 9.51 (17)	63.08 ± 10.43 (1001)
Median	61.95	62.92
(Q1, Q3)	(55.74, 67.05)	(55.32, 70.84)
Range (min, max)	(47.95, 79.61)	(31.59, 90.64)
[95% Confidence Interval] ¹	[57.55, 67.33]	[62.44, 63.73]
Male Subjects	70.6% (12/17)	68.6% (687/1001)
[95% Confidence Interval] ¹	[44.04%, 89.69%]	[65.66%, 71.50%]
Height (cm)		
Mean ± SD (n)	167.0 ± 9.8 (17)	171.7 ± 10.1 (987)
Median	165.0	173.0
(Q1, Q3)	(163.0, 170.0)	(165.0, 180.0)
Range (min, max)	(150, 185)	(142, 196)
[95% Confidence Interval] ¹	[161.9, 172.1]	[171.1, 172.4]
Weight (kg)		
Mean ± SD (n)	88.1 ± 19.4 (17)	90.4 ± 19.0 (988)
Median	90.0	89.0
(Q1, Q3)	(79.0, 101.0)	(77.0, 102.0)
Range (min, max)	(54, 118)	(42, 167)
[95% Confidence Interval] ¹	[78.1, 98.0]	[89.2, 91.6]
Body Mass (kg/m ²)		
Mean ± SD (n)	31.71 ± 8.12 (17)	30.54 ± 5.91 (987)
Median	31.07	29.76
(Q1, Q3)	(26.48, 33.28)	(26.49, 33.58)
Range (min, max)	(21.29, 50.92)	(12.36, 54.98)
[95% Confidence Interval] ¹	[27.53, 35.89]	[30.17, 30.91]
Current Tobacco Use	29.4% (5/17)	23.1% (227/983)
[95% Confidence Interval] ²	[10.31%, 55.96%]	[20.49%, 25.86%]
Diabetes Mellitus	29.4% (5/17)	29.0% (290/999)
[95% Confidence Interval] ²	[10.31%, 55.96%]	[26.23%, 31.95%]
Diabetes Mellitus Requiring Medication	23.5% (4/17)	25.4% (254/999)
[95% Confidence Interval] ²	[6.81%, 49.90%]	[22.75%, 28.25%]
Hypertension Requiring Medication	82.4% (14/17)	75.5% (755/1000)
[95% Confidence Interval] ²	[56.57%, 96.20%]	[72.71%, 78.14%]
Hypercholesterolemia Requiring Medication	58.8% (10/17)	73.3% (722/985)
[95% Confidence Interval] ²	[32.92%, 81.56%]	[70.42%, 76.04%]
All Prior Cardiac Intervention	29.4% (5/17)	31.4% (313/998)
[95% Confidence Interval] ²	[10.31%, 55.96%]	[28.49%, 34.34%]
Prior Cardiac Intervention on Target Vessel(s)	12.5% (2/16)	10.8% (106/981)
[95% Confidence Interval] ²	[1.55%, 38.35%]	[8.93%, 12.92%]
MI within 2 Months	0.0% (0/17)	2.7% (26/979)
[95% Confidence Interval] ²	[0.00%, 19.51%]	[1.74%, 3.87%]

¹ By normal approximation.

² By Clopper-Pearson exact confidence interval.

The number of stents placed per subject varied between 1 and 2. The total dose of everolimus received by subjects ranged from 53 to 181 µg. Table 6-40 presents the distribution of treatments received.

Table 6-40 Total Stent Dose of Everolimus Received by SPIRIT III Subjects, US

Total stent dose (μg)	53	88	113	132	141	176	181
# stents	1	1	1	1	2	2	1
# subjects	1	3	2	2	1	2	6**

** One subject was not evaluated at all time points

All 17 subjects were treated for single-vessel disease. The two subjects in the 176 μg group received two overlapping 3.0 x 18 mm stents. The one subject in the 141 μg group received a 2.5 x 18 mm stent and a 3.5 x 8 mm stent as a bailout.

Pharmacokinetics: The last time point up to which whole blood concentrations could be quantified ranged from 12 to 168 hours after implantation of the last stent. Everolimus was not detectable in any samples at 30 days post implantation.

Across all dose levels individual t_{max} values ranged from 0.07 to 1.88 hours. Individual C_{max} ranged from 0.17 to 2.40 ng/mL. $\text{AUC}_{0-24\text{h}}$ values ranged from 2.907 to 16.35 ng.h/mL. AUC_{0-t} values ranged from 2.345 to 48.75 ng.h/mL. Table 6-41 presents those subject groups (88 μg and 181 μg) with a sample size greater than two.

Terminal half-life varied with the ability to quantify everolimus in the blood and ranged from 18 to 165 hours. However, terminal half-life could not be characterized accurately in any subject. As a result $\text{AUC}_{0-\infty}$ and CL are provided as estimates

Table 6-41 Pharmacokinetic Parameters of Everolimus

<i>Pharmacokinetics of everolimus</i> (mean \pm SD, t_{max} : median (range))	88 μg	181 μg
n	3 ^b	6 ^c
t_{max} , h	0.50 (0.50 - 1.88)	0.50 (0.07 - 1.00)
C_{max} , ng/mL	0.3867 \pm 0.09866	1.175 \pm 0.6817
$\text{AUC}_{0-24\text{h}}$, ng.h/mL	3.458 \pm 0.1981	9.601 \pm 4.015
AUC_{0-t} , ng.h/mL	5.319 \pm 4.114	23.73 \pm 13.63
$\text{AUC}_{0-\infty}$, ng.h/mL ^a	-	44.00 \pm 28.67
$t_{1/2\text{term}}$, h ^a	-	79.08 \pm 57.24
CL, L/h ^a	-	5.130 \pm 2.114

^a Accurate determination not possible

^b n = 2 for $\text{AUC}_{0-24\text{h}}$

^c n = 5 for $\text{AUC}_{0-24\text{h}}$ and n = 4 for $\text{AUC}_{0-\infty}$, $t_{1/2\text{term}}$ and CL

Dose-normalized C_{max} is shown here plotted versus total dose (see Figure 6-6). Across the entire dosing range (53 to 181 μg) the plots show that the data are evenly distributed around the median value indicating that the pharmacokinetic parameters determined for whole blood everolimus increase proportionally to the total dose (see Figure 6-6).

Considering the variability in relation to the sample size, the R^2 values for linear regression against total dose were $C_{\text{max}} = 0.4235$, $\text{AUC}_{0-24\text{h}} = 0.4295$, $\text{AUC}_{0-t} = 0.4281$ and $\text{AUC}_{0-\infty} = 0.4597$.

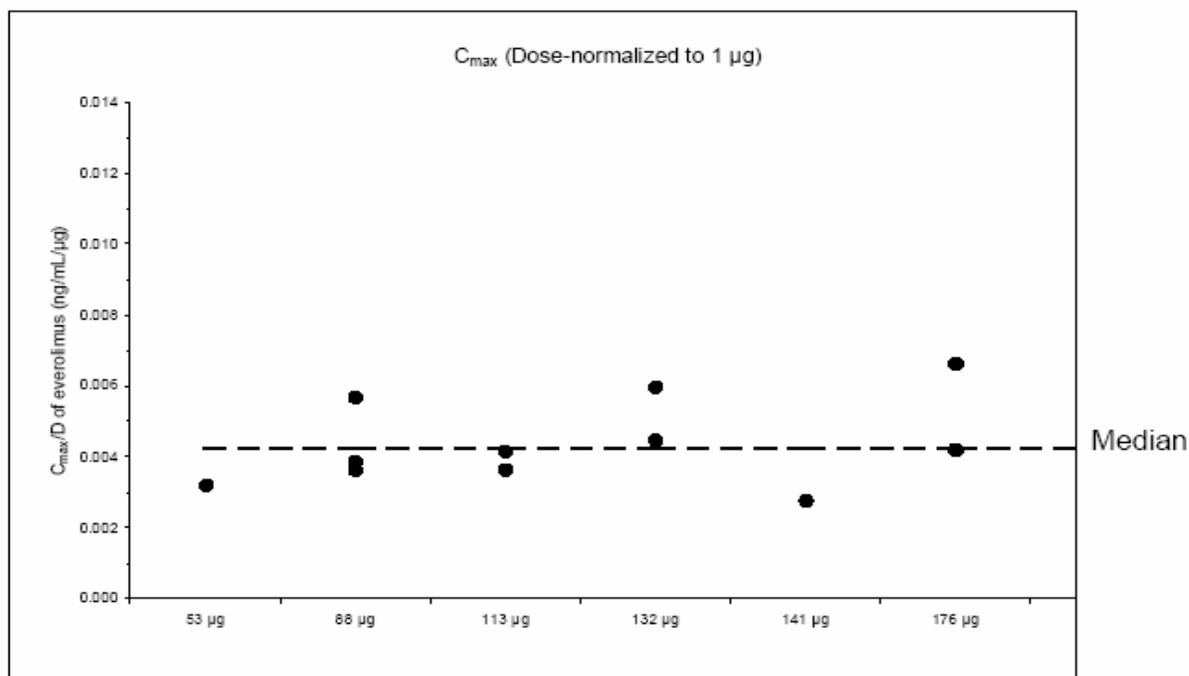


Figure 6-6 C_{max} Normalized by Dose

The results of this substudy demonstrate that whole blood concentrations of everolimus increase proportionally to the total dose (ranging from 53 to 181 µg). Individual t_{max} values ranged from 0.07 and 1.88 hours, with a median value of about 0.5 hour and were not dependent on dose. Individual C_{max} values ranged from 0.17 to 2.40 ng/mL. AUC_{0-24h} values ranged from 2.097 to 16.35 ng.h/mL. AUC_{0-last} values ranged from 2.345 to 48.75 ng.h/mL. The last time point up to which whole blood concentrations could be quantified ranged from 12 to 168 hours after implantation of the last stent. Everolimus was not detectable in any samples at 30 days post implantation. Terminal half-life could not be characterized accurately. These results suggest that everolimus eluted from the XIENCE™ V EECS provides limited systemic exposure.

SPIRIT III Pivotal Clinical Trial, (Japan Registry)

The purpose of the pharmacokinetic substudy was to determine the pharmacokinetics of everolimus delivered by the XIENCE V EECS in the Japanese arm of the SPIRIT III trial. All subjects were screened per the protocol inclusion and exclusion criteria. Enrolled subjects who volunteered to participate in the pharmacokinetic substudy had blood drawn prior to the first stent implant, and at 10, 30 minutes, and at 1, 2, 4, 6, 12, 24, 36, 48, 72, 168 and 720 hours (30 days) after completion of implantation of the last stent (14 sampling points). The methodologies for the conduct of the Japan pharmacokinetic study were the same as the US trial.

Data was summarized by dose based upon the number and size of stents implanted (Table

6-42). The results were expressed as means and standard deviations determined for each dose group. Pharmacokinetic correlations were evaluated by linear regression analysis.

Results (SPIRIT III Pivotal Trial, Japan Registry)

Subject Enrollment and Disposition: A total of 17 subjects who provided signed informed consent were enrolled into the pharmacokinetic substudy at 9 Japanese investigational sites.

The number of stents placed per subject varied between 1 and 3. The total dose of everolimus received by subjects ranged from 88 to 264 μg . Table 6-42 presents the distributions of treatments received.

Table 6-42 Total Stent Dose of Everolimus Received by SPIRIT III Subjects, Japan

Total stent dose (μg)	88	113	176	201	220	254	264
# stents	1	1	2	2	2	3	3
# subjects	6	4	2	1	2	1	1

Of the 17 subjects treated, ten had single-vessel disease and seven had dual-vessel disease. All single vessel subjects received a single stent. Five of seven subjects in the dual-vessel group received two stents. One subject in the dual-vessel group who received 254 μg had one lesion treated with a 2.5 x 18 mm stent and the other lesion was treated with a 3.5 x 18 mm stent that required a 3.5 x 8 mm bailout. One subject in the dual-vessel group who received 264 μg had one lesion treated with two 3.0 x 18 mm overlapping stents and the other lesion was treated with a 3.0 x 18 mm stent.

Pharmacokinetics: The last time point up to which whole blood concentrations could be quantified ranged from 12 to 168 hours after implantation of the last stent. Everolimus was not detectable in any samples at 30 days post implantation.

Across all dose levels individual t_{max} values ranged from 0.50 to 1.33 hours. Individual C_{max} values ranged from 0.29 to 2.11 ng/mL. The highest concentration determined, 2.11 ng/mL, was associated with the highest dose delivered (264 μg). Individual $\text{AUC}_{0-24\text{h}}$ values ranged from 2.942 to 19.72 ng.h/mL. Individual AUC_{0-t} values ranged from 2.218 to 54.49 ng.h/mL. Table 6-43 presents those subject groups (88 μg and 113 μg) with a sample size greater than two.

Terminal half-life varied with the ability to quantify everolimus in the blood and ranged from from 13 to 94 hours. However, terminal half-life could not be characterized accurately therefore $\text{AUC}_{0-\infty}$ and CL are presented as estimation for all subjects.

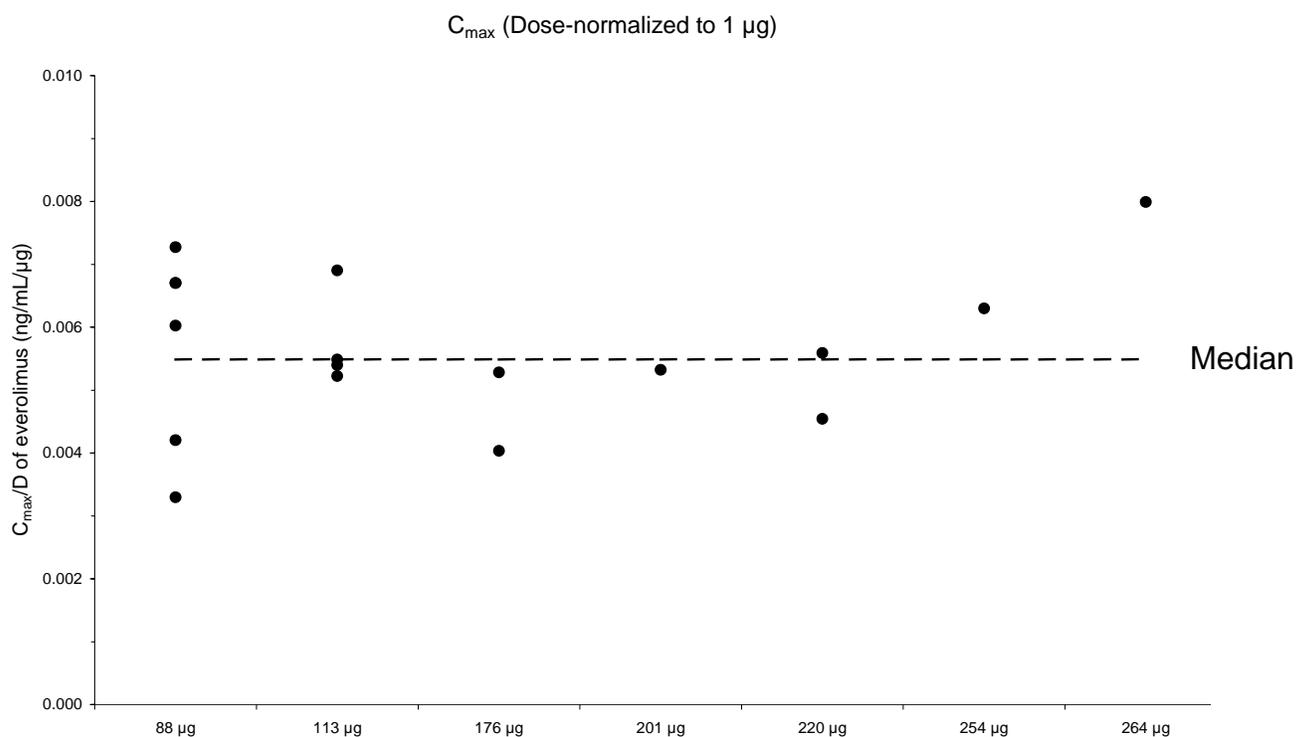
Table 6-43 Pharmacokinetic Parameters of Everolimus

<i>Pharmacokinetics of everolimus</i> (mean \pm SD, t_{max} , median (range))	88 μg	113 μg
n	6	4
t_{max} , h	1.00 (0.50 - 1.02)	0.51 (0.50 - 0.53)
C_{max} , ng/mL	0.5017 \pm 0.1398	0.6500 \pm 0.08756
AUC _{0-24h} , ng.h/mL	4.476 \pm 1.087	6.154 \pm 0.7523
AUC _{0-t} , ng.h/mL	5.049 \pm 2.138	11.02 \pm 4.002
AUC _{0-∞} , ng.h/mL ^a	12.98 \pm 7.078	19.97 \pm 7.890
$t_{1/2term}$, h ^a	45.22 \pm 35.08	53.57 \pm 19.34
CL, L/h ^a	9.286 \pm 6.069	6.471 \pm 2.807

^a Accurate determination not possible

Dose-normalized C_{max} is shown here plotted versus total dose (see Figure 6-7). Across the entire dosing range (88 to 264 μ g) the plots show that the data are evenly distributed around the median value indicating that the pharmacokinetic parameters determined for whole blood everolimus increase proportionally to the total dose.

These findings are supported by linear regression against total dose with R^2 values of C_{max} = 0.8139, AUC_{0-24h} = 0.8551, AUC_{0-t} = 0.6958 and AUC_{0- ∞} = 0.7468.

**Figure 6-7 C_{max} Normalized by Dose**

The results of this substudy demonstrate that whole blood concentrations of everolimus increase proportionally to the total stent dose (ranging from 88 to 264 μg). Individual t_{max} values ranged from 0.50 to 1.33 hours. Individual C_{max} values ranged from 0.29 to 2.11 ng/mL. Individual $\text{AUC}_{0-24\text{h}}$ values ranged from 2.942 to 19.72 ng.h/mL. Individual AUC_{0-t} values ranged from 2.218 to 54.49 ng.h/mL. The last time point up to which whole blood concentrations could be quantified ranged from 12 to 168 hours after implantation of the last stent. Everolimus was not detectable in any samples at 30 days post implantation. These data suggest that systemic exposure is also limited in the Japanese population.

SPIRIT II, Supporting Clinical Trial, OUS

The purpose of the pharmacokinetic substudy was to determine the pharmacokinetics of everolimus delivered by the XIENCE V EECS in the SPIRIT II trial. All subjects were screened per the protocol inclusion and exclusion criteria. Enrolled subjects who volunteered to participate in the pharmacokinetic substudy had blood drawn prior to the first stent implant, and at 10, 30 minutes, and at 1, 2, 4, 6, 12, 24, 36, 48, 72, 168 and 720 hours (30 days) after completion of implantation of the last stent (14 sampling points). The methodologies for the conduct of SPIRIT II pharmacokinetic study were the same as the US SPIRIT III trial.

Data was summarized by dose based upon the number and size of stents implanted (Table 6-45). The results were expressed as means and standard deviations determined for each dose group. Pharmacokinetic correlations were evaluated by linear regression analysis.

Results (SPIRIT II, Supporting Clinical Trial, OUS)

Subject Enrollment and Disposition: A total of 39 subjects who provided signed informed consent were enrolled into the pharmacokinetic substudy at investigational sites outside the United States. Table 6-44 presents the baseline characteristics of the subjects that participated in the pharmacokinetic sub-study and the overall population. The subjects in the sub-study had similar characteristics to the overall population.

Table 6-44 Key Demographics, Physical Measurements and Risk Factors – Per-Subject Analysis (Intent-to-Treat Population) (SPIRIT II PK Subgroup vs. Overall Population)

	PK OUS (N= 39)	SPIRIT II (N= 300)
Age (year)		
Mean ± SD (n)	63.33± 10.33 (39)	61.94± 10.06 (300)
Median	65.07	61.85
Q1,Q3	56.41, 72.25	54.75, 68.39
Range (min, max)	(34.62, 82.44)	(34.62, 86.97)
[95% Confidence Interval] ¹	[59.98, 66.68]	[60.80, 63.08]
Male Subjects	71.8% (28/ 39)	73.0% (219/ 300)
[95% Confidence Interval] ²	[55.1%, 85.0%]	[67.6%, 77.9%]
Current Tobacco Use	23.5% (8/ 34)	31.2% (86/ 276)
[95% Confidence Interval] ²	[10.7%, 41.2%]	[25.7%, 37.0%]
All Diabetes Mellitus	28.2% (11/ 39)	23.1% (69/ 299)
[95% Confidence Interval] ²	[15.0%, 44.9%]	[18.4%, 28.3%]
Diabetes Mellitus Requiring Medication	25.6% (10/ 39)	20.4% (61/ 299)
[95% Confidence Interval] ²	[13.0%, 42.1%]	[16.0%, 25.4%]
Hypertension Requiring Medication	76.9% (30/ 39)	66.7% (200/ 300)
[95% Confidence Interval] ²	[60.7%, 88.9%]	[61.0%, 72.0%]
Hypercholesterolemia Requiring Medication	61.5% (24/ 39)	70.3% (206/ 293)
[95% Confidence Interval] ²	[44.6%, 76.6%]	[64.7%, 75.5%]
All Prior Cardiac Interventions	20.5% (8/ 39)	23.0% (69/ 300)
[95% Confidence Interval] ²	[9.3%, 36.5%]	[18.4%, 28.2%]
Prior Cardiac Intervention on Target Vessel(s)	2.7% (1/ 37)	3.7% (11/ 296)
[95% Confidence Interval] ²	[0.1%, 14.2%]	[1.9%, 6.6%]
MI within 2 Months	20.5% (8/ 39)	15.6% (46/ 294)
[95% Confidence Interval] ²	[9.3%, 36.5%]	[11.7%, 20.3%]

¹ By normal approximation.

² By Clopper-Pearson exact confidence interval.

The number of stents placed per subject varied between 1 and 4. The total dose of everolimus received by the subjects varied from 53 to 588 µg. Table 6-45 presents the distributions of treatments received.

Table 6-45 Total Stent Dose of Everolimus received by SPIRIT II Subjects, OUS

Total stent dose (µg)	53	88	113	125	132	169	181	201	206	219	220	234	245	257	314	588
# stents	1	1	1	2	1	2	1	2	3	3	2	2	2	3	3	4
# subjects	2	13*	4	1	2	1	4**	2	1	1	2	2	1	1	1	1

*4 subjects were not evaluated at all time points

** 1 subject was not evaluated at all time points

Of the 39 subjects treated, 31 had single-vessel disease and eight had dual-vessel disease. Of the 31 subjects with single-vessel disease 25 received a single stent, three received overlapping stents that were planned as part of the procedure, two received bailout stents, and one subject in the 219 µg group received a 3.5 x 18 mm and a 3.5 x 8 mm stent as part

of the planned procedure that required bailout with a 3.5 x 8 mm stent. Of the eight subjects with dual-vessel disease, four received two stents as part of a planned procedure, two subjects received three stents as part of a planned procedure, and two subjects required bailout stenting resulting in the placement of three stents in one subject and four stents in the other. The subject that received 588 µg had a 3.5 x 18 mm stent placed in one lesion and a 3.5 x 28 mm stent placed in the second lesion that required bailout by a 3.5 x 28 mm and a 3.5 x 18 mm stent.

Pharmacokinetics: The last time point up to which whole blood concentrations could be quantified ranged per subject from 4 to 720 hours (30 days) after implantation of the last stent.

Individual t_{max} values ranged from 0.13 and 2.17 hours. Individual C_{max} values ranged from 0.14 to 2.79 ng/mL. AUC_{0-24h} ranged from 0.5698 to 29.85 ng.h/mL and AUC_{0-last} ranged from 0.4532 to 164.1 ng.h/mL. The highest concentration determined was 2.79 ng/mL in a subject receiving a total dose of 588 µg. Descriptive statistics were calculated for dose levels (88, 113 and 181 µg) that had more than 2 subjects (Table 6-46).

Terminal half-life values varied with the ability to quantify everolimus in the blood and ranged from 11 to 624 hours. However, terminal half-life could not be characterized accurately in any subject. As a result AUC_{∞} and Cl could only be estimated.

Table 6-46 Pharmacokinetic Parameters of Everolimus by Total Dose

<i>Pharmacokinetics of everolimus</i> (mean ± SD, t_{max} : median (range))	88 µg	113 µg	181 µg
n	13 ^b	4 ^c	4
t_{max} , h	0.50 (0.13 - 2.17)	0.50 (0.50 - 0.50)	0.46 (0.17 - 1.00)
C_{max} , ng/mL	0.4369 ± 0.1507	0.5850 ± 0.2630	0.7925 ± 0.1406
AUC_{24h} , ng.h/mL	5.156 ± 1.976	6.820 ± 4.373	10.27 ± 1.035
AUC_{last} , ng.h/mL	8.255 ± 5.863	42.54 ± 58.83	28.07 ± 13.18
AUC_{∞} , ng.h/mL ^a	19.60 ± 15.30	22.79 ± 31.47	52.71 ± 27.40
$t_{1/2term}$, h ^a	54.08 ± 35.78	47.60 ± 62.13	103.4 ± 64.17
CL, L/h ^a	8.066 ± 6.443	16.96 ± 13.07	5.332 ± 5.048

^a Accurate determination not possible

^b n = 12 for AUC_{24h}

^c n = 3 for AUC_{∞} , $t_{1/2term}$ and CL

Dose-normalized C_{max} is shown here plotted versus total dose (see Figure 6-8). Across the entire dosing range (53 to 588 µg) the plots show that the data are evenly distributed around the median value indicating that the pharmacokinetic parameters determined for whole blood everolimus increased proportionally to the total stent dose. However, due to high variability, dose-proportionality was less apparent for AUC_{0-last} and $AUC_{0-\infty}$. These findings are supported by linear regression against total stent dose with R^2 values of C_{max} = 0.7235, AUC_{0-24h} = 0.7322, AUC_{last} = 0.2512 and AUC_{∞} = 0.243.

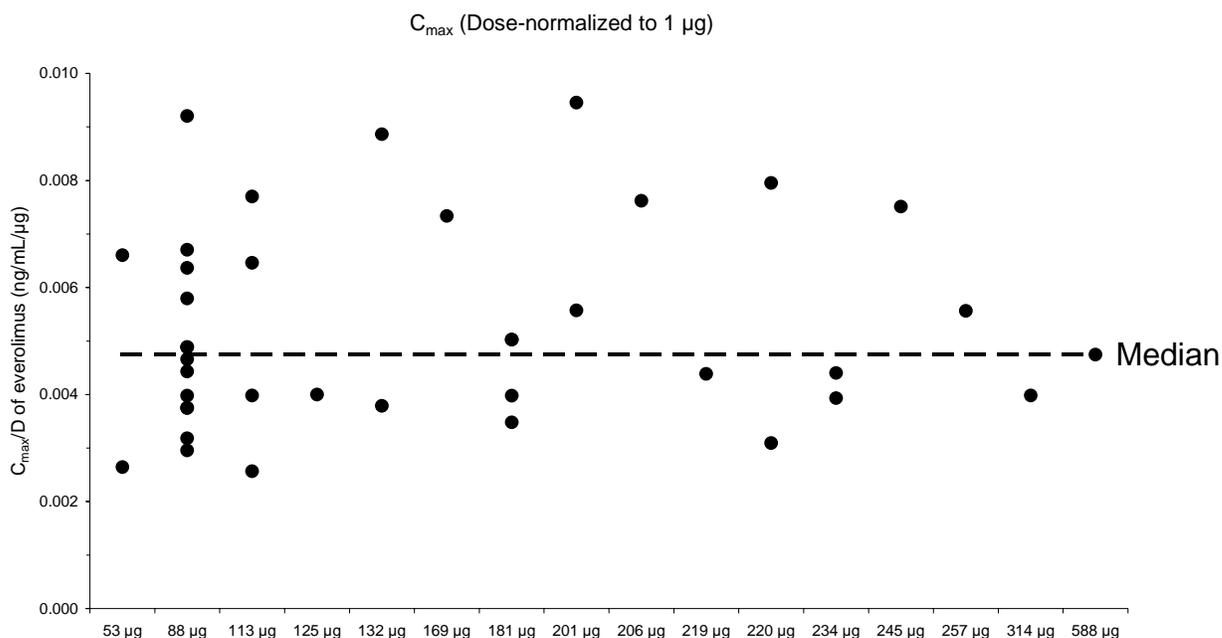


Figure 6-8 C_{max} Normalized by Dose

The results of this substudy demonstrate that whole blood concentrations of everolimus increase proportionally to the total stent dose (ranging from 53 to 588 μg). Individual t_{max} values ranged from 0.13 to 2.17 hours, with a median value of about 0.5 hour. Individual C_{max} values ranged from 0.14 to 2.79 ng/mL. AUC_{24h} values ranged from 0.5698 to 29.85 ng.h/mL. AUC_{last} values ranged from 0.4532 to 164.1 ng.h/mL. The last time point up to which whole blood concentrations could be quantified ranged from 4 to 720 hours (30 days) after implantation of the last stent. Terminal half-life could not be characterized accurately. Once again, the systemic exposure of everolimus is limited in this population despite the administration of doses as high as 588 μg .

Discussions

The pharmacokinetics of everolimus eluted from the XIENCE V EECS have been evaluated in three different substudies in three different geographies. One of the substudies was done in association with the SPIRIT II trial which was conducted outside the US and two of the substudies were done in association with SPIRIT III, a trial conducted in the US and Japan.

The global pharmacokinetic data includes a total of 73 subjects. Abbott Vascular believes that the global pharmacokinetic studies have adequately characterized the pharmacokinetic profile of everolimus in human whole blood. These studies demonstrated that whole blood concentrations of everolimus increase proportionally to the

total stent dose (ranging from 53 to 588 µg). The findings were consistent across studies and geographies.

The pharmacokinetic parameters associated with the elution of everolimus from the XIENCE V EECS were consistent in all three substudies in all three geographies. The C_{max} values ranged from 2.2 to 2.7 ng/mL and these values were all associated with the highest dose of everolimus administered. These values are also consistent with the C_{max} values seen in pre-clinical studies.

Dose-normalized C_{max} values were evaluated versus the total stent dose in all three substudies. Across the geographies the evaluation showed that the data were evenly distributed around the median value indicating that the pharmacokinetic parameter, C_{max} , increased proportionally to the total stent dose.

Statistical testing was also done to show consistency between the US and Japanese populations in SPIRIT III. The statistical results comparing the pharmacokinetics of everolimus determined in the US and Japanese populations are presented in Table 6-47. For both populations more than 50% of the individual values of $AUC_{0-\infty}$, λ_z and $t_{1/2,term}$ could not be determined accurately. Therefore $AUC_{0-\infty}$ was rejected as a primary pharmacokinetic parameter in the overall statistical analysis and AUC_{0-24h} was used instead.

Table 6-47 Statistical Comparison of the Dose-Normalized Everolimus Pharmacokinetics between the US and Japanese populations

Parameter (Dose Normalized)	LS means ^a		LS means ratio (%)	90% CI (%)	p-value
	US population (reference)	Japanese population (test)			Country
C_{max} , ng/mL	0.004719	0.005530	117.2	97.16 - 141.3	0.1613
AUC_{0-24h} , ng.h/mL	0.04878	0.05276	108.2	92.05 - 127.1	0.4148
AUC_{0-t} , ng.h/mL	0.07771	0.07791	100.3	71.83 - 139.9	0.9895

^a n=17 for the Japanese and US populations, except for AUC_{0-24h} where n=13 for the US population

Based on the ratios of the least square (LS) means from the US and Japanese populations, the C_{max} and AUC_{0-24h} values of everolimus determined for the Japanese population were similar to the US population, respectively increased by approximately 17% and 8%. Table 6-48 presents the baseline characteristics for both populations. The differences in pharmacokinetic values are not unexpected based upon the differences in BMI shown in Table 6-48. The differences in C_{max} and AUC_{0-24h} values were not statistically significant. The LS mean values of AUC_{0-t} were the same for the US and Japanese populations.

Table 6-48 Key Demographics, Physical Measurements and Risk Factors – Per Subject Analysis (Intent-To-Treat Population) (SPIRIT III US PK vs Japan PK)

	PK US (N=17)	PK Japan (N=17)
Age (year) Mean ± SD (n) Median (Q1, Q3) Range (min, max) [95% Confidence Interval] ¹	62.44 ± 9.51 (17) 61.95 (55.74, 67.05) (47.95, 79.61) [57.55, 67.33]	66.10 ± 8.54 (17) 70.03 (60.25, 72.21) (49.07, 78.60) [61.71, 70.49]
Male Subjects [95% Confidence Interval] ²	70.6% (12/17) [44.04%, 89.69%]	64.7% (11/17) [38.33%, 85.79%]
Height (cm) Mean ± SD (n) Median (Q1, Q3) Range (min, max) [95% Confidence Interval] ¹	167.0 ± 9.8 (17) 165.0 (163.0, 170.0) (150, 185) [161.9, 172.1]	160.7 ± 10.2 (17) 163.0 (156.0, 165.0) (140, 178) [155.4, 166.0]
Weight (kg) Mean ± SD (n) Median (Q1, Q3) Range (min, max) [95% Confidence Interval] ¹	88.1 ± 19.4 (17) 90.0 (79.0, 101.0) (54, 118) [78.1, 98.0]	61.1 ± 10.9 (17) 60.0 (55.0, 65.0) (40, 82) [55.5, 66.7]
Body Mass Index (kg/m ²) Mean ± SD (n) Median (Q1, Q3) Range (min, max) [95% Confidence Interval] ¹	31.71 ± 8.12 (17) 31.07 (26.48, 33.28) (21.29, 50.92) [27.53, 35.89]	23.50 ± 2.58 (17) 23.26 (21.99, 24.39) (20.36, 30.80) [22.17, 24.82]
Current Tobacco Use [95% Confidence Interval] ²	29.4% (5/17) [10.31%, 55.96%]	35.3% (6/17) [14.21%, 61.67%]
All Diabetes Mellitus [95% Confidence Interval] ²	29.4% (5/17) [10.31%, 55.96%]	11.8% (2/17) [1.46%, 36.44%]
Diabetes Mellitus Requiring Medication [95% Confidence Interval] ²	23.5% (4/17) [6.81%, 49.90%]	11.8% (2/17) [1.46%, 36.44%]
Hypertension Requiring Medication [95% Confidence Interval] ²	82.4% (14/17) [56.57%, 96.20%]	70.6% (12/17) [44.04%, 89.69%]
Hypercholesterolemia Requiring Medication [95% Confidence Interval] ²	58.8% (10/17) [32.92%, 81.56%]	47.1% (8/17) [22.98%, 72.19%]
All Prior Cardiac Interventions [95% Confidence Interval] ²	29.4% (5/17) [10.31%, 55.96%]	23.5% (4/17) [6.81%, 49.90%]
Prior Cardiac Intervention on Target Vessel(s) [95% Confidence Interval] ²	12.5% (2/16) [1.55%, 38.35%]	11.8% (2/17) [1.46%, 36.44%]
MI within 2 Months [95% Confidence Interval] ²	0.0% (0/17) [0.00%, 19.51%]	5.9% (1/17) [0.15%, 28.69%]

¹ By normal approximation.

² By Clopper-Pearson exact confidence interval.

Because there were no statistically significant differences between the primary pharmacokinetic parameters of the US and Japanese populations, a linear regression analysis on the combined primary pharmacokinetic results from both populations against total stent dose was also performed (see Figure 6-9). Taking into account the variability in relation to the sample size, observed for the populations in the US, R^2 values from the combined linear regression were $C_{\max} = 0.582$, $AUC_{0-24h} = 0.7125$, $AUC_{0-t} = 0.5739$ and $AUC_{0-\infty} = 0.5081$. Although R^2 is influenced by inter-individual variability, the analysis shows that the pharmacokinetic parameters determined for whole blood everolimus in US and Japanese subjects increase proportionally to the total stent dose. These results are similar to the results observed with systemic administration of everolimus where no statistical differences were seen between the Japanese and US populations (Certican Investigators' Brochure, Edition 9, dated August 27, 2007).

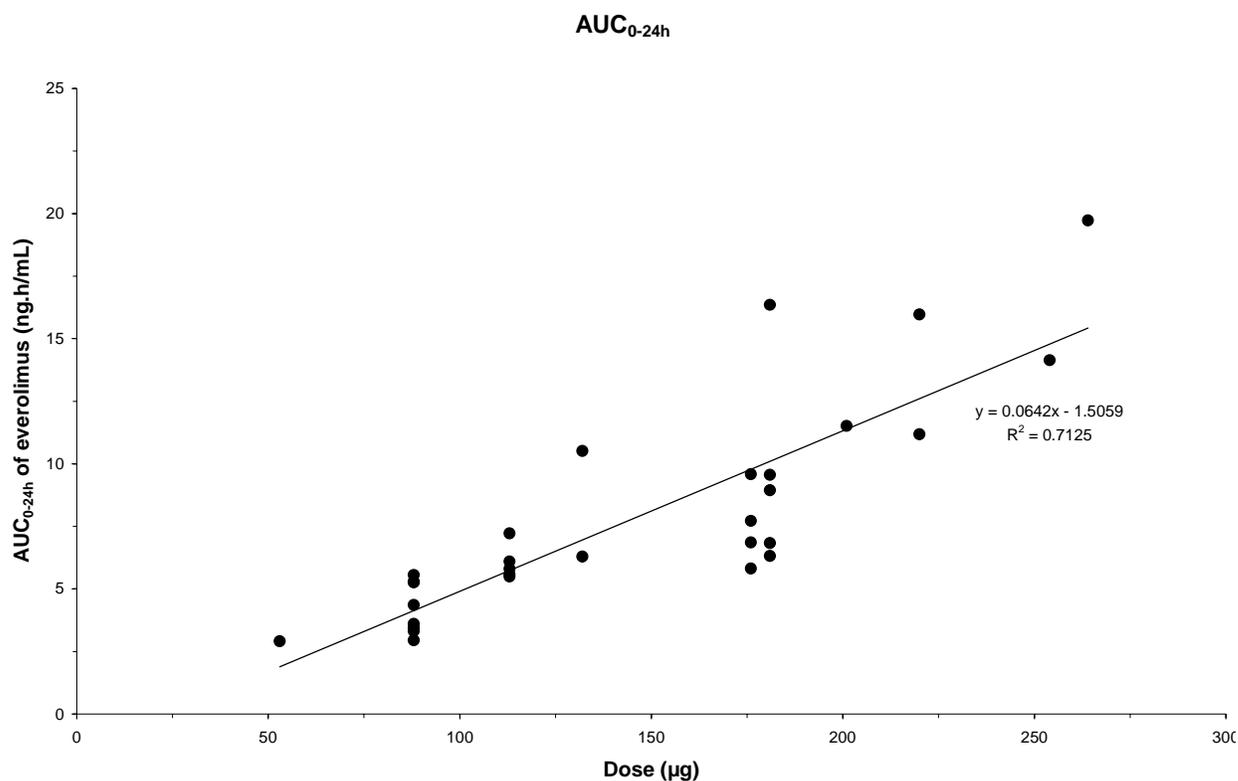


Figure 6-9 Pharmacokinetic Parameter Regression Plots of Everolimus, AUC_{0-24h}

The maximum time to the disappearance of everolimus was 168 hours in all subjects with the exception of one subject in SPIRIT II that still had detectable levels at 30 days. In all three geographies, the C_{\max} value never reached the minimum therapeutic value of 3.0 ng/ml necessary for effective systemic administration to prevent organ rejection. The pharmacokinetic parameters that represent elimination; $t_{1/2,term}$, AUC_{last} , AUC_{∞} , and CL could also not be determined accurately because of the rapid disappearance of everolimus from blood in subjects. These types of results have been seen with other drug eluting stents.

The disappearance of everolimus from the circulation after implantation of the XIENCE V EECS should further limit the systemic extent of exposure. Therefore, subjects exposed to the XIENCE V EECSS should have limited exposure to the adverse events associated with long term systemic administration of everolimus at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies. Successful local delivery has also been confirmed by in-stent late loss values in the SPIRIT II clinical study. The SPIRIT II study evaluated the pharmacokinetic profile of everolimus and demonstrated the safety and effectiveness of the XIENCE V EECSS when compared to TAXUS PECSS.

Conclusion

The pharmacokinetic profile for everolimus eluted from the XIENCE V EECS is consistent across all geographies. The pharmacokinetic profile in clinical trials of the XIENCE V EECSS is consistent with the pre-clinical profile. The local arterial delivery and limited systemic exposure provide the opportunity for successful treatment of coronary lesions with limited risk associated with systemic exposure.

Overall Conclusions

Principal XIENCE V safety and effectiveness evidence is derived from the SPIRIT III clinical trial and is supported by the SPIRIT FIRST and SPIRIT II clinical trials. These studies evaluated XIENCE V performance in patients with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries.

The results from SPIRIT clinical trials and other approval trial further validated the TVF model. Figure 6-10 below shows the results from the approval trials that included lesions treated with stents whose length ≤ 28 mm and diameters 2.5 – 3.5 mm. Given that ID-TVF is a binary endpoint, only those arms of the RCT’s that had a sample size greater than 200 were included to assure a reasonable stable estimate. Therefore, SPIRIT II XIENCE V arm, SPIRIT III both arms, ENDEAVOR II both arms, ENDEAVOR III ENDEAVOR arm, ENDEAVOR IV both arms, TAXUS IV both arms, SIRIUS both arms and the VISION registry were included. SPIRIT FIRST both arms, SPIRIT II TAXUS arm and ENDEAVOR III CYPHER arm were not included. All results, with the exception of the EXPRESS², fall within the confidence interval of the model. Additionally, all the results follow the trend of higher late loss translating to higher ID-TVF rates.

ID-TVF Rate @ 270 days

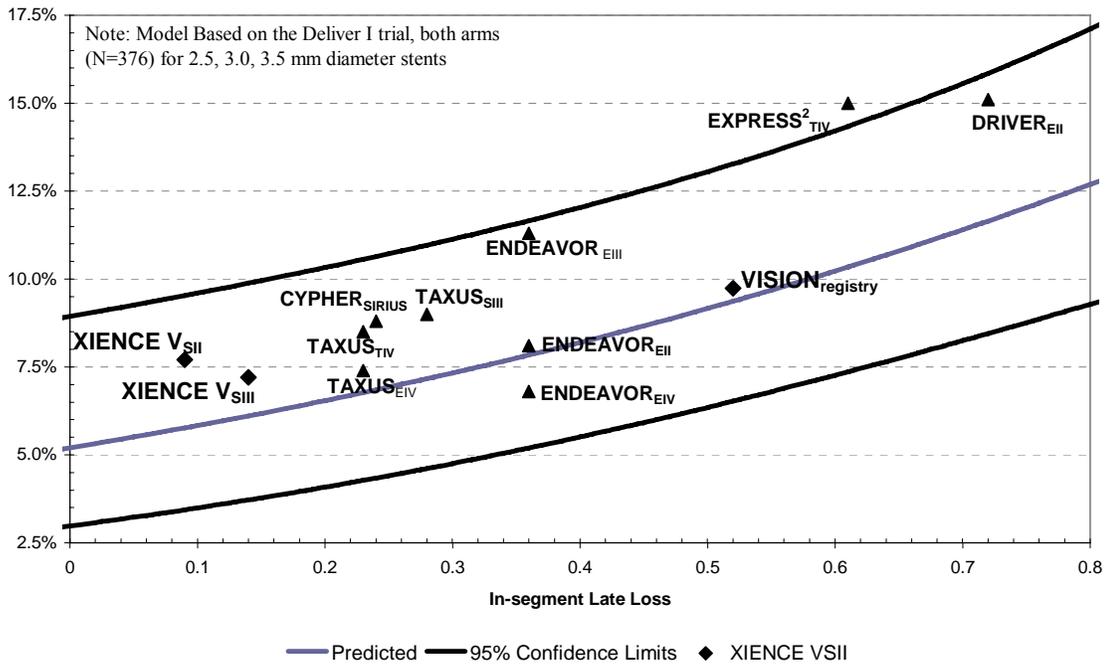


Figure 6-10 Validation of ID-TVF Model Results

In addition, the results from the studies that were not included in the Pocock model, ENDEAVOR II, ENDEAVOR III, SPIRIT II, and SPIRIT III results were plotted against Pocock model. Figure 6-11 shows an expanded portion of the Pocock model. In addition, the figure also has an insert at the upper left showing the full model with the expanded

area identified for reference. The results from ENDEAVOR II, ENDEAVOR III, SPIRIT II, and SPIRIT III were added to the plot. The ENDEAVOR stent is shown in green, DRIVER in yellow, VISION in light blue, TAXUS in red and XIENCE V in purple. Since the average RVD for each of these trials is within 2.5 – 3.0 mm, it would be expected that the results would follow the 2.5 – 3.0 mm curve as they do in Figure 6-11. This indicates that late loss continues to be a good predictor of clinical efficacy over time including XIENCE V.

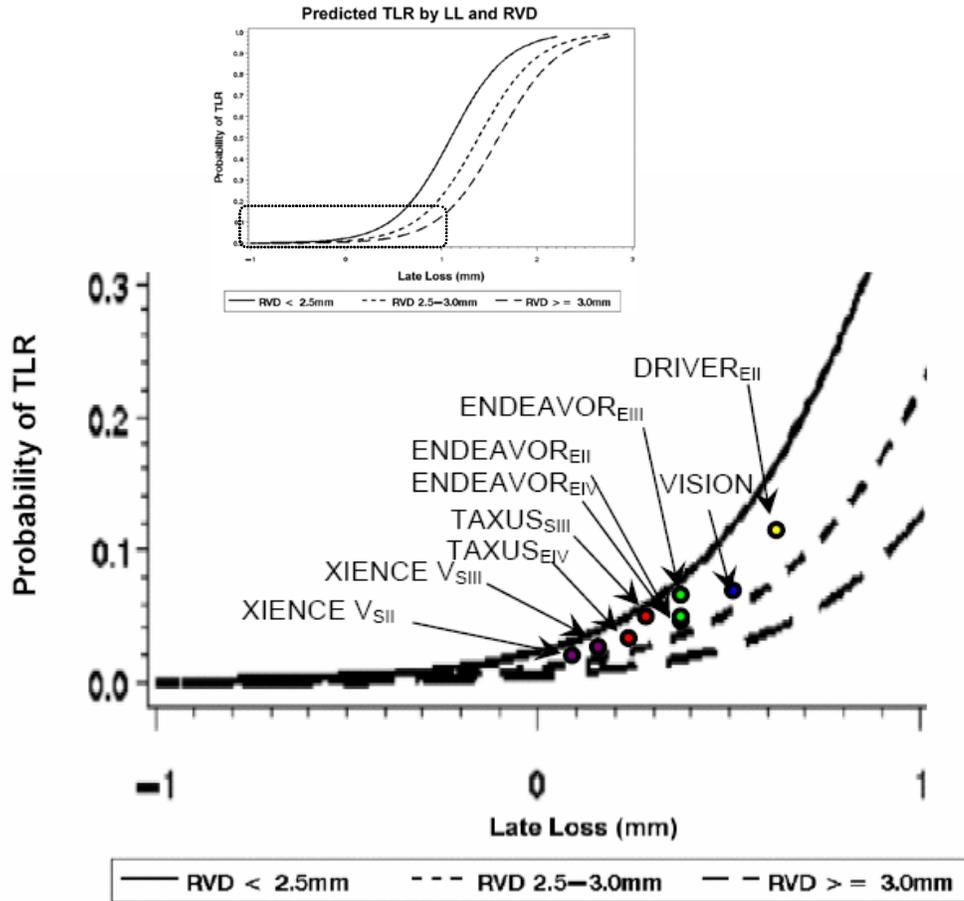


Figure 6-11 Pocock Model Results

Based on the similar results seen in the Abbott Vascular ID-TVF Model of XIENCE V in SPIRIT II and SPIRIT III (see Figure 6-10), a one year meta analysis of the pooled populations was conducted. The pooled population from SPIRIT II and SPIRIT III RCT consisted of 1302 subjects. Of the 1302 subjects 892 were randomized to XIENCE V and 410 were randomized to TAXUS. Table 6-49 presents the baseline characteristics for each treatment. Both groups were similar with respect to their baseline characteristics.

Table 6-49 Baseline Characteristics

	XIENCE V (N=892)	TAXUS (N=410)
Age (years)	62.9 ± 10.5	62.6 ± 10.1
Male	70.3%	68.2%
Diabetes	27.9%	27.1%
- treated with insulin	7.1%	5.7%
Hypertension	74.0%	72.3%
Hypercholesterolemia	72.8%	72.1%
Current smoker	25.3%	23.8%
Prior MI	23.7%	19.3%
Unstable angina	20.8%	26.5%

Table 6-50 presents the angiographic characteristics for each treatment. Both groups were similar with respect to their angiographic characteristics.

Table 6-50 Angiographic Characteristics

	XIENCE V (N=892)	TAXUS (N=410)
LAD	41.1%	43.8%
LCX	28.0%	26.4%
RCA	30.7%	29.6%
LMCA	0.1%	0.2%
RVD (mm)	2.75 ± 0.47	2.77 ± 0.48
MLD (mm)	0.88 ± 0.43	0.89 ± 0.41
% DS	67.7 ± 13.6	67.5 ± 13.6
Lesion length (mm)	14.3 ± 5.7	14.5 ± 5.9

Table 6-51 presents the key elements of design for the two studies. The studies were similar in their conduct. Randomization in SPIRIT II was allocated 3 to 1 while randomization was 2 to 1 in the SPIRIT III RCT. Follow-up for both studies is continuing out to five years.

Table 6-51 Key Elements of Design

	SPIRIT II	SPIRIT III
Number, sites	300 pts at 31 sites	1002 pts at 65 sites
XIENCE V: TAXUS	3:1 (223:77)	2:1 (669:333)
Geography	Europe, Asia	USA
Vessel Diameter (mm)	2.5 – 4.0	2.5 – 3.75
Lesion length (mm)	≤ 28	≤ 28
N lesions, vessels	1-2 lesions, 1/vessel	1-2 lesions, 1/vessel
Clinical Visits (First Year)	1, 6, 9, 12 m	1, 6, 8, 9, 12 m

Poolability for a meta-analysis is justified because these two studies have subjects with similar baseline and angiographic characteristics and the key elements of study design including inclusion and exclusion criteria and endpoint definitions are comparable. Table 6-52 presents the hierarchical counts of adverse events for the SPIRIT II and SPIRIT III RCT pooled population through 393 days. The observed MACE rate through 393 days for the XIENCE V group was 5.3% (46/873) and the MACE rate for the TAXUS group was 10.1% (40/397). The relative risk was 0.52 with confidence intervals of 0.35 to 0.79. The observed TVF rate through 393 days for the XIENCE V group was 7.7% (67/873) and the TVF rate for the TAXUS group was 10.8% (43/397). The relative risk was 0.71 with confidence intervals of 0.49 to 1.02. These reductions in relative risk for both MACE and TVF suggest that XIENCE V has lower cardiac event rates in comparison with TAXUS. The confidence intervals are presented for descriptive purposes and have not been adjusted for multiple comparisons.

**Table 6-52 Hierarchical Subject Counts of Adverse Events through 393 Days
(SPIRIT II and SPIRIT III RCT Pooled Population)
(ITT)**

	XIENCE V (N=892)	TAXUS (N=410)	Total (N=1302)	Relative Risk [95% CI] ¹	Difference [95% CI] ²
0 to 393 days					
MACE (Cardiac Death, MI, TLR)	5.3% (46/873)	10.1% (40/397)	6.8% (86/1270)	0.52 [0.35, 0.79]	-4.81% [-8.12%, -1.50%]
TVF (Cardiac Death, MI, TLR, TVR, non-target lesion)	7.7% (67/873)	10.8% (43/397)	8.7% (110/1270)	0.71 [0.49, 1.02]	-3.16% [-6.69%, 0.37%]
Cardiac Death	0.6% (5/873)	1.0% (4/397)	0.7% (9/1270)	0.57 [0.15, 2.11]	-0.43% [Assump. not met]
QMI	0.2% (2/873)	0.0% (0/397)	0.2% (2/1270)	NC [NC]	0.23% [Assump. not met]
NQMI	1.9% (17/873)	3.5% (14/397)	2.4% (31/1270)	0.55 [0.27, 1.11]	-1.58% [-3.61%, 0.45%]
TLR CABG	0.1% (1/873)	0.0% (0/397)	0.1% (1/1270)	NC [NC]	0.11% [Assump. not met]
TLR PCI	2.4% (21/873)	5.5% (22/397)	3.4% (43/1270)	0.43 [0.24, 0.78]	-3.14% [-5.61%, -0.67%]
TVR CABG, non-target lesion	0.5% (4/873)	0.3% (1/397)	0.4% (5/1270)	1.82 [0.20, 16.22]	0.21% [Assump. not met]
TVR PCI, non-target lesion	1.9% (17/873)	0.5% (2/397)	1.5% (19/1270)	3.87 [0.90, 16.65]	1.44% [Assump. not met]

¹ Relative risk=XIENCE V/TAXUS; SE=sqrt[(1-p1)/n1+1+(1-p2)/n2]; CI=exp(ln(RR)±1.96*SE).

² By normal approximation.

Note: Subjects are only counted once for each type of event in each time period.

Note: Subjects are only counted once in the hierarchical order of Cardiac Death, QMI, NQMI, TLR CABG, TLR PCI, TVR CABG, and TVR PCI.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: In-hospital is defined as hospitalization less than or equal to 7 days post index procedure.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

Note: NC=Not Calculatable.

Note: Includes events identified after unblinding and that were not included in the 270-day Clinical Report.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Stent thrombosis was categorized as acute (≤ 1 day), subacute (> 1 day ≤ 30 days) and late (> 30 days) and was defined as any of the following:

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (angiographic appearance of thrombus within or adjacent to a previously treated target lesion)
- In the absence of angiography, any unexplained death or acute MI (ST segment elevation or new Q-wave) in the distribution of the target lesion within 30 days.

Any thromboses that occurred less than 30 days after the index procedure were not counted as restenosis.

Table 6-53 presents the non-hierarchical counts of stent thrombosis for the pooled population according to the protocol definition. Rates were low for both treatments in this meta-analysis and consistent with the published literature¹⁰.

Table 6-53 Stent Thrombosis per Protocol Definition through 393 Days (SPIRIT II and SPIRIT III RCT Pooled Population) (ITT)

	XIENCE V (N=892)	TAXUS (N=410)	Total (N=1302)	Relative Risk [95% CI] ²	Difference [95% CI] ³
Stent Thrombosis					
Acute (< 1 day)	0.1% (1/892)	0.0% (0/407)	0.1% (1/1299)	NC [NC]	0.11% [Assump. not met]
Subacute (1 to 30 days)	0.2% (2/890)	0.0% (0/407)	0.2% (2/1297)	NC [NC]	0.22% [Assump. not met]
Late (>30 days)	0.3% (3/866)	0.8% (3/394)	0.5% (6/1260)	0.45 [0.09, 2.24]	-0.42% [Assump. not met]

¹ Revascularization includes both TLR and TVR, non-target lesion.

² Relative risk=XIENCE V/TAXUS; SE=sqrt[(1-p1)/n11+(1-p2)/n21]; CI=exp(ln(RR)±1.96*SE).

³ By normal approximation.

Note: Subjects are only counted once for each type of event in each time period.

Note: This table includes TLRs and TVRs on all lesions for subjects with two target lesions treated.

Note: In-hospital is defined as hospitalization less than or equal to 7 days post index procedure.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

Note: NC=Not Calculatable.

Note: Includes events identified after unblinding and that were not included in the 270-day Clinical Report.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Stent Thrombosis per ARC was also analyzed for the pooled population through 393 days. There results are presented in Table 6-54.

Table 6-54 Stent Thrombosis per ARC through 393 Days (SPIRIT II and SPIRIT III RCT Pooled Population)

	XIENCE (N=892) [95% CI]	TAXUS (N=410) [95% CI]
ARC definite + probable (TLR-uncensored)	0.8% (7/868) [0.32%, 1.65%]	0.8% (3/394) [0.16%, 2.21%]

¹⁰ Ellis SG CA, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol.* . 2007;49:1043-1051.

Table 6-55 displays TVF rates through 393 days for a variety of subgroups identified within the population. One of the advantages of pooling studies is the increased numbers of subjects and the ability to survey subgroups that exist within the pooled population. However, caution should be exercised in the interpretation of this data especially when the number of subjects within a subgroup is small or the 95% confidence interval of the difference cannot be calculated. The confidence intervals are presented for descriptive purposes and have not been adjusted for multiple comparisons. To identify subgroups that exhibited potential clinical differences between treatments, the confidence interval of the difference was used. If the confidence interval of the difference did not include zero, the TVF rate for the treatment in that subgroup suggested a clinical benefit. The No Diabetes Mellitus subgroup met this criterion. The observed TVF rate for No Diabetes Mellitus subgroup treated with XIENCE V was 6.4% (40/629) compared with 12.8% (37/290) for subjects treated with TAXUS.

Table 6-55 TVF through 393 Days (SPRIT II and SPIRIT III RCT Pooled Population) (ITT)

	XIENCE V (N=892)	TAXUS (N=410)	Total (N=1302)	Difference [95% CI]¹
All Diabetes Mellitus	11.1% (27/244)	5.8% (6/104)	9.5% (33/348)	5.30% [-0.67%, 11.26%]
Non Diabetics	6.4% (40/629)	12.8% (37/290)	8.4% (77/919)	-6.40% [-10.69%, -2.11%]
Single Vessel Treated	6.8% (50/735)	8.4% (28/333)	7.3% (78/1068)	-1.61% [-5.10%, 1.89%]
Dual Vessel Treated	12.3% (17/138)	23.4% (15/64)	15.8% (32/202)	-11.12% [-22.86%, 0.62%]
Gender Male	6.7% (41/615)	8.2% (22/269)	7.1% (63/884)	-1.51% [-5.33%, 2.31%]
Female	10.1% (26/258)	16.4% (21/128)	12.2% (47/386)	-6.33% [-13.72%, 1.06%]

¹By normal approximation.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

Table 6-56 displays the MACE rates by treatment through 393 days for a variety of subgroups identified within the population. Caution should be exercised in the interpretation of this data especially when the number of subjects within a subgroup is small or the 95% confidence interval of the difference cannot be calculated. The confidence intervals (CI) are presented for descriptive purposes and have not been adjusted for multiple comparisons.

Table 6-56 MACE through 393 Days (SPIRIT II and SPIRIT III RCT Pooled Population) (ITT)

	XIENCE V (N=892)	TAXUS (N=410)	Total (N=1302)	Difference [95% CI]¹
All Diabetes Mellitus	8.6% (21/244)	3.8% (4/104)	7.2% (25/348)	4.76% [Assump. not met]
No Diabetes Mellitus	4.0% (25/629)	12.4% (36/290)	6.6% (61/919)	-8.44% [-12.53%, -4.35%]
Single Vessel Treated	4.8% (35/735)	7.5% (25/333)	5.6% (60/1068)	-2.75% [-5.97%, 0.48%]
Dual Vessel Treated	8.0% (11/138)	23.4% (15/64)	12.9% (26/202)	-15.47% [-26.79%, -4.15%]
Gender Male	4.4% (27/615)	7.8% (21/269)	5.4% (48/884)	-3.42% [-7.01%, 0.18%]
Female	7.4% (19/258)	14.8% (19/128)	9.8% (38/386)	-7.48% [-14.41%, -0.54%]

¹By normal approximation.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

To identify subgroups that exhibited potential clinical differences between treatments, the confidence interval of the difference was used. If the confidence interval of the difference did not include zero, the MACE rate for the treatment in that subgroup suggested a clinical benefit. Table 6-57 displays the MACE rates for XIENCE V and the MACE rates for TAXUS that met this criterion

Table 6-57 MACE through 393 Days (SPIRIT II and SPIRIT III RCT Pooled Population) (Subgroups with 95% CI Not Including Zero)

	XIENCE V (N=892)	TAXUS (N=410)	Total (N=1302)	Difference [95% CI]¹
Non Diabetics	4.0% (25/629)	12.4% (36/290)	6.6% (61/919)	-8.44% [-12.53%, -4.35%]
Dual Vessel Treated	8.0% (11/138)	23.4% (15/64)	12.9% (26/202)	-15.47% [-26.79%, -4.15%]
Gender: Female	7.4% (19/258)	14.8% (19/128)	9.8% (38/386)	-7.48% [-14.41%, -0.54%]

¹By normal approximation.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only

In the meta-analysis of the SPIRIT II and SPIRIT III RCT clinical studies, key clinical and endpoints observed in XIENCE V arm were lower than those observed in the TAXUS arm. Therefore, this meta-analysis study provides additional evidence regarding the safety and performance of the XIENCE V EECSS, when compared to a commercially available safe and effective active control.

Table 6-58 presents the In-Stent and In-Segment Late Loss, TVF, MACE, and Cardiac Death and MI for all studies. For ease of review, XIENCE V has been shaded. The results are consistent across all studies and all geographies. Comparability and consistency across studies can be justified because all studies were designed as randomized controlled clinical

trials. The subjects that were enrolled met similar inclusion and exclusion criteria. The subjects enrolled in these trials had similar baseline and angiographic characteristics. The studies were analyzed using common endpoint definitions for both effectiveness and safety. Finally, poolability for the meta-analysis that combined SPIRIT III and SPIRIT III can be justified because these two studies were designed as randomized controlled clinical trials comparing XIENCE V with TAXUS. These studies enrolled subjects with similar inclusion and exclusion criteria. The subjects enrolled had similar baseline and angiographic characteristics and the key elements of study design including and endpoint definitions were comparable.

Table 6-58 In-Stent Late Loss, In-Segment Late Loss, TVF, MACE and Cardiac + MI Across SPIRIT Trials

	Time Point	SPIRIT FIRST	SPIRIT II		SPIRIT III		SPIRIT III 4.0 mm	Combined SPIRIT II & III RCT	
			XIENCE V	TAXUS	XIENCE V	TAXUS		XIENCE V	TAXUS
In-stent late loss (Analysis Lesion)	6M	0.10±0.23 (23)	0.10 ± 0.27 (201)	0.36 ± 0.39 (73)	-	-	-	-	-
MACE	6M	7.7% (2/26)	2.7% (6/222)	6.5% (5/77)	2.6% (17/663)	4.6% (15/326)	5.9% (4/68)	-	-
Cardiac Death + MI	6M	3.8% (1/26)	0.9% (2/222)	3.9% (3/77)	1.5% (10/663)	3.1% (10/326)	5.9% (4/68)	-	-
TVF	6M	7.7% (2/26)	3.6% (8/222)	6.5% (5/77)	3.8% (25/663)	4.9% (16/326)	5.9% (4/68)	-	-
In-stent late loss (Analysis Lesion)	8M	-	-	-	0.16 ± 0.41 (301)	0.31 ± 0.55 (134)	0.12 ± 0.34 (49)	-	-
In-segment late loss (Analysis Lesion)	8M	-	-	-	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	0.17 ± 0.38 (49)	-	-
MACE	9M	7.7% (2/26)	2.7% (6/220)	6.6% (5/76)	5.0% (33/657)	8.8% (28/320)	5.9% (4/68)	4.4% (39/877)	8.6% (34/397)
Cardiac Death + MI	9M	3.8% (1/26)	0.9% (2/220)	3.9% (3/76)	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	2.4% (21/877)	3.8%(15/397)
TVF	9M	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)	9.3% (37/397)
MACE	12M	15.4% (4/26)	2.7% (6/220)	9.2% (7/76)	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	5.3% (46/873)	10.1% (40/397)
Cardiac Death + MI	12M	7.7% (2/26)	0.9% (2/220)	3.9% (3/76)	3.4% (22/653)	4.7%(15/320)	5.9% (4/68)	2.7% (24/873)	4.5% (18/397)
TVF	12M	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)	10.8% (43/397)

Note: All Spirit First subjects were treated with single, *de novo*, native coronary artery lesion.

Note: 6M = 194 days for Spirit First, Spirit II, Spirit III and Combined SPIRIT II & III.

Note: 8M = 240 days for Spirit II, Spirit III and Combined SPIRIT II & III.

Note: 9M = 270 days for Spirit II, 284 days for Spirit First, Spirit III and Combined SPIRIT II & III.

Note: 12M = 365 days for Spirit II, 393 days for Spirit First, Spirit III and Combined SPIRIT II & III.

In summary, these three studies have demonstrated superiority of XIENCE V in the following angiographic measures:

- In-stent late loss compared to VISION in SPIRIT FIRST
- In-stent late loss compared to TAXUS in SPIRIT II
- In-segment late loss compared to TAXUS in SPIRIT III

The studies also show consistent angiographic, clinical, and pharmacokinetic results for XIENCE V across all geographies. The observed lower MACE rates compared to TAXUS, and the low incidence of late stent thrombosis confirm the safety of XIENCE V.