# FDA Executive Summary Memorandum

Prepared for the November 29, 2007, meeting of the
Circulatory System Devices Advisory Panel

P070015
Abbott Vascular, Inc.
XIENCE V Everolimus Eluting Coronary Stent System &
Over-the-Wire (OTW) and Rapid Exchange (RX)
Delivery Systems

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## 1. PROPOSED INDICATIONS FOR USE

The XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

## 2. DEVICE DESCRIPTION

The XIENCE V Everolimus Eluting Coronary Stent System is a device-drug combination product comprised of a L-605 cobalt chromium (CoCr) alloy balloon expandable stent platform coated with two polymer layers and a drug layer mounted on either a rapid exchange (RX) or over-the-wire (OTW) delivery system. The CoCr stent is identical to the MULTILINK VISION™ (P020047) stent and the MULTI-LINK MINI VISION™ (P020047/S003) stent. The stent coating consists of two layers: a primer layer of poly (n-butyl methacrylate) (PBMA) and a drug matrix layer consisting of a copolymer of vinylidene fluoride and hexafluoropropylene (PVDF-HFP) blended with the anti-proliferative drug everolimus (Certican®, Novartis Pharmaceuticals Corporation) in an 83%/17% (w:w) proportion. Both the primer and drug matrix layer are applied over the entire stent surface. Both PBMA and PVDF-HFP have been used in other FDA-approved vascular devices. Everolimus, also known as Certican®, is under review as a New Drug Application (NDA) in the US for the prevention of organ transplant rejection and has obtained market approval outside of the US. Novartis has received two approvable letters from the FDA. Abbott Vascular is seeking approval for the following stent diameters and lengths:

**TABLE 1. XIENCE V EECSS Device Matrix**

| Diameter (mm) | Stent Length (mm) | | | | | |
|---|---|---|---|---|---|---|
| | 8 | 12 | 15 | 18 | 23 | 28 |
| **2.50** | X | X | X | X | X | X |
| **2.75** | X | X | X | X | X | X |
| **3.0** | X | X | X | X | X | X |
| **3.5** | X | X | X | X | X | X |
| **4.0** | X | X | X | X | X | X |

The drug matrix layer of PVDF-HFP and everolimus is applied to the stent at a drug loading of 100 $\mu g/cm^2$. The longest stent (28 mm) contains the maximum nominal drug content of 181 µg.

XIENCE V stents are supplied pre-mounted on one of two delivery systems: Over-The-Wire (OTW) or Rapid Exchange (RX). Both of the delivery systems are similar in design and performance specifications to the MULTI-LINK RX and OTW VISION™ CSS and MULTI-LINK MINI VISION™ RX and OTW CSS. All delivery catheters contain a semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. Two radiopaque markers located on the distal segment of the inner member are positioned to mark the working length of the balloon. The stent is mounted on the balloon such that the markers reflect the expanded stent length. Deployment of the stent to nominal size is completed with balloon expansion. The delivery catheter is also designed for post-stent dilation using pressures less than or equal to the rated burst pressure, 16 atm. All systems are compatible with a 0.014" guide wire. The OTW and RX systems are compatible with a 6F guide catheter.

Please refer to the Product Description section of this panel pack (provided by Abbott Vascular) for further details.

## 3. REGULATORY HISTORY

XIENCE™ V EECSS was developed by Guidant Vascular and was acquired by Abbott Vascular in April 2006. The clinical investigations for the XIENCE™ V Everolimus-Eluting Coronary Stent System (EECSS) began in December 2003 with SPIRIT FIRST, a 60 patient randomized superiority trial of XIENCE V versus the VISION bare metal stent conducted at 9 investigational sites in Germany, The Netherlands, and Denmark. Enrollment was completed in April 2004. The primary endpoint was angiographic in-stent late loss at 6 months; the XIENCE™ V late loss of 0.10 represented an 88% reduction relative to the VISION™ bare metal stent control group (0.84).

Guidant Vascular initiated SPIRIT II, a 300 patient randomized non-inferiority study of the XIENCE V EECSS versus TAXUS® Express$^{2}$™ (3:1, XIENCE V:TAXUS) at 28 sites in Europe, India and New Zealand. Enrollment began in July 2005 and was completed in November 2005. Abbott met its primary angiographic endpoint of in-stent late loss (LL) at 180 days to show non-inferiority of the XIENCE V versus TAXUS (XIENCE V 0.11 ± 0.27 mm vs. TAXUS 0.36 ± 0.39 mm). An additional pre-specified superiority analysis of the primary endpoint demonstrated the superiority of XIENCE to TAXUS in terms of the primary endpoint of in-stent LL at 180 days ($p < 0.0001$).

FDA did not review the SPIRIT FIRST and SPIRIT II study protocols prior to their commencement. Based on encouraging results observed in SPIRIT I and II, Guidant moved forward with further development of the Xience program and developed a pivotal trial to meet US regulatory requirements.

In March 2005, Guidant Vascular proposed SPIRIT III, a US pivotal trial for the XIENCE V EECSS. The SPIRIT III Clinical Trial is composed of five parts; a US randomized clinical trial (RCT) and four non-randomized arms. The non-randomized arms consist of a 4.0 mm diameter stent, a 2.25 mm diameter stent, a 38 mm length stent, and one Japanese non-randomized arm. In addition, a pharmacokinetic (PK) substudy was conducted in a subset of subjects in the RCT, 4.0 nonrandomized arm, and Japan arm. Enrollment was never started for the 2.25 mm diameter and 38 mm length arms and Abbott does not intend to initiate the 38 mm length arm.

The SPIRIT III randomized arm was a 1002 patient randomized, non-inferiority study of the XIENCE V EECSS versus TAXUS Express2 (2:1, XIENCE V:TAXUS) at 65 U.S. sites. Enrollment began in June 2005 and was completed in March 2006. The definition of study success for SPIRIT III required that both the angiographic endpoint of in-segment late loss at 240 days and clinical endpoint of ischemia-driven target vessel failure (TVF) be met. The XIENCE V met its angiographic endpoint of in-segment late loss (LL) at 240 days to show non-inferiority of the XIENCE V versus TAXUS (XIENCE V 0.14 ± 0.41 mm vs. TAXUS 0.28 ± 0.48 mm, $p < 0.0001$). XIENCE V also met its clinical endpoint of TVF at 270 days to show non-inferiority of XIENCE V to TAXUS (XIENCE V 7.2% vs. TAXUS 9.0%, $p < 0.0001$). Additionally, since non-inferiority was demonstrated in this study, a superiority analysis of the angiographic

endpoint was performed, which showed the superiority of XIENCE to TAXUS for the primary endpoint of in-segment late loss at 240 days ($p = 0.0037$).

The SPIRIT III 4.0 mm arm was a single arm registry that compared 240-day in-segment late loss to the TAXUS control arm of the SPIRIT III RCT. The 4.0 mm arm in-segment late loss was 0.17 mm, which was found to be non-inferior to the TAXUS control arm of 0.28 mm ($p<0.0001$). The in-segment late loss was found to be comparable to the XIENCE V arm of the RCT.

The SPIRIT III Japanese non-randomized arm is a single arm registry designed to evaluate XIENCE V EECSS in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 4.25 mm. This study was designed to enroll up to 88 subjects at up to 12 sites in Japan. The primary endpoint is 240-day in-segment late loss, which will be compared to the TAXUS control arm of the SPIRIT III RCT. Enrollment commenced on December 13, 2005 and was completed on March 28, 2007. In addition, a pharmacokinetic substudy was conducted. The purpose of the pharmacokinetic substudy was to determine the pharmacokinetics of everolimus delivered by the XIENCE V in the Japanese arm of the SPIRIT III trial. The pharmacokinetic data is available at this time, but data concerning the primary endpoint is not available.

Abbott proposed the inclusion of SPIRIT FIRST, SPIRIT II and SPIRIT III RCT for submission in a PMA application. FDA agreed at the time of initiation of Spirit III that the number of patients in the overall clinical program was appropriate for a DES that incorporated a "studied drug." FDA considers everolimus to be a "studied drug," that is, a molecular entity that has been previously approved or studied under IND, and for which access to these study data are available. Novartis Pharmaceuticals Corporation has provided FDA the right to review these data in support of the Abbott IDE and PMA applications. Access to these data has given FDA the ability to see that key safety questions regarding everolimus have been addressed previously by Novartis Pharmaceuticals Corporation.

FDA received the XIENCE V EECSS PMA submission on June 1, 2007. Additional information has been requested by FDA over the course of the review. The following clinical datasets (with latest available patient follow-up data) were provided for review within the PMA and its amendments: SPIRIT FIRST (patient follow-up through 3 years), SPIRIT II (1 year), SPIRIT III RCT (1 year), and SPIRIT III 4.0 mm (1 year). Two year data from SPIRIT II should be available at the end of the 2007.

*Additional studies*

In August 2006, Abbott Vascular initiated the SPIRIT IV study to further evaluate XIENCE V EECSS and potentially to contribute additional data to the analysis of the SPIRIT III major secondary endpoint of 240-day TVF. A flexible study design was proposed that would combine Spirit IV clinical data with the original Spirit III dataset in a manner that would increase the effective sample size of the pivotal cohort. However, after a planned interim analysis of SPIRIT III, an independent statistician that was

specifically utilized for the prespecified flexible design strategy determined that data from SPIRIT IV would not be needed to provide sufficient statistical power to evaluate the SPIRIT III RCT co-primary endpoint of 270-day TVF.

Following this decision, Abbott decided to increase the sample size of SPIRIT IV and to further study the Xience V in a more complex patient population. The SPIRIT IV trial is a 3,690 patient single-blinded, multi-center, randomized trial (2:1, XIENCE V: TAXUS® Express$^{2}$™) in subjects with a maximum of three de novo native coronary artery lesions, with a maximum of two lesions per epicardial vessel, and lesions may be located at a bifurcation. Overlapping stents are allowed for lesions > 22 mm. The primary endpoint is ischemia-driven major adverse cardiac events (MACE) at 270 days. This study is still currently enrolling subjects and any collected data is still blinded.

The Sponsor has continued to develop a robust clinical development program. Additional studies not presented in this PMA are the following: The SPIRIT V study is an outside the U.S. study consisting of two concurrent studies: the Diabetic Study (300 patients) and the Registry (2700). The SPIRIT V Diabetic Study is a randomized multi-center study comparing the XIENCE V EECSS to the TAXUS® Liberté™ (2:1) in the treatment of diabetic patients with coronary artery lesions who fulfill the eligibility criteria (per protocol). The SPIRIT V Registry is a single arm, multi-center registry evaluating performance of the XIENCE V in real-world use, per its Instructions for Use (IFU). The study will involve up to 150 investigational sites outside of the United States in countries where XIENCE V is approved, with exception of Canada and Thailand, where SPIRIT V is being conducted as an investigational clinical trial. The SPIRIT V study will enroll approximately 3,000 patients. Enrollment commenced in the Registry on November 6, 2006. As of February 28, 2007 28 international sites have enrolled 292 patients in the Registry. The Diabetic Study enrollment is anticipated to begin in March 2007. The SPIRIT V protocol was not reviewed by FDA.

Abbott is conducting two additional studies outside of the US, SPIRIT WOMEN and XIENCE V India. SPIRIT WOMEN is a 2000 patient all-comers study. Of these, 1550 will be part of a registry arm and 450 will be randomized between XIENCE V and Cypher (2:1). Enrollment began in July 2007. XIENCE V India is planned to be a 1000 patient single arm registry. Enrollment has not yet begun. Neither protocol was reviewed by FDA.

## 4. STUDIES OF THE DRUG SUBSTANCE

The active pharmaceutical ingredient in XIENCE V EECSS is everolimus [40-O-(2-hydrosyethyl)-rapamycin] provided by Novartis Pharmaceuticals Corporation. Everolimus, also known as Certican®, is a novel semi-synthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Rapamycin (INN: Sirolimus) is a secondary macrolide metabolite produced by certain actinomycete strains. The structure of everolimus consists of a 2-hydroxyethyl group in position 40 of sirolimus. Everolimus is currently under review as a New Drug Application (NDA) in the US for the prevention of organ transplant rejection and has obtained market approval in over 60 countries including 25 countries in the European Union. Novartis has received two approvable letters from the FDA and is currently conducting additional clinical studies to support dose recommendations with Cyclosporin in kidney and heart transplantation.

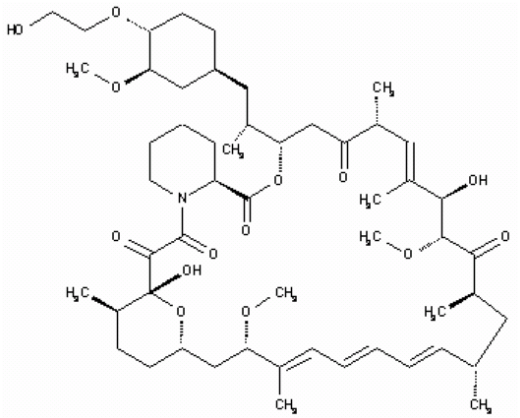


**Figure 1: Chemical Structure of Everolimus**

Novartis Pharmaceuticals Corporation, manufacturer of everolimus, has provided Abbott Vascular with the right to reference their IND and NDA to support the XIENCE V EECSS PMA application.

### a. Safety Pharmacology

Everolimus (Certican®), an analog of rapamycin, is an immunosuppressive agent that inhibits growth factor-induced cell proliferation and consequently is being developed for prevention of restenosis in stented arteries. The no observed adverse effect level (NOAEL) for orally administered everolimus is 1.5 mg/kg/day (Cmax 110 ng/ml, $AUC_{0-24}$ 1142 ng.hr/ml) in the monkey which is about 80- and 133-fold higher than the peak and exposure levels of everolimus obtained from a single Xience V everolimus stent (100 μg/cm$^2$, 169 μg/stent) implant in the pig (Cmax 1.4 ng/ml, $AUC_{0-24}$ 8.6 ng.hr/ml). The Cmax and $AUC_{0-24}$ from human implantation of a Xience V stent (181 μg/stent) implant were 2.2 ng/ml and 15 ng.hr/ml, which is about 50- and 75-fold lower than the NOAEL systemic exposure of orally administered everolimus in the monkey (Cmax 110 ng/ml, $AUC_{0-24}$ 1142 ng.hr/ml).

Reviews of these data did not indicate any safety concerns and supported initiation of the human clinical studies of the XIENCE V EECSS.

**b. Toxicology**

Toxicology information on everolimus was incorporated by reference to the Novartis NDA. FDA has reviewed this information; there are no remaining concerns.

Based on this information, the labeling proposed by the applicant contains the following precaution:

> Pregnancy Category C: There are no adequate Everolimus or XIENCE V related studies in pregnant women. XIENCE V effects on pre- and post-natal rat development were no different than the controls. Everolimus when administered at oral doses of 0.1 mg/kg and above showed effects on pre- and post-natal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.
>
> Effective contraception should be initiated before implanting a XIENCE V Stent and continued for one year post-implantation. The XIENCE V Stent should be used in pregnant women only if potential benefits justify potential risks. XIENCE V safety has not been evaluated in males intending to father children.

**c. Absorption, Distribution, Metabolism, and Excretion (ADME) Studies**

FDA recommends ADME studies of the drug substance in several animal models. The purpose of this testing is to characterize the absorption, distribution, metabolism, and excretion profiles in each species. This information has been incorporated by reference to the Novartis NDA. FDA has reviewed this information; there are no remaining concerns.

Based on this information, the labeling proposed by the applicant contains the following precaution:

> **6.3 Drug Interactions**
> Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of Everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with XIENCE V Stent. Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V Stent in a subject taking a drug with known interaction with Everolimus. Everolimus, when prescribed as an oral medication may interact with the following drugs/foods:
>
> - CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers)

- Inducers of CYP3A4 isozyme (rifampicin, rifabutin, carbamazepin, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (Terfenadine, astemizole)
- Grapefruit juice

## 5. PRE-CLINICAL STUDIES

### a. Stent Functional Testing

FDA recommends stent functional testing as outlined in our guidance document "Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems." The purpose of this testing is to ensure that the stent platform (i.e., metal stent) functions as intended. The following tests were performed on the XIENCE V EECSS and results were submitted to the FDA for review:

- Material Analysis (stent: chemical analysis, grain size, inclusion content, SEM)
- Stent Corrosion Resistance
- Dimensional Verification
- Percent Surface Area
- Uniformity of Expansion
- Foreshortening
- Recoil
- Radial (Hoop) Strength
- Stent Integrity
- Mechanical Properties
- Stress Analysis
- Accelerated Fatigue
- MRI Safety
- Radiopacity

Clarifications have been requested of the sponsor regarding the stent functional testing. The FDA is working interactively with the sponsor to ensure that these issues are resolved in a timely fashion.

### b. Stent Coating Testing

For drug-eluting stents, FDA recommends additional testing of the stent coating to ensure that the integrity of the coating will be maintained over the simulated use of the device. The following stent coating tests were performed on the XIENCE V EECSS and results were submitted to the FDA for review:

- Coating Thickness and Uniformity
- Cross Sectional Analysis
- Content Uniformity Along the Stent Length
- Coating Balloon Adhesion
- Microstructure Analysis
- Coating Adhesion Characterization
- Stent Coating Surface Integrity

- Coating Stress Analysis
- Particulate Analysis

Clarifications have been requested of the sponsor regarding the pre-clinical coating test results and test methods utilized. The FDA is working interactively with the sponsor to ensure that these issues are resolved in a timely fashion.

**c. Stent Delivery System Testing**

FDA recommends stent functional testing as outlined in our guidance document "Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems." The purpose of this testing is to ensure that the stent delivery systems function as intended. The following stent delivery system tests were performed on the XIENCE V EECSS and results were submitted to the FDA for review:

- Delivery, Deployment and Retraction
- Balloon Rated Burst Pressure (RBP=16atm)
- Balloon Fatigue
- Stent Diameter vs. Balloon Pressure (Compliance Chart)
- Bond Strength
- Crossing Profile
- Inflation and Deflation Time
- Stent Securement
- Delivery System Guiding Catheter Pullback Test
- Delivery System Preparation Test
- Delivery System Shaft Pressure Test
- Delivery System Inner Membrane Collapse Test
- Delivery System Coating Friction Test
- Delivery System Coating Adhesion Test

Clarifications have been requested of the sponsor regarding the stent delivery system testing. The FDA is working interactively with the sponsor to ensure that these issues are resolved in a timely fashion.

**d. Animal Studies**

Abbott Vascular has conducted 33 animal studies of the XIENCE V EECSS. *In vivo* animal testing was conducted to demonstrate the safety of the XIENCE™ V EECSS. Studies were carried out in a porcine non-atherosclerotic coronary artery model at multiple time points to determine the clinical dose of everolimus that should be incorporated into XIENCE V, to determine the pharmacokinetics of XIENCE V and to evaluate the safety of XIENCE V. Animal studies were also utilized to assess the safety of overlapping two XIENCE V stents, to assess a maximum dose based a determined drug safety margin, and to evaluate the safety of the polymer alone at both an equivalent loading to that in the XIENCE V and using a bulk polymer system. Supportive safety data and overlapping stent safety data have also been generated in a rabbit non-

atherosclerotic iliac model. Overall, the animal studies have demonstrated the safety of the XIENCE V stent in two animal models at multiple time points. The Xience V incorporating a drug loading of 100 ug/$cm^2$ and the polymer-coated stent without Everolimus appear to illicit similar biologic responses to those seen with the MULTI-LINK VISION® bare metal cobalt chromium stent when implanted in the pig model. FDA has reviewed the submitted animal studies and no further concerns remain.

**e. Chemistry, Manufacturing, & Controls (CMC)**

The drug substance, everolimus, is purchased from Novartis Pharma AG of Basel, Switzerland. CMC information describing the manufacture and controls of everolimus drug substance is proprietary to Novartis, and is incorporated in the Xience V PMA by authorized reference to two NDAs. The CMC information for the drug substance was reviewed by FDA and found to be acceptable.

For the finished product, Abbott Vascular has provided the details of the manufacturing process, the quantitative composition of the product, and controls for each of the components used in the manufacture of the XIENCE V stent (i.e., everolimus drug substance, and polymer), including the analytical test methods and supporting validation data.

Abbott Vascular has also proposed complete finished product specifications, including the analytical procedures and supporting validation data. At this time, the specifications have not been finalized and are still under discussion with FDA.

Abbott has submitted 6-month primary stability data, 3-month site-specific stability data, up to 12-month clinical stability data, and up to 20-month supportive stability data. Stress studies are completed and data are presented as well. Based on the stability data, Abbott has proposed 9-months of shelf life for their product. Although the stability data appear to support the proposed shelf life, shelf life can not be determined until the specifications are finalized.

**f. Sterilization**

The XIENCE V Everolimus Eluting Coronary Stent System is provided sterile. After reviewing the information submitted by the sponsor, FDA has concluded that under the stated exposure conditions, the ethylene oxide cycle will render the XIENCE V sterile at a sterility assurance level of $10^{-6}$, or the probability of one survivor in one million products sterilized. Ethylene oxide and ethylene chlorohydrin residual analysis was performed to confirm that residual levels are below those considered tolerable and safe per accepted standards. Likewise, Limulus Amebocyte Lysate analysis was performed to confirm that bacterial endotoxin levels are below stated acceptance criteria. Packaging studies were performed to demonstrate that the current packaging configuration will maintain a sterile barrier to support a one year shelf life claim.

**g. Biocompatibility**

Abbott Vascular has identified all material components of the stent and delivery systems.

Abbott Vascular has provided data from the following biocompatibility evaluations of the finished drug-eluting stent: cytotoxicity, sensitization, intracutaneous reactivity, hemocompatibility, implantation, genotoxicity, teratogenicity, and carcinogenicity.

Data from testing of the finished drug-eluting stent and delivery system has been provided from the following biocompatibility evaluations: cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, pyrogenicity, hemocompatibility, clotting time (coagulation).

Additionally, Abbott has provided data from the following biocompatibility evaluations of the polymer-only coated stent – cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, and implantation.

Clarifications have been requested of the sponsor regarding teratogenicity and carcinogenicity testing. FDA is working interactively with the sponsor to ensure that these issues are resolved in a timely fashion.

**h. Manufacturing**

FDA has reviewed the manufacturing information and facility inspections are pending.

## 6. DEFINITIONS & ABBREVIATIONS

**Acute Success**
Acute Success is classified according to the following definitions:

- **Clinical Device Success**
  Successful delivery and deployment of the first inserted study stent (in overlapping stent setting a successful delivery and deployment of the first and second study stent) at the intended target lesion and successful withdrawal of the stent delivery system with attainment of final residual stenosis of less than 50% of the target lesion by QCA (by visual estimation if QCA unavailable). Standard pre-dilation catheters and post-dilatation catheters (if applicable) may be used. Bailout subjects will be included as device success only if the above criteria for clinical device are met.
- **Clinical Procedure Success**
  Successful delivery and deployment of the study stent or stents at the intended target lesion and successful withdrawal of the stent delivery system with attainment of final residual stenosis of less than 50% of the target lesion by QCA (by visual estimation if QCA unavailable) and/or using any adjunctive device without the occurrence of major adverse cardiac event (MACE) during the hospital stay with a maximum of first seven days post index procedure. In dual lesion setting both lesions must meet clinical procedure success.

**Adverse Event**
An adverse event is any untoward medical occurrence in a subject or clinical investigation when subject was administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the investigational product

**Analysis lesion**
Analysis lesion is defined as the target lesion for subjects with single *de novo* lesion and a randomly selected lesion for subjects with two *de novo* lesions. If the randomized analysis lesion cannot be treated for any reason, the other target lesion, by default, becomes the analysis lesion.

**Angiographic Binary Restenosis (ABR) Rate**
Percent of subjects with a follow-up percent diameter stenosis of ≥ 50% per QCA.

**Anticipated Adverse Event**
Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or Instructions For Use (IFU), that is identified or worsens or occurs in frequency that is not considered normal during a clinical trial.

**Death**

- ***Cardiac death*** is defined as any death in which a cardiac cause cannot be excluded. (This includes but is not limited to acute myocardial infarction, cardiac perforation/pericardial tamponade, arrhythmia or conduction abnormality, cerebrovascular accident within 30 days of the procedure or cerebrovascular accident suspected of being related to the procedure, death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.)
- ***Non-cardiac death*** is defined as a death not due to cardiac causes (as defined above).

**Incomplete Apposition**
Failure of the stent to completely appose to the vessel wall after placement is defined as one or more stent strut separated from the vessel wall with evidence of blood speckles behind the strut in the ultrasound image.

**In-Stent**
Within the margins of the stent.

**In-Segment**
Within the margins of the stent and 5 mm proximal and 5 mm distal to the stent.

**Intent To Treat (ITT) Population**
The principle of including outcomes of all subjects in the analysis who are randomized into the trial, regardless of the treatment actually received.

**Ischemia-Driven Major Adverse Cardiac Event (MACE)**
The composite endpoint comprised of:
- cardiac death
- myocardial infarction (MI, classified as Q-wave and Non-Q wave MI)
- ischemia-driven target lesion revascularization (TLR) by CABG or PCI

**Ischemia-Driven Target Lesion Revascularization (TLR)**
Revascularization at the target lesion associated with any of the following:
- positive functional ischemia study
- ischemic symptoms and angiographic minimal lumen diameter stenosis ≥ 50% by core laboratory quantitative coronary angiography (QCA)
- revascularization of a target lesion with diameter stenosis ≥ 70% by core laboratory QCA without either ischemic symptoms or a positive functional study

**Ischemia-Driven Target Vessel Failure (TVF)**
The composite endpoint comprised of
- cardiac death
- myocardial infarction (Q wave and Non-Q wave)
- ischemia-driven target lesion revascularization by CABG or PCI
- ischemia-driven target vessel revascularization by CABG or PCI

**Ischemia-Driven Target Vessel Revascularization (TVR)**
Revascularization in the target vessel associated with any of the following:

- positive functional ischemia study
- ischemic symptoms and an angiographic minimal lumen diameter stenosis ≥ 50% by core laboratory quantitative coronary angiography (QCA)
- revascularization of a target vessel with diameter stenosis ≥ 70% by core laboratory QCA without either ischemic symptoms or a positive functional study

**Late-Acquired Incomplete Apposition**
Incomplete apposition of the stent at follow-up, which was not present post-procedure. See also "Incomplete Apposition."

**Late Loss (LL)**
General definition: Calculated as MLD post-procedure – MLD at follow-up

- **In-segment Late Loss:** in-segment MLD post-procedure – in segment MLD at follow-up
- **In-stent Late Loss:** in-stent MLD post-procedure – in-stent MLD at follow-up
- **Proximal Late Loss:** proximal MLD post-procedure – proximal MLD at follow-up (proximal defined as within 5 mm of healthy tissue proximal to stent placement)
- **Distal Late Loss:** distal MLD post-procedure – distal MLD at follow-up (distal defined as within 5 mm of healthy tissue distal to stent placement)

**MACE**
The composite endpoint comprised of

- cardiac death
- myocardial infarction (Q wave and Non-Q wave)
- ischemia-driven target lesion revascularization by CABG or PCI

**Minimum Lumen Diameter (MLD)**
The average of two orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent or in segment. MLD is visually estimated during angiography by the Investigator; it is measured during QCA by the Angiographic Core Lab.

**Myocardial Infarction (MI)**

- ***Q wave MI***
  Development of new, pathological Q wave on the ECG
- ***Non-Q wave MI***
  Elevation of CK levels to ≥ **two** times the upper limit of normal (ULN) with elevated CKMB in the absence of new pathological Q waves

**Percent Diameter Stenosis**
The value calculated as 100 * (1 - MLD/RVD) using the mean values from two orthogonal views (when possible) by QCA.

**Percent Volume Obstruction**
Defined as stent intimal hyperplasia and calculated as 100*(Stent Volume – Lumen Volume)/Stent Volume by IVUS.

**Persisting Incomplete Apposition**
Incomplete apposition at follow-up that was present post-procedure. See also "Incomplete Apposition."

**Per-Treatment-Evaluable Populations**
A subset of subjects in the full analysis set, who are characterized by those subjects

- who received a study device at the target lesion (subjects to be analyzed based on the treatment stent that they actually received)
- with no 'major procedural protocol deviations'* except deviations relating to treatment arm
- for whom follow-up data is available

**Reference Vessel Diameter (RVD)**
An approximation of the diameter of the vessel at the location of the target lesion. RVD is visually estimated during angiography by the Investigator and it is measured during QCA by the Angiographic Core Laboratory

**Restenosis**
Re-narrowing of the artery following the removal or reduction of a previous narrowing.

**Serious Adverse Event (SAE)**
An event that is fatal or leads to a serious deterioration in health that

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject or subject and/or may require intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Stent Thrombosis**
Stent thrombosis will be categorized as acute (≤ 1day), subacute (>1day ≤ 30 days) and late (>30 days) and will be 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. *(Non-specific ST/T changes, and cardiac enzyme elevations do not suffice)

  Any thromboses that occur less than 30 days after the index procedure will not be counted as restenosis.

***Stent thrombosis per ARC definition***
Stent Thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed.

**Timing:**
- Acute stent thrombosis*: 0 - 24 hours post stent implantation
- Subacute stent thrombosis*: > 24 hours to 30 days post stent implantation
- Late stent thrombosis†: 30 days - 1 year post stent implantation
- Very late stent thrombosis†: > 1 year post stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0 - 30 days) - this definition is currently used in the community.

† Including "primary" as well as "secondary" late stent thrombosis; "secondary" late stent thrombosis is a stent thrombosis after a target segment revascularization.

**Categories (Definite, Probable, and Possible)**

**Definite stent thrombosis**
Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

**Angiographic confirmation of stent thrombosis***
The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
- Nonocclusive
  - Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
- Occlusive thrombus

- TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

† Intracoronary thrombus

* The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

**Pathological confirmation of stent thrombosis**

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

**Probable stent thrombosis**

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days‡
- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

‡ For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

**Possible stent thrombosis**

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

**Stent Thrombosis After TLR: Censored vs. Non-Censored**

Censoring stent thrombosis events that occur post-TLR performed for stent restenosis may be appropriate as the thrombosis may be related to the treatment chosen to treat restenosis (e.g., brachytherapy) rather than the type of stent used in the index procedure. Alternatively, censoring stent thrombosis events that occur after TLR may bias results in favor of devices with higher restenosis risks. Therefore, stent thrombosis data presented in this review will report both TLR-censored and TLR-uncensored rates as follows:

- ***ARC Definite + probable (TLR-censored):*** Adjudicated stent thrombosis meeting the definite or probable ARC definition with censoring of any definite or probable stent thrombosis events that may have occurred after a TLR.

- ***ARC Definite + probable (TLR-uncensored):*** Adjudicated stent thrombosis meeting the definite or probable ARC definition including any

definite or probable stent thrombosis events that may have occurred after a TLR.

The ARC definitions are available in the following publication: Cutlip DE, Windecker S, Mehran R, Boam A, et al. Academic Research Consortium. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation. 2007; 115: 2344-51.

**Target Lesion**
Lesion that has met the angiographic inclusion and exclusion criteria and that is to be treated during the index procedure. A maximum of two *de novo* lesions can be treated in this study. (Physician has to number the lesions prior to contacting the randomization service)

**Target Vessel**
The entire epicardial vessel in which the treated lesion is located.

## 7. CLINICAL STUDIES

Data from SPIRIT FIRST, SPIRIT II, and SPIRIT III US have been provided to support this application. Table 2 below provides a brief overview of each study design:

**TABLE 2. Summary of XIENCE V EECSS Clinical Trials**

| | SPIRIT FIRST (First in Man OUS) | SPIRIT II OUS | SPIRIT III Pivotal US Studies | | SPIRIT III Japan |
|---|---|---|---|---|---|
| | | | RCT | 4.0 mm Registry | |
| **Study Type/ Design** | • Multi-center<br>• Randomized<br>• Single-blinded<br>• BMS Control | • Multi-center<br>• Randomized<br>• Single-blinded<br>• Active Control | • Multi-center<br>• Randomized<br>• Single-blinded<br>• Active Control | • Multi-center<br>• Single-arm<br>• Open-label | • Multi-center<br>• Single-arm<br>• Open-label |
| **Planned Number of Subjects** | Total: 60<br>XIENCE V: 30<br>Control BMS: 30 | Total: 300<br>XIENCE V: 225<br>Taxus: 75 | Total: 1,002<br>XIENCE V: 668<br>Taxus: 334 | Total: 80 | Total: 88 |
| **Treatment** | Single de novo lesion | Up to two de novo lesions in different epicardial vessels | Up to two de novo lesions in different epicardial vessels | Up to two de novo lesions in different epicardial vessels | Up to two de novo lesions in different epicardial vessels |
| **Lesion Size** | RVD: 3 mm by QCA<br><br>Length: ≤ 12 mm | RVD: ≥ 2.5 to ≤ 4.25 mm<br><br>Length: ≤ 28 mm | RVD: ≥2.5 to ≤3.75 mm<br><br>Length: ≤ 28 mm | RVD: > 3.75 to ≤ 4.25 mm<br><br>Length: ≤ 28 mm | RVD: ≥ 2.5 ≤ 4.25 mm<br><br>Length: ≤ 28 mm |
| **Stent Sizes (XIENCE V)** | D: 3.0 mm<br>L: 18 mm<br><br>Planned overlapping was not allowed | D: 2.5, 3.0, 3.5, 4.0mm<br>L: 8, 18, 28 mm<br><br>Planned overlap: 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 | D: 2.5, 3.0, 3.5 mm<br>L: 8, 18, 28 mm<br><br>Planned overlap: 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 | D: 4.0 mm<br>L: 8, 18, 28 mm<br><br>Planned overlap: 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 | D: 2.5, 3.0, 3.5, 4.0 mm<br>L: 8, 18, 28 mm<br><br>Planned overlap: 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 |
| **Post-procedure Anti-platelet Therapy** | Clopidogrel 3 months (or ticlopidine per site standard), | Clopidogrel 6 months (or ticlopidine per site standard), Aspirin 1 year | Clopidogrel 6 months (or ticlopidine per site standard), Aspirin 5 years | 4.0 mm: same as RCT | Ticlopidine 3 months, Aspirin 5 years |

| | | | | | |
|---|---|---|---|---|---|
| | Aspirin 1 year | | | | |
| **Primary Endpoint** | In-stent late loss at 180-day | In-stent late loss at 180-day | In-segment late loss at 240-day | In-segment late loss at 240-day | In-segment late loss at 240-day |
| **Major Secondary Endpoint** | %VO at 180-day | None | TVF at 270-day | None | None |
| **Clinical Follow-up Schedule** | 30, 180, 270 days, 1 to 5 years | 30, 180, 270 days, 1 to 5 years | 30, 180, 240, 270 days, 1 to 5 years | 30, 180, 240, 270 days, 1 to 5 years | 30, 180, 240, 270 days, 1 to 5 years |
| **Follow-up Available to Date** | 3 year | 1 year | 1 year | 1 year | Follow-up is ongoing. The 270-day follow-up data lock is anticipated in Feb 2008 |
| **Angiographic Follow-up** | 180-day<br>1-year (all) | 180-day (all)<br>2-year (N=152) | 240 days (N=564) | 240 days | 240 days |
| **IVUS Follow-up** | 180-day<br>1-year (all) | 180-day<br>2-year (N=152) | 240 days (N=240) | None | 240 days |
| **PK Study** | None | Min 15 subjects with single lesion, max 20 with dual lesions | US: Min 15 subjects with single lesion, max 20 with dual lesions | | Japan: Min 10 subjects with single lesion, max 20 with dual lesions |

All studies utilized core labs for evaluation of angiographic, IVUS, and ECG data. Trials were monitored by Data Safety Monitoring Boards and events were adjudicated by Clinical Events Committees. SPIRIT I and II both utilized Cardialysis B.V. (Rotterdam, The Netherlands) as the QCA and IVUS core labs. SPIRIT III utilized Cardiovascular Research Foundation (New York, NY) as the QCA core lab and the Center for Research in Cardiovascular Interventions (Stanford, CA) as the IVUS core lab.

### a. SPIRIT FIRST

**Objective**: The objective of the SPIRIT FIRST clinical trial was to assess the feasibility and performance of XIENCE V (called MULTI-LINK VISION-E RX Drug Eluting Stent System in SPIRIT FIRST) in the treatment of subjects with a single *de novo* target lesion in a native coronary artery with reference vessel diameter (RVD) of 3.0 mm and lesion length ≤ 12mm assessed by QCA.

**Primary endpoint**: In-stent late loss at 180 days.

**Important secondary endpoints**
The major secondary endpoint was in-stent percent volume obstruction (%VO) at 180 days that was measured by 3D IVUS analysis [(stent volume-lumen volume)/stent volume]. Other endpoints included target vessel failure (TVF), major adverse cardiac event (MACE) and stent thrombosis at each follow-up time-point.

**Design**: The SPIRIT FIRST clinical trial was a prospective, single-blinded, 1:1 randomized, controlled, parallel two-arm, multicenter, superiority trial designed to enroll 60 subjects.

**Randomization**: Subjects were randomly assigned to receive either XIENCE V or MULTI-LINK VISION bare metal stent in a 1:1 ratio. Randomization was stratified by site and diabetic status to balance the distribution of subjects across treatment arms.

**Key Inclusion Criteria:**
1. Subjects ≥ 18 years of age
2. Had angina or a positive functional test identified for elective stenting
3. A single *de novo* target lesion in a native coronary artery
4. Reference vessel diameter (RVD) of 3.0 mm and lesion length ≤ 12 mm assessed by QCA (Quantitative Coronary Angiography)
5. % diameter stenosis (%DS) of ≥ 50% and < 100%
6. TIMI flow of ≥ 1

**Key Exclusion Criteria:**
1. Recent myocardial infarction (within 3 days)
2. Unstable arrhythmia
3. Left ventricular ejection fraction ≤ 30%
4. Target lesion located in an ostium, bifurcation lesion, unprotected left main trunk, excessive tortuosity, extreme angulation (≥ 90°), moderate to heavy calcification, target vessel containing thrombus or other significant lesions (≥ 40% DS) in the target

**Stent procedure:** Eligible subjects underwent mandatory pre-dilatation of the target lesion by standard balloon angioplasty. 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.

**Antiplatelet therapy:** Subjects were maintained on 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.

**Study site and dates of enrollment:** The first subject was enrolled on December 16, 2003 and the last subject was enrolled on April 1, 2004. A total of 60 subjects were randomized and enrolled consecutively in this trial at 9 European investigational sites. To date, 54 of 56 per treatment evaluable subjects (96%) have completed follow-up evaluations at the *three-year* timepoint.

**Follow up schedule:** Subjects were clinically evaluated at 30, 180 and 270 days and at 1 and 2 years following the index procedure. Further clinical observations will be performed at 3, 4 and 5 years. Angiography and IVUS follow-up were to be performed in all subjects at 180 days and at 1 year.

**Statistical Analyses:** Analysis of the follow-up data was performed in the per-treatment evaluable population. The trial had a 95% statistical power based on the primary endpoint to detect a 0.48 mm difference in in-stent late loss with a 0.05 one-sided alpha, assuming 70% of the follow-up angiographies were available.

***Results:***

The total enrollment in SPIRIT FIRST was 60 patients; of 56 treatment evaluable patients, 27 received the Xience V stent and 29 received the VISION stent. Angiographic follow-up for the primary endpoint at 6 months was 89.3% (50/56). The baseline demographics, lesion characteristics, and vessel characteristics are outlined in Tables 3 and 4. Comparison of baseline demographic and angiographic variables for each arm of SPIRIT FIRST is limited by the small sample size in this First in Man study.

**Table 3. SPIRIT FIRST Baseline Demographics**

| | XIENCE V (n=27) | VISION (n=29) | Difference [95% CI] |
|---|---|---|---|
| **Subject Demography** | | | |
| Age (yrs) | 64.21± 9.56 (27) | 61.36± 9.31 (29) | -2.85% [ -7.91, 2.21] |
| Male | 70.4% (19/27) | 75.9% (22/29) | -5.49% [-27.79%, 17.15%] |
| Current Cigarette Use | 28.0% (7/25) | 31.0% (9/29) | -3.03% [-25.82%, 20.89%] |
| Any Diabetes | 11.1% (3/27) | 10.3% (3/29) | 0.77% [-16.84%, 19.01%] |
| Diabetes Req. Medication | 3.7% (1/27) | 3.4% (1/29) | 0.26% [-13.81%, 15.11%] |

| | | | |
|---|---|---|---|
| Hypertension Req. Medication | 70.4% (19/27) | 41.4% (12/29) | 28.99% [ 3.01%, 50.00%] |
| Hyperlipidemia Req. Medication | 70.4% (19/27) | 75.9% (22/29) | -5.49% [-27.79%, 17.15%] |
| Prior Myocardial Infarction | 24.0% (6/25) | 13.8% (4/29) | 10.21% [-10.71%, 31.33%] |
| Prior CABG on Target Vessel | 0.0% (0/27) | 0.0% (0/29) | 0.00% [-11.70%, 12.46%] |
| Prior Cardiac Intervention | 19% (5/27) | 7% (2/29) | 11.62% [ -6.65%, 30.47%] |
| **Target Vessel** | | | |
| LAD | 48.1% (13/27) | 44.8% (13/29) | 3.32% [-21.45%, 27.58%] |
| LCX | 22.2% (6/27) | 20.7% (6/29) | 1.53% [-19.64%, 23.01%] |
| RCA | 29.6% (8/27) | 34.5% (10/29) | -4.85% [-27.66%, 18.96%] |
| **Number of diseased vessels >50% stenosed** | | | |
| Single | 74.1% (20/27) | 79.3% (23/29) | -5.24% [-26.90%, 16.58%] |
| Double | 22.2% (6/27) | 17.2% (5/29) | 4.98% [-15.86%, 25.87%] |
| Triple | 3.7% (1/27) | 3.4% (1/29) | 0.26% [-13.81%, 15.11%] |
| **Indication for PCI** | | | |
| **History of Angina** | 96.3% (26/27) | 93.1% (27/29) | 3.19% [-12.22%, 18.57%] |
| Stable Angina (CCS III or IV) | 37.0% (10/27) | 51.7% (15/29) | -14.69% [-37.61%, 10.81%] |
| Unstable Angina (Braunwald III) | 0.0% (0/27) | 3.4% (1/29) | -3.45% [-17.18%, 9.33%] |
| **GP IIb/IIIa inhibitor Use*** | 7.4% (2/27) | 3.4% (1/29) | 3.96% [-10.77%, 20.17%] |
| **Lesion Morphology** | | | |
| Calcification (moderate/severe) | 22.2% (6/27) | 48.3% (14/29) | -26.05% [-46.89%, -0.98%] |
| Thrombus | 3.7% (1/27) | 0.0% (0/29) | 3.70% [ -8.38%, 18.28%] |
| Eccentric Lesion | 100.0% (27/27) | 89.7% (26/29) | 10.34% [ -3.83%, 26.39%] |
| Lesion Angulation > 45deg | 14.8% (4/27) | 0.0% (0/29) | 14.81% [ 0.12%, 32.48%] |

*Diabetes Req. Insulin data were not available for SPIRIT FIRST.
*Prior PCI and Prior CABG were not captured on CRF. Instead Prior CABG on Target Vessel and Prior Cardiac Intervention were captured.
*Stable and Unstable angina not available for this study. Instead, History of Angina was captured.
*Data on pre- and post-procedure GP IIb/IIIa was not collected. Timepoint was not specified on CRF.
*The Exact 95% confidence interval is calculated using Wilson score method

**TABLE 4. SPIRIT FIRST Treatment Lesions: Baseline Lesion and Vessel Characteristics**

| | Xience (n=27) | VISION (n=29) | Difference [95% CI] |
|---|---|---|---|
| **Total number of lesions treated** | | | |
| One | 100% (27/27) | 100% (29/29) | 0.00% [-12.46%, 11.70%] |
| Two | 0% (0/27) | 0% (0/29) | 0.00% [-11.70%, 12.46%] |
| **Number of vessels treated** | | | |
| One | 100% (27/27) | 100% (29/29) | 0.00% [-12.46%, 11.70%] |
| Two | 0% (0/27) | 0% (0/29) | 0.00% [-11.70%, 12.46%] |
| **TARGET LESION** | | | |
| **RVD, mm** | 2.61 ± 0.40 (26) | 2.71 ± 0.28 (29) | 0.09 [ -0.09, 0.28] |
| **Lesion length, mm** | 10.08 ± 2.56 (26) | 10.88 ± 3.31 (29) | 0.80 [ -0.79, 2.40] |
| **Pre-procedure % Diameter Stenosis** | 64.25 ± 9.32 (26) | 61.17 ± 10.38 (29) | -3.08 [ -8.41, 2.24] |
| **Vessel Location** | | | |
| LAD | 48.1% (13/ 27) | 44.8% (13/ 29) | 3.32% [-21.45%, 27.58%] |
| LCX | 22.2% (6/ 27) | 20.7% (6/ 29) | 1.53% [-19.64%, 23.01%] |
| RCA | 29.6% (8/ 27) | 34.5% (10/ 29) | -4.85% [-27.66%, 18.96%] |
| **Post-procedure % Stenosis** | | | |
| In-Stent | 12.34± 4.02 (27) | 15.37 ± 5.63 (29) | 3.03 [ 0.42, 5.64] |
| In-Segment | 20.82± 7.65 (27) | 23.66 ± 8.04 (29) | 2.84 [ -1.36, 7.04] |

*The Exact 95% confidence interval is calculated using Wilson score method

***Primary endpoint*:** At 180 days, in-stent late loss, the primary endpoint, was 0.10 ± 0.23 mm in the XIENCE 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.

**TABLE 5. SPIRIT FIRST Primary Endpoint**

| | XIENCE (n=27) | VISION (n=29) | Difference [95% CI] | p-Value |
|---|---|---|---|---|
| **Primary Endpoint** 180-day In-stent Late Loss, mm | 0.10 ± 0.23 (23) | 0.85 ± 0.36 (27) | -0.76 [-0.93, -0.59] | < 0.0001 |

***Secondary endpoint:*** At 180 days, the in-stent % volume obstruction (%VO), was 7.95 ± 10.44% in the XIENCE arm (n = 21) and 28.11 ± 13.98% in the MULTI-LINK VISION arm (n = 24), a 72% reduction.

**TABLE 6. SPIRIT FIRST Major Secondary Endpoint**

| | XIENCE (n=27) | VISION (n=29) | Difference [95% CI] | p-Value* |
|---|---|---|---|---|
| **Major Secondary Endpoint** 180-day in-stent %Volume Obstruction | 7.95 ± 10.44 (21) | 28.11 ± 13.98 (24) | -20.16 [-27.53, -12.79] | <0.0001 |

- Analysis was performed in per-treatment evaluable population
- Numbers are shown in (mean ± standard deviation). Standard deviation calculated assuming a normal distribution
- * p-value not adjusted for multiple comparisons

***Clinical Outcomes***

**TABLE 7. SPIRIT FIRST Major Clinical Endpoints 0-1 year**

| | | XIENCE (n=27) | VISION (n=29) | Difference |
|---|---|---|---|---|
| **0 to 1 year** | **TVF** | 15.4% (4/26) | 21.4% (6/28) | -6.04% |
| | **MACE** | 15.4% (4/26) | 21.4% (6/28) | -6.04% |
| | **All Death** | 0.0% (0/26) | 0.0% (0/28) | 0.00% |
| | Cardiac Death | 0.0% (0/26) | 0.0% (0/28) | 0.00% |
| | **MI** | 7.7% (2/26) | 0.0% (0/28) | 7.69% |
| | QMI | 3.8% (1/26) | 0.0% (0/28) | 3.85% |
| | NQMI | 3.8% (1/26) | 0.0% (0/28) | 3.85% |
| | **TLR** | 7.7% (2/26) | 21.4% (6/28) | -13.74% |
| | **TVR (CABG/PCI), non Target Lesion** | 0.0% (0/26) | 3.6% (1/28) | -3.57% |
| | **Stent Thrombosis** | | | |
| | Protocol defined | 0.0% (0/26) | 0.0% (0/28) | 0.00% |
| | ARC definite + probable (TLR not censored) | 0.0% (0/26) | 0.0% (0/28) | 0.00% |
| | ARC definite + probable (TLR censored) | 0.0% (0/26) | 0.0% (0/28) | 0.00% |

***Non-hierarchical patient counts except for TVF and MACE**
**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 (excluding TLR), CABG: Coronary Artery Bypass Graft, PCI: Percutaneous Coronary Intervention

**TABLE 8. SPIRIT FIRST Major Clinical Endpoints 0-3 year**

| | XIENCE V (n=27) | VISION (n=29) | Difference [95%CI] |
|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **0 to 3 years** | **TVF** | 15.4% (4/26) | 32.1% (9/28) | -16.76% [-37.45%, 6.29%] |
| | **MACE** | 15.4% (4/26) | 25.0% (7/28) | -9.62% [-30.16%, 12.32%] |
| | **All Death** | 0.0% (0/26) | 0.0% (0/28) | 0.00% [-12.06%, 12.87%] |
| | Cardiac Death | 0.0% (0/26) | 0.0% (0/28) | 0.00% [-12.06%, 12.87%] |
| | **MI** | 7.7% (2/26) | 0.0% (0/28) | 7.69% [ -5.59%, 24.14%] |
| | QMI | 3.8% (1/26) | 0.0% (0/28) | 3.85% [ -8.63%, 18.89%] |
| | NQMI | 3.8% (1/26) | 0.0% (0/28) | 3.85% [ -8.63%, 18.89%] |
| | **TLR** | 7.7% (2/26) | 25.0% (7/28) | -17.31% [-36.49%, 3.25%] |
| | **TVR (CABG/PCI), non Target Lesion** | 0.0% (0/26) | 10.7% (3/28) | -10.71% [-27.20%, 3.94%] |
| | **Stent Thrombosis** | | | |
| | Protocol defined | 0.0% (0/26) | 0.0% (0/28) | 0.00% [-12.06%, 12.87%] |
| | ARC definite + probable (TLR not censored) | 0.0% (0/26) | 0.0% (0/28) | 0.00% [-12.06%, 12.87%] |
| | ARC definite + probable (TLR censored) | 0.0% (0/26) | 0.0% (0/28) | 0.00% [-12.06%, 12.87%] |

***Non-hierarchical patient counts except for TVF and MACE**
**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 (excluding TLR), CABG: Coronary Artery Bypass Graft, PCI: Percutaneous Coronary Intervention
*The Exact 95% confidence interval is calculated using Wilson score method
** Assumption of normal approximation is not met due to small sample size or frequency of events

**TABLE 9. SPIRIT FIRST Angiographic and IVUS Results**

| | XIENCE (n=27) | VISION (n=29) | Difference [95% CI] |
|---|---|---|---|
| **QCA Data** | | | |
| **180-day Follow-up, In-stent** | | | |
| %DS | 15.57 ± 7.64 (23) | 38.61 ± 14.25 (27) | -23.05 [-29.45, -16.64] |
| ABR | 0.0% (0/ 23) | 25.9% (7/ 27) | -25.93% [**] |
| Late Loss, mm | 0.10 ± 0.23 (23) | 0.85 ± 0.36 (27) | -0.76 [-0.93, -0.59] |
| **1-Year Follow-up, In-Stent** | | | |
| %DS | 18.02 ± 12.15 (22) | 37.31 ± 16.90 (25) | -19.29 |

| | | | |
|---|---|---|---|
| | | | [-27.88, -10.70] |
| ABR | 4.5% (1/22) | 28.0% (7/25) | -23.45% [**] |
| Late Loss, mm | 0.23 ± 0.29 ( 22) | 0.81 ± 0.44 ( 25) | -0.58 [-0.80, -0.36] |
| **IVUS Data** | | | |
| **180-day Follow-up** | | | |
| In-Stent Plaque volume, $mm^3$ | 10.29 ± 13.32 ( 21) | 38.29 ± 19.08 (24) | -28.00 [-37.82, -18.19] |
| In-Stent %VO | 7.95 ± 10.44 ( 21) | 28.11 ± 13.98 (24) | -20.16 [-27.53, -12.79] |
| **1-Year Follow-up** | | | |
| In-Stent Plaque volume, $mm^3$ | 13.26 ± 8.46 ( 18) | 36.40 ± 17.69 ( 23) | -23.15 [-31.68, -14.61] |
| In-Stent %VO | 10.71 ± 6.92 ( 18) | 26.92 ± 12.78 ( 23) | -16.21 [-22.55, -9.86] |
| **Abbreviations:** IVUS: Intravascular Ultrasound, CI: Confidence Interval, QCA: Quantitative Coronary Angiography, %DS: Percent Diameter Stenosis, ABR: Angiographic Binary Restenosis Rate, %VO: Percent Volume Obstruction<br>** Assumption of normal approximation is not met due to small sample size or frequency of events | | | |

**Summary of Results:** The SPIRIT FIRST study met its primary endpoint, demonstrating lower 180-day in-stent late loss for the Xience stent compared to the bare metal control. Angiographic data demonstrated consistently lower rates of angiographic measures of restenosis versus the bare metal stent control. No stent thrombosis events were observed from 0 to 3 years in this study.

***Key Limitations of the SPIRIT FIRST Study:***

- *Small sample size*
- *Study was not powered to adequately assess clinical endpoints or safety outcomes*

**b. SPIRIT II**

**Objective**: The SPIRIT II clinical study was designed to demonstrate non-inferiority of XIENCE V to the TAXUS EXPRESS[2] drug eluting stent in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel.

**Primary endpoint**: The primary endpoint of the SPIRIT II clinical trial was in-stent late loss (LL) at 180 days.

**Secondary endpoints:**

- Acute success
- 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)
- Stent thrombosis at 30, 180, 270 days, and 1 and 2 years follow-up time points

**Design**: SPIRIT II was a prospective, randomized, active controlled, single blinded, parallel two-group, multi-center, non-inferiority study designed to enroll **300** subjects.

**Randomization**: Subjects were randomly assigned to a treatment group (randomized 3:1; XIENCE V: TAXUS). 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).

**Key Inclusion Criteria:**

- Subjects ≥ 18 years of age
- Evidence of angina, myocardial ischemia or a positive functional test
- A maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel
- Reference vessel diameter (RVD) of ≥ 2.5 mm and ≤ 4.25 mm
- Lesion length ≤ 28 mm by visual estimation
- % diameter stenosis (%DS) of ≥ 50% and < 100%
- TIMI flow of ≥ 1

**Key Exclusion Criteria:**

- De novo target lesion(s) located in a major epicardial vessel or a side branch that has been previously treated with any type of percutaneous intervention < 9 months prior to index procedure
- Target lesion(s) restenotic from previous intervention
- Target lesion has:
  - left main or aorto-ostial location
  - excessive tortuousity

- extreme angulation (≥ 90°)
- heavy calcification
- target vessel containing thrombus

Eligibility of patients for the SPIRIT II trial was generally similar to SPIRIT III.

**Stent procedure:** The XIENCE V stents used in the study included diameters of 2.5, 3.0, 3.5 and 4.0 mm and lengths of 8, 18 and 28 mm. The XIENCE V 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.

**Antiplatelet therapy:** 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 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.

**Study sites and dates of enrollment:** The first subject was enrolled on July 5, 2005 and the last subject was enrolled on November 10, 2005. SPIRIT II was conducted at European, Indian and New Zealand investigational sites. FDA did not have oversight of the study and did not participate in protocol development.

**Follow up schedule:** 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 was performed at 180 days post index procedure. Additionally, 2-year angiography and IVUS will be performed in a subset of subjects.

**Statistical Analyses:** 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 demonstrate non-inferiority of XIENCE V to TAXUS with a non-inferiority delta of 0.16 mm and *overall* 0.05 alpha (one-tailed). Four interim analyses were prospectively planned after 40, 80, 120 and 160 patients enrolled, followed by the final analysis. Sequential monitoring was based on an O'Brien-Fleming alpha spending function for this group sequential design. For the interim and final analyses, the p-value was compared to a nominal alpha threshold. If the p-value was below the threshold, the null hypothesis was rejected in favor of the alternative, non-inferiority. However, only the interim analyses for 80 and 120 patient follow-up were actually conducted. Abbott Vascular followed the statistical analysis plan and applied the appropriate nominal alpha to the interim and final analyses as if all analyses had been completed. The interim analyses were not done to terminate the enrollment early.

In the subjects with two *de novo* coronary artery lesions that met the angiographic inclusion and exclusion criteria, lesions were numbered prior to calling the randomization service. The randomization service then randomly assigned A, B or B, A sequence to the numbered lesions. Based on this random assignment, one of the target lesions was identified as the 'analysis lesion.'

Due to the inclusion of two vessel/lesion treatment groups, the 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 using all target lesions was also performed and compared with the analysis using 'analysis lesion.' Additionally, a pre-specified superiority analysis was performed after determining that the XIENCE V was non-inferior to TAXUS for the primary endpoint of in-stent LL.

***Results***

The total enrollment in SPIRIT II was 300 patients; 223 received the Xience V stent and 77 received the TAXUS stent. Angiographic follow-up at the primary endpoint at 180 days was 91.7% (275/300) at the patient level, 92.0% (323/351) at the lesion level and 91.3% (274/300) at the Analysis lesion level. Clinical follow-up at 12 months was 98.3% (295/300). The baseline demographics, lesion characteristics, and vessel characteristics are outlined in Tables 10 and 11.

The majority of the baseline characteristics in the Tables below appear to be balanced between the two arms. Except for "Lesion Angulation > 45deg" (p=0.006), the differences below are not statistically significant at the 0.05 level. One cannot rule out that perceived imbalances in the variables are due to random chance which could be exacerbated by the relatively small number of subjects in the control arm.

**Table 10. SPIRIT II Baseline Demographics**

| | **XIENCE V N=223 M=260** | **TAXUS N=77 M=91** |
|---|---|---|
| **Subject Demography** | | |
| Age (yrs) | 61.95 ± 10.29 (223) | 61.92 ± 9.44 (77) |
| Male | 70.9% (158/223) | 79.2% (61/77) |
| Current Cigarette Use | 31.6% (66/209) | 29.9% (20/67) |
| Any Diabetes | 22.9% (51/223) | 23.7% (18/76) |
| Diabetes Req. Insulin | 4.9% (11/223) | 6.6% (5/76) |
| Hypertension Req. Medication | 67.3% (150/223) | 64.9% (50/77) |
| Hyperlipidemia Req. Medication | 68.7% (149/217) | 75.0% (57/76) |
| Prior Myocardial Infarction | 34.8% (77/221) | 24.7% (19/77) |
| Prior PCI | 22.0% (49/223) | 22.1% (17/77) |
| Prior CABG | 3.1% (7/223) | 1.3% (1/77) |
| **Target Vessel** | | |
| LAD | 40.8% (106/260) | 47.3% (43/91) |

| | | |
|---|---|---|
| LCX | 28.5% (74/260) | 18.7% (17/91) |
| RCA | 30.0% (78/260) | 34.1% (31/91) |
| **Number of diseased vessels >50% stenosed** | | |
| Single | 69.5% (155/223) | 70.1% (54/77) |
| Double | 26.0% (58/223) | 26.0% (20/77) |
| Triple | 4.5% (10/223) | 3.9% (3/77) |
| **Indication for PCI** | | |
| Stable Angina | 61.9% (138/223) | 62.3% (48/77) |
| Unstable Angina | 26.9% (60/223) | 32.5% (25/77) |
| **GP IIb/IIIa inhibitor Use** | 9.4% (21/223) | 7.8% (6/77) |
| **Lesion Morphology** | | |
| Calcification (moderate/severe) | 30.4% (76/250) | 25.8% (23/89) |
| Thrombus | 0.8% (2/250) | 1.1% (1/89) |
| Eccentric Lesion | 98.8% (247/250) | 100.0% (89/89) |
| Lesion Angulation > 45deg | 6.8% (17/250) | 18.0% (16/89) |
| Data for GP IIb/IIIa inhibitor use was not collected for pre and post procedure. Timepoint was not specified on CRFs.<br>Note: N is the total number of subjects; M is the total number of lesions | | |

**Table 11. SPIRIT II Treatment Lesions: Baseline Lesion and Vessel Characteristics**

| | XIENCE V<br>N=223<br>M=260 | TAXUS<br>N=77<br>M=91 |
|---|---|---|
| **Total number of lesions treated** | | |
| One | 83.4% (186/223) | 81.1% (63/77) |
| Two | 16.6% (37/223) | 18.2% (14/77) |
| **Number of vessels treated** | | |
| One | 83.4% (186/223) | 81.1% (63/77) |
| Two | 16.6% (37/223) | 18.2% (14/77) |
| **Target LESION(s)** | | |
| **RVD, mm** | 2.70 ± 0.52 (246) | 2.82 ± 0.58 (87) |
| **Lesion length, mm** | 12.98 ± 5.72 (246) | 13.20 ± 6.41 (87) |
| **Pre-procedure % Diameter Stenosis** | 60.88 ± 11.97 (256) | 59.25 ± 9.83 (89) |
| **Vessel Location** | | |
| LAD | 40.8% (106/260) | 47.3% (43/91) |
| LCX | 28.5% (74/260) | 18.7% (17/91) |
| RCA | 30.0% (78/260) | 34.1% (31/91) |
| Ramus | 0.8% (2/260) | 0.0% (0/91) |
| **Post-procedure % Stenosis** | | |
| In-Stent | 13.01 ± 6.02 (260) | 12.66 ± 5.53 (91) |
| In-Segment | 22.51 ± 8.98 (260) | 23.36 ± 11.20 (91) |

The SPIRIT II clinical trial allowed for up to two lesions to be treated each in a different epicardial vessel. Therefore, the number of lesions treated per patient equals the number of vessels treated.
Note: N is the total number of subjects; M is the total number of lesions

***Primary endpoint*:** The primary endpoint, in-stent LL was 0.11 ± 0.27 mm for the XIENCE V group and 0.36 ± 0.39 mm for the TAXUS group. The data indicate that XIENCE V was non-inferior to TAXUS with respect to in-stent LL at 180 days and considering a delta margin of 0.16 mm (non-inferiority p-value < 0.0001). The difference between the two stents (-0.24 mm) represented a 72% reduction in in-stent late loss. Additionally, 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 to TAXUS in terms of the primary endpoint of in-stent LL at 180 days ($p < 0.0001$).

**TABLE 12. SPIRIT II Primary Endpoint**

| | XIENCE V (N=223) | TAXUS (N=77) | Difference [95% CI] | Non-inferiority p-value | Superiority p-value |
|---|---|---|---|---|---|
| **Primary Endpoint (Analysis Lesion):** 180-day In-stent Late Loss, mm | 0.11 ± 0.27 (201) | 0.36 ± 0.39 (73) | -0.24 [-0.34, -0.15] | <0.0001 | <0.0001 |

***Secondary endpoints:*** The clinical device success rates in the XIENCE V and TAXUS groups were comparable at 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. Key secondary angiographic and IVUS endpoints are tabulated below.

***Clinical Outcomes***

**Table 13. SPIRIT II Major Clinical Endpoint Results**

| | | XIENCE V N=223 | TAXUS N=77 | Difference [95% CI] |
|---|---|---|---|---|
| **0 to 1 year** | TVF | 4.5% (10/220) | 9.2% (7/76) | -4.67% [-11.73%, 2.40%] |
| | MACE | 2.7% (6/220) | 9.2% (7/76) | -6.48% [-13.33%, 0.37%] |
| | Death | 0.9% (2/222) | 1.3% (1/76) | -0.41% [**] |
| | Cardiac Death | 0.0% (0/222) | 1.3% (1/76) | -1.32% [**] |
| | MI | 0.9% (2/220) | 3.9% (3/76) | -3.04% [**] |
| | QMI | 0.0% (0/220) | 0.0% (0/76) | 0.00% [**] |
| | NQMI | 0.9% (2/220) | 3.9% (3/76) | -3.04% [**] |
| | TLR | 1.8% (4/220) | 6.6% (5/76) | -4.76% [**] |
| | TVR (CABG/PCI), non TL | 1.8% (4/220) | 1.3% (1/76) | -2.94% [-9.04%, 3.16%] |
| | **Stent Thrombosis** | | | |
| | Protocol defined | 0.5% (1/220) | 1.3% (1/76) | -0.86% [**] |
| | ARC definite + probable (TLR *not* censored)[1] | 0.0% (0/220) | 1.3% (1/76)* | -1.32% [**] |
| | ARC definite + probable (TLR censored) | 0.0% (0/220) | 1.3% (1/76)* | -1.32% [**] |

Non-hierarchical patients counts, except for TVF and MACE
**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 (non-target lesion), CABG: Coronary Artery Bypass Graft, PCI: Percutaneous Coronary Intervention
[1]Hierarchical stent thrombosis count. One subject in the TAXUS arm had two stent thromboses per ARC definition: one definite stent thrombosis that occurred on Day 9 prior any TLR event and another probable stent thrombosis that occurred on Day 54 after a TLR event.
* One patient in the TAXUS arm had two stent thromboses per ARC definition: one definite stent thrombosis that occurred on Day 9 prior any TLR event and another probable stent thrombosis that occurred on Day 54 after a TLR event.
** Assumption of normal approximation is not met due to small sample size or frequency of events

**TABLE 14. SPIRIT II Key Secondary Angiographic and IVUS Endpoints**

| All Target Lesions Analysis | XIENCE V N=223 M=260 | TAXUS N=77 M=91 | Difference [95% CI] |
|---|---|---|---|
| **QCA Data: 180-day Follow-up** | | | |
| In segment Late Loss, mm | 0.07 ± 0.33 (237) | 0.15 ± 0.38 (86) | -0.08 [-0.17, 0.01] |
| In-stent %DS | 15.70 ± 9.88 (237) | 20.89 ± 11.59 (86) | -5.18 [-7.96, -2.41] |
| In-segment %DS | 23.61 ± 11.65 (237) | 27.05 ± 12.68 (86) | -3.44 [-6.53, -0.35] |
| In-stent ABR | 1.3% (3/237) | 3.5% (3/86) | -2.22% [**] |
| In-segment ABR | 3.4% (8/237) | 5.8% (5/86) | -2.44% [-7.89%, 3.02%] |
| **IVUS Data: 180-day Follow-up** | **N=113 M=132** | **N=39 M=45** | |
| NIH volume, $mm^3$ | 3.83 ± 6.55 (99) | 14.42 ± 16.03 (40) | -10.60 [-15.87, -5.32] |
| In-stent %VO | 2.51 ± 4.68 (99) | 7.36 ± 7.05 (40) | -4.85 [-7.27, -2.42] |
| Post-procedure Inc. Apposition | 6.5% (7/108) | 5.6% (2/36) | 0.93% [**] |
| Incomplete Apposition | 2.9% (3/103) | 0.0% (0/39) | 2.91% [**] |
| Persisting Incomplete Apposition | 2.5% (3/120) | 0.0% (0/42) | 2.50% [**] |
| Late acquired Incomplete Apposition | 0.0% (0/104) | 0.0% (0/39) | 0.00% [**] |

**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 - MLD/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 ≥ 50%. Late Loss: Calculated as MLD post-procedure – MLD at follow-up %VO: Defined as stent intimal hyperplasia and calculated as 100*(Stent Volume - Lumen Volume)/Stent
Note: N is the total number of subjects; M is the total number of lesions
** Assumption of normal approximation is not met due to small sample size or frequency of events

***Summary of SPIRIT II Results:***
Data from the SPIRIT II trial indicates that the XIENCE V stent was non-inferior to TAXUS with respect to in-stent LL at 180 days and considering a non-inferiority margin of 0.16 mm (non-inferiority p-value < 0.0001). Additionally, there was a consistent trend of lower rates of angiographic restenosis across multiple angiographic and IVUS-based

secondary endpoints. Although rates of clinical events and stent thrombosis were infrequent, the study was not powered to adequately evaluate these endpoints.

***Key Limitations of the SPIRIT II Study:***

- Study was not adequately powered to allow robust comparisons between the treatment and control arms with respect to clinical endpoints
- Interim analyses may have increased the potential for the introduction of bias
- Complete follow-up data on all subjects out to the two year timepoint is currently unavailable

### c. SPIRIT III

Based on encouraging results observed in SPIRIT I and II, Guidant moved forward with further development of the XIENCE V program by developing a pivotal US trial to meet regulatory requirements, SPIRIT III.

The SPIRIT III clinical trial consists of a US randomized clinical trial (SPIRIT III RCT), a non-randomized 4.0 mm diameter stent arm in the US, and one non-randomized arm in Japan. 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 PMA.

**Objective**: The SPIRIT III RCT, a pivotal trial, was designed to demonstrate non-inferiority of XIENCE V EECSS to the TAXUS EXPRESS$^2$ Paclitaxel Eluting Coronary Stent System (TAXUS PECSS).

**Primary endpoints**: The primary endpoint of the SPIRIT III trial was **240-day in-segment late loss (LL)**. Additionally, the SPIRIT III RCT included a co-primary endpoint (also referred to as the "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

***SPIRIT III RCT study success was defined as meeting both 240-day in-segment LL and 9-month TVF endpoints.***

**Important secondary endpoints:**

- TVF, TLR, and MACE at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Persisting incomplete stent apposition, late-acquired incomplete stent apposition, and thrombosis at 240 days
- Acute success (clinical device and clinical procedure)
- Proximal, distal and in-stent LL at 240 days
- In-stent and in-segment percent diameter stenosis (%DS) and percent angiographic binary restenosis (% ABR) rate at 240 days
- In-stent percent volume obstruction (%VO) at 240 days

**Design**:

**RCT**

The SPIRIT III RCT was a prospective, 2:1 randomized, active-controlled, single blinded, parallel, multi-center clinical evaluation of the XIENCE V compared to

TAXUS 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.

**4.0 mm Arm**
The SPIRIT III 4.0 mm arm was a non-randomized, prospective, multicenter, single arm evaluation of XIENCE V compared to TAXUS 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.

**Key Inclusion Criteria:**

- Subject must be at least 18 years of age
- 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)
- 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 if in the US RCT
    - >3.75 mm and ≤ 4.25 mm if in the US non-randomized 4.0 mm diameter arm
- The target lesion(s) must be in a major artery or branch with a visually estimated stenosis of ≥ 50% and < 100% with a TIMI flow of ≥1
- Target lesion(s) must measure:
    - ≤ 28 mm (RCT and 4.0 mm non-randomized arm) in length by visual estimation

**Key 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
- Left ventricular ejection fraction (LVEF) < 30%
- Subject has known renal insufficiency (e.g., serum creatinine level > 2.5 mg/dL) or is on dialysis
- The target vessel contains thrombus
- The target lesion meets any of the following criteria:
    - Left main or aorto-ostial location
    - Located within an arterial or saphenous vein graft or distal to a diseased 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 or a side branch that has been previously treated with any type of PCI

- Excessive tortuosity proximal to or within the lesion
- Extreme angulation (≥ 90°) proximal to or within the lesion
- Heavy calcification

**Stent procedure:** The XIENCE V used in the RCT and 4.0 mm arm included stent diameters of 2.5, 3.0, 3.5, 4.0 mm, and lengths of 8, 18 and 28 mm. The XIENCE V 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.

Treatment of a maximum of two *de novo* lesions, each in a different epicardial vessel, was allowed.

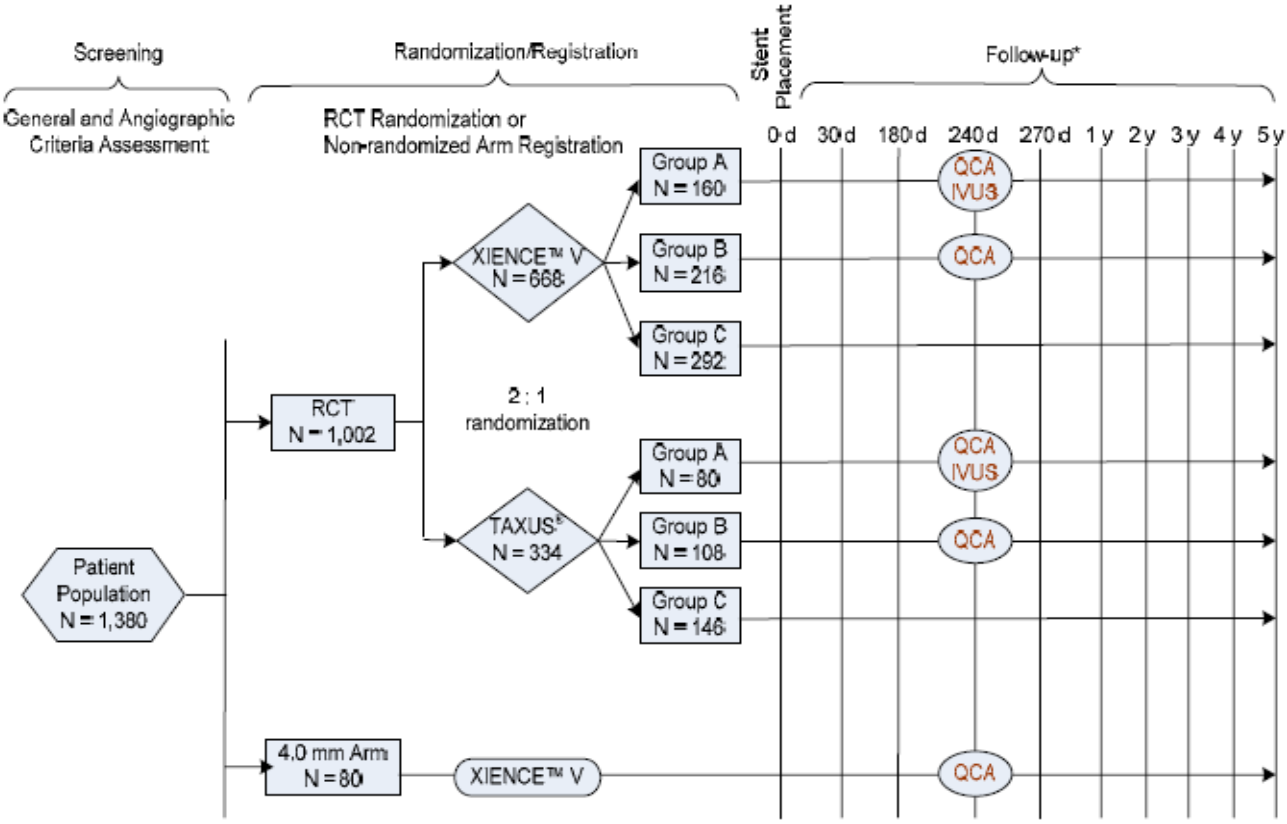
**Antiplatelet therapy:** All subjects in the US who received XIENCE V were to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of 6 months following the procedure. All subjects who received TAXUS were to be maintained on clopidogrel bisulfate for 6 months. All subjects were also required to receive ≥ 80 mg of aspirin daily to be taken throughout the length of the trial (5 years).

**Study site and dates of enrollment:** A total of 77 sites received IRB approval for the SPIRIT III study in the US of which 65 sites enrolled at total of 1,002 subjects into the RCT. 30 sites enrolled 69 subjects into the 4.0 mm arm. 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.

Enrollment commenced in the 4.0 mm arm on September 10, 2005. During the course of enrollment in the 4.0 mm arm, testing of XIENCE V identified that a small percentage (< 1%) of the inventory may have not met specifications for finished good analytical outputs. Abbott Vascular suspended enrollment on March 28, 2006. At the time of the suspension, enrollment in the RCT was completed, and 69 of the planned 80 subjects were enrolled in the 4.0 mm arm at 30 sites. Data on these 69 subjects has been submitted to the FDA to support approval of the 4.0mm stent.

**Follow up schedule:** Subjects were evaluated at 30, 180, 240, 270 days and 1 year following the index procedure. Further clinical observations will be performed at 2, 3, 4 and 5 years. Angiography was to be performed on all subjects at 240-day follow-up. 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 IVRS. 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).

**Figure 2. SPIRIT III Study Design**




**Statistical Analyses:**

**RCT**

The *primary endpoint* of in-segment LL at 240 days was analyzed for both the intent-to-treat and the per-treatment evaluable populations. The hypothesis testing was based on the per-subject analysis of the intent-to-treat population using 'analysis lesion.' Non-inferiority was defined by a one-sided alpha of 0.025 and a difference of in-segment late loss between the XIENCE V and TAXUS arms of no more than 0.195 mm (delta). If non-inferiority was demonstrated and a numerically smaller in-segment late loss was observed in the XIENCE V arm, then a superiority analysis would be performed using a two-sided t-test at the 0.05 alpha level.

In subjects with two *de novo* coronary artery lesions that met the angiographic inclusion and exclusion criteria, lesions were numbered prior to calling the randomization service. The randomization service then randomly assigned A, B or B, A sequence to the numbered lesions. Based on this random assignment, one of the target lesions was identified as the 'analysis lesion'.

As a secondary analysis, a repeated measures analysis using all target lesions was performed and compared with the analysis using the 'analysis lesion.'

The co-primary endpoint of ischemia driven TVF at 270 days was analyzed using the intent-to-treat population and the per-treatment evaluable population. Non-inferiority was defined by a one-sided alpha of 0.05 and a difference in TVF rate of no more than 5.5%.

Since both the primary and major secondary endpoint had to be met in order to have a successful study for the randomized arms, no adjustment of the type I error was needed.

**4.0mm Arm**

An interim analysis was planned for the 4.0 mm arm. The analysis was performed after 69 subjects enrolled in the 4.0 mm arm completed their 9- month follow-up and after the unblinding of the randomized arm of the SPIRIT III clinical trial.

At the interim analysis, the 69 subjects in the 4.0 mm arm were compared to the subjects in the TAXUS RCT arm. The hypothesis testing was based on the per-subject analysis of 4.0 mm arm (only one lesion was treated in all subjects) versus the per subject analysis of using 'analysis lesion' for the TAXUS RCT arm. The interim analysis was intended for early demonstration of efficacy (in-segment LL at 240 days) and would involve an adjustment to the type I error rate. Group sequential boundaries based on the Pocock alpha spending function would be applied to the analysis of the in-segment late loss. Therefore, non-inferiority was defined by a one-sided nominal alpha of 0.0377 and a difference of in-segment late loss between XIENCE V and TAXUS arms of no more than 0.195 mm (delta).

***Results***

Data for the SPIRIT III RCT is presented first, followed by separate analyses of the SPIRIT III 4.0mm arm.

The total enrollment in SPIRIT III RCT was 1002 patients; 669 received the Xience V stent and 333 received the TAXUS stent. Angiographic follow-up at the primary endpoint at 240 days was 77%. Overall clinical follow-up at 270 days and 12 months were 97.1% (973/1002) and 96.0% (962/1002), respectively. The baseline demographics, lesion characteristics, and vessel characteristics are outlined in Tables 15 and 16. The only two variables that have statistically significant differences between treatment arms at the 0.05 level are "Prior CABG" (p=0.005) and "Unstable Angina" (p=0.024).

**TABLE 15. SPIRIT III RCT Baseline Demographics**

| | XIENCE V N=669 | TAXUS N=333 |
|---|---|---|
| **Subject Demography** | | |

| | | |
|---|---|---|
| Age (yrs) | 63.23 ± 10.53 (669) | 62.80 ± 10.24 (332) |
| Male | 70.1% (469/669) | 65.7% (218/332) |
| Current Cigarette Use | 23.4% (154/659) | 22.5% (73/324) |
| Any Diabetes | 29.6% (198/669) | 27.9% (92/330) |
| Diabetes Req. Insulin | 7.8% (52/669) | 5.5% (18/330) |
| Hypertension Req. Medication | 76.2% (510/669) | 74.0% (245/331) |
| Hyperlipidemia Req. Medication | 74.2% (489/659) | 71.5% (233/326) |
| Prior Myocardial Infarction | 19.9% (130/652) | 18.0% (59/327) |
| Prior PCI | 26.3%(175/666) | 27.7%(92/332) |
| Prior CABG | 8.56%(57/666) | 3.61%(12/332) |
| **Target Vessel** | | |
| LAD | 41.3% (317/768) | 42.9% (164/382) |
| LCX | 25.5% (196/768) | 26.2% (100/382) |
| RCA | 31.0% (238/768) | 28.5% (109/382) |
| **Number of diseased vessels >50% stenosed** | | |
| Single | 64.4% (431/669) | 67.2% (223/332) |
| Double | 26.0% (174/669) | 23.8% (79/332) |
| Triple | 9.6% (64/669) | 8.7% (29/332) |
| **Indication for PCI** | | |
| Stable Angina | 53.3% (350/657) | 47.7% (156/327) |
| Unstable Angina | 18.7% (123/657) | 25.1% (82/327) |
| **GP IIb/IIIa inhibitor Use** | | |
| During Procedure | 27.5% (184/669) | 24.7% (82/332) |
| **Lesion Morphology** | | |
| Calcification (moderate/severe) | 26.4% (202/766) | 23.8% (91/382) |
| Thrombus | 2.1% (16/767) | 1.3% (5/382) |
| Eccentric Lesion | 19.8% (152/767) | 23.8% (91/382) |
| Lesion Angulation > 45deg | 15.3% (117/766) | 14.0% (53/379) |

**TABLE 16. SPIRIT III RCT. Treatment Lesions: Baseline Lesion and Vessel Characteristics**

| | **XIENCE N=669** | **TAXUS N=333** |
|---|---|---|
| **Total number of lesions treated** | | |
| One | 84.6% (566/669) | 84.6% (281/332) |
| Two | 15.4% (103/669) | 15.4% (51/332) |
| **Number of vessels treated[1]** | | |
| One | 84.6% (566/669) | 84.6% (281/332) |
| Two | 15.4% (103/669) | 15.4% (51/332) |
| **TARGET LESION(S)[2]** | | |
| **RVD, mm** | 2.77 ± 0.45 (767) | 2.76 ± 0.46 (382) |
| **Lesion length, mm** | 14.70 ± 5.59 (767) | 14.73 ± 5.70 (379) |
| **Pre-procedure % Diameter Stenosis** | 69.96 ± 13.34 (767) | 69.44 ± 13.62 (382) |
| **Vessel Location** | | |
| LAD | 41.3% (317/768) | 42.9% (164/382) |
| LCX | 25.5% (196/768) | 26.2% (100/382) |

| | | |
|---|---|---|
| RCA | 31.0% (238/768) | 28.5% (109/382) |
| **Post-procedure % Diameter Stenosis** | | |
| In-Stent | 0.33 ± 8.93 (762) | -0.22 ± 9.94 (379) |
| In-Segment | 13.54 ± 7.58 (765) | 14.40 ± 7.10 (379) |

[1] The SPIRIT III clinical trial allowed for up to two lesions to be treated each in a different epicardial vessel. Therefore, the number of lesions treated per patient is equal to the number of vessels treated.
[2] In the SPIRIT III clinical trial reports, lesion characteristics were presented for all target lesions treated. The analysis lesion was identified only for the primary endpoint analysis. Therefore, the data presented here is for all target lesions.

***Primary endpoint*:** XIENCE V was demonstrated to be non-inferior to TAXUS for the primary endpoint of **in-segment LL at 240 days**, with a LL of 0.14 mm for XIENCE V compared with 0.28 mm for TAXUS.

**TABLE 17. SPIRIT III RCT Primary Endpoint**

| | XIENCE V (n=376) | TAXUS (n=188) | Difference [95% CI] | Non-inferior p-value[1] |
|---|---|---|---|---|
| **240-Day In-segment Late Loss (mm)** | 0.14 ± 0.41 (301) | 0.28 ± 0.48 (134) | -0.14 [-0.23, -0.05] | <0.0001 |

[1] One-sided non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.

***Co-Primary Endpoint:*** The XIENCE V demonstrated non-inferiority to TAXUS for the co-primary (or "major secondary") endpoint of 270-day TVF, with a TVF rate of 7.6% (50/657) for XIENCE V compared with 9.7% (31/320) for TAXUS, P < 0.0001, non-inferiority delta = 5.5%).

**TABLE 18. SPIRIT III RCT Co-Primary Endpoint**

| | XIENCE V (n=669) | TAXUS (n=333) | Difference [95% CI] | Non-inferior p-value[1] |
|---|---|---|---|---|
| **9 month TVF** | 7.6% (50/657) | 9.7% (31/320) | -2.08% [-5.90%, 1.75%] | <0.0001 |

TVF defined as Cardiac Death, MI, TLR, non-target lesion-TVR
[1]One-sided non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

***Other Secondary Endpoints***

The observed values for other angiographic endpoints were also lower in the XIENCE V arm when compared to TAXUS, such as in-stent LL at 240 days (0.16 mm vs. 0.31 mm), in-stent %DS (6.26% vs. 10.61%), and in-segment %DS (18.82% vs. 23.22%). For key clinical endpoints through 284 days, the XIENCE V arm had a consistent trend toward lower observed event rates than the TAXUS arm.

*Clinical Outcomes*

**TABLE 19. SPIRIT III RCT Major Clinical Endpoint Results at 9 Months**

| | | XIENCE V N=669 | TAXUS N=333 | Difference [95% CI] |
|---|---|---|---|---|
| **0 to 9 months** | **TVF[1]** | **7.6% (50/657)** | **9.7% (31/320)** | **-2.08% [-5.90%, 1.75%]** |
| | MACE | 5.0% (33/657) | 8.8% (28/320) | -3.73% [-7.24%, -0.21%] |
| | All Death | 1.1% (7/658) | 0.9% (3/321) | 0.13% [**] |
| | Cardiac Death | 0.6% (4/657) | 0.6% (2/320) | -0.02% [**] |
| | MI | 2.3% (15/657) | 3.1% (10/320) | -0.84% [-3.06%, 1.38%] |
| | QMI | 0.2% (1/657) | 0.0% (0/320) | 0.15% [**] |
| | NQMI | 2.1% (14/657) | 3.1% (10/320) | -0.99% [-3.20%, 1.21%] |
| | TLR | 2.7% (18/657) | 5.0% (16/320) | -2.26% [-4.95%, 0.43%] |
| | TVR (CABG/PCI), non TL | 2.9% (19/657) | 4.1% (13/320) | -1.17% [-3.68%, 1.34%] |
| | **Stent Thrombosis to 9 months** | | | |
| | Protocol defined | 0.6% (4/654) | 0.0% (0/319) | 0.61% [**] |
| | ARC definite + probable (TLR *not* censored) | 0.9% (6/655) | 0.0% (0/319) | 0.92% [**] |
| | ARC definite + probable (TLR censored) | 0.9% (6/655) | 0.0% (0/319) | 0.92% [**] |

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

Note: All Death: Denominators exclude subjects who are lost to follow-up through the timepoint without any All TVF events (all death, MI, ischemia-driven and non ischemia-driven TLR and TVR, non-target lesion).

Note: None of the adjudicated cases of stent thrombosis per ARC criteria occurred after an intervening target lesion revascularization (TLR).

** Assumption of normal approximation is not met due to small sample size or frequency of events

[1] Adjusted TVF rate after additional events noted after study unblinding

**TABLE 20. SPIRIT III RCT 240-day Key Secondary Angiographic and IVUS Results**

| | XIENCE V N=669 M = 772 | TAXUS N=333 M= 383 | Difference [95% CI] |
|---|---|---|---|
| **QCA Data: 240-day Follow-up** | | | |
| In stent late loss, mm | 0.16 ± 0.41 (342) | 0.30 ± 0.53 (158) | -0.15 [-0.24, -0.05] |
| In-stent %DS | 5.92 ± 16.40 (343) | 10.30 ± 21.43 (158) | -4.38 [-8.16, -0.60] |
| In-segment %DS | 18.77 ± 14.43 (344) | 22.82 ± 16.35 (158) | -4.05 [-7.03, -1.06] |
| 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%] |
| **IVUS Data: 240-day Follow-up** | | | |
| NIH volume, $mm^3$ | 10.13 ± 11.46 (101) | 20.87 ± 31.51 (41) | -10.74 [-20.92, -0.56] |
| %VO | 6.91 ± 6.35 (98) | 11.21 ± 9.86 (39) | -4.30 [-7.72, -0.88] |
| **Incomplete Apposition:** | | | |
| Post-procedure | 34.4% (31/90) | 25.6% (11/43) | 8.86% [-7.46%, 25.19%] |
| Persisting | 24.4% (22/90) | 14.0% (6/43) | 10.49% [-3.15%, 24.13%] |
| Late acquired | 1.1% (1/90) | 2.3% (1/43) | -1.21% [**] |

**Abbreviations:** IVUS: Intravascular Ultrasound, CI: Confidence Interval, QCA: Quantitative Coronary Angiography, %DS: Percent Diameter Stenosis, ABR: Angiographic Binary Restenosis Rate, %VO: Percent Volume Obstruction.
Note: N is the total number of subjects; M is the total number of lesions
** Assumption of normal approximation is not met due to small sample size or frequency of events

*Incomplete Apposition*

A possible marker of increased risk of stent thrombosis is incomplete stent apposition (ISA), which is assessed by IVUS. In SPIRIT III, ISA was defined as failure of the stent to completely appose to the vessel wall after placement as evidenced by one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut in the ultrasound image.

ISA may be categorized as post-procedure (observed at the time of stent implantation) persisting (ISA present early and at follow-up), or late acquired (ISA absent early and present at late follow-up). Late acquired ISA is believed to occur as a result of vessel dilatation (positive remodeling) creating a space between the luminal surface of the artery and the overlying stent. Of the three types of ISA, late acquired ISA is likely to be more clinically relevant to DES use, as it has been postulated that positive remodeling may occur secondary to inflammatory responses to the DES.

The higher rate of post-procedure incomplete apposition in Xience did not appear to be associated with higher rates of late acquired incomplete apposition.

### *12 MONTH FOLLOW-UP DATA*

**TABLE 21. SPIRIT III RCT Major Clinical Endpoint Results**

| | | XIENCE V N=669 | TAXUS N=333 | Difference [95% CI] |
|---|---|---|---|---|
| **0 to 1 year** | TVF | 8.6% (56/653) | 11.3% (36/320) | -2.67% [-6.75%, 1.40%] |
| | MACE | 6.0% (39/653) | 10.3% (33/320) | -4.34% [-8.14%, -0.54%] |
| | All Death | 1.2% (8/655) | 1.2% (4/321) | -0.02% [**] |
| | Cardiac Death | 0.8% (5/653) | 0.9% (3/320) | -0.17% [**] |
| | MI | 2.8% (18/653) | 4.1% (13/320) | -1.31% [-3.81%, 1.20%] |
| | QMI | 0.3% (2/653) | 0.3% (1/320) | -0.01% [**] |
| | NQMI | 2.5% (16/653) | 3.8% (12/320) | -1.30% [-3.70%, 1.10%] |
| | TLR | 3.4% (22/653) | 5.6% (18/320) | -2.26% [-5.13%, 0.62%] |
| | TVR (CABG/PCI), non TL) | 3.1% (20/653) | 4.4% (14/320) | -1.31% [-3.91%, 1.29%] |
| | **Stent Thrombosis at 12 months** | | | |
| | Protocol defined | 0.8% (5/647) | 0.6% (2/317) | 0.14% [**] |
| | ARC definite + probable (TLR *not* censored) | 1.1% (7/648) | 0.6% (2/317) | 0.45% [**] |
| | ARC definite + probable (TLR censored) | 1.1% (7/648) | 0.6% (2/317) | 0.45% [**] |

**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 non-target lesion, CABG: Coronary Artery Bypass Graft, PCI: Percutaneous Coronary Intervention
Note: All Death: Denominators exclude subjects who are lost to follow-up through the timepoint without any All TVF events (all death, MI, ischemia-driven and non ischemia-driven TLR and TVR, non-target lesion).
Note: None of the adjudicated cases of stent thrombosis per ARC criteria occurred after an intervening target lesion revascularization (TLR).
** Assumption of normal approximation is not met due to small sample size or frequency of events

**TABLE 22. SPIRIT III 12-month Stent Thrombosis**

| | XIENCE V N=669 | TAXUS N=333 |
|---|---|---|
| **Protocol defined Confidence Interval*** | 0.8% (5/647) [0.25%, 1.79%] | 0.6% (2/317) [0.08%, 2.26%] |
| **ARC definite + probable (TLR *not* censored) Confidence interval*** | 1.1% (7/648) [0.44%, 2.21%] | 0.6% (2/317) [0.08%, 2.26%] |
| **ARC definite + probable** | 1.1% (7/648) | 0.6% (2/317) |

| | | |
|---|---|---|
| **(TLR censored) Confidence interval*** | [0.44%, 2.21%] | [0.08%, 2.26%] |

* Due to the low frequency of events, exact binomial confidence intervals are provided.

**Summary of SPIRIT III RCT Results:**

The SPIRIT III RCT successfully met both of its co-primary endpoints by demonstrating non-inferiority of Xience V to Taxus with respect to 240-day in-segment late loss and 270 day Target Vessel Failure (TVF).

Although SPIRIT III was not designed to evaluate differences in outcomes between the two arms, the observed rates of revascularizations, myocardial infarctions and death were comparable. Although infrequent, Xience V had higher observed rates of protocol and ARC-defined stent thrombosis. Assessing differences in the rates of stent thrombosis between the Xience and Taxus arms is difficult due to low event rates in both arms. Although confidence intervals may help indicate where true stent thrombosis rates may lie, their utility is limited given that this study by itself was neither designed nor powered to provide precise estimation of the true rates of stent thrombosis.

Although the protocol defined rates of stent thrombosis are comparable between the two arms, the observed rates of ARC-defined stent thrombosis are numerically higher in the Xience arm. However, because the SPIRIT program allowed for dual vessel disease, potentially higher rates of stent thrombosis are possible. The impact of dual vessel disease on clinical outcomes and stent thrombosis is discussed in the SPIRIT II and III combined analysis.

The confidence intervals of the secondary endpoints were not statistically adjusted for multiplicity; however, the angiographic and IVUS results suggest a trend toward lower restenosis in the Xience arm compared to the Taxus arm of SPIRIT III.

The 12-month SPIRIT III data demonstrates comparable frequencies of clinical events between the Xience and Taxus arms. No unusual clinical results or trends are apparent at a follow-up timepoint 3 months later than the 9-month primary analysis.

***Key Limitations of the SPIRIT III RCT:***

- As in many experimental studies, SPIRIT III was not designed to establish safety and efficacy in specific patient subgroups or secondary clinical endpoints
- Post-hoc data analyses and apparent trends toward significance need to be interpreted cautiously when assessing performance in specific patient subgroups or across multiple secondary endpoints.
- 199 subjects at 37 sites overall (140 XIENCE V and 59 TAXUS subjects) were evaluated by unblinded study personnel at 9-month follow-up visit, representing nearly 20% (199/1002) of the total SPIRIT III RCT cohort. However, excluding the subjects that were evaluated by unblinded study personnel did not alter the study outcome.

- Evaluable angiographic data (QCA) was available for only 77% of subjects randomized to receive 8-month angiography for analysis of the primary endpoint of in-segment late loss. The impact of this protocol deviation was evaluated by single and multiple imputation, neither of which altered the non-inferiority outcome of the trial.
- *Complete* follow-up data on all subjects out to the two year timepoint is currently unavailable

**SPIRIT III 4.0mm Arm**

Subjects who provided consent and satisfied the general and angiographic enrollment criteria, and for whom predilatation of the target lesion was successful (in the case of two target lesions, predilatation of the first lesion) were eligible to be registered into the 4.0 mm arm of the SPIRIT III clinical study.

Other than vessel size, eligibility criteria were generally similar to the SPIRIT III RCT population. Target lesion(s) must have been located in a native coronary artery with visually estimated diameter of >3.75 mm and ≤ 4.25 mm. If two target lesions met the inclusion criteria they must have been in different epicardial vessels. Target lesion(s) must have measured ≤ 28 mm in length by visual estimation (≥ 3 mm of non-diseased tissue on either side of the target lesion covered by XIENCE V). Lesions were excluded if they had a left main or aorto-ostial location, or were located within 2mm of the origin of the LAD or LCX.

*Primary Endpoint*

The primary endpoint in the SPIRIT III 4.0 mm arm study was in-segment LL at 240 days. In-segment LL at 240 days in the 4.0 mm XIENCE V arm was compared with that of the TAXUS arm from the RCT with a non-inferiority margin (delta) of 0.195 mm and one-tailed alpha of 0.05. The angiographic sample size of the TAXUS RCT arm was assumed to be 169 subjects for sample size calculations. Assumptions included a true mean in-segment LL of 0.24 mm in both the 4.0 mm XIENCE V arm and the TAXUS RCT arm (standard deviation assumed to be 0.47 mm in both arms). Given the above assumptions, a sample size of 72 subjects (80 subjects including 10% dropouts) in the Xience 4.0mm would ensure confirmation of non-inferiority for in-segment LL.

*Primary Analysis*

An interim analysis was prospectively planned after 69 subjects enrolled in the 4.0 mm arm had completed their scheduled follow up and after unblinding of the randomized arm (RCT) of the SPIRIT III clinical trial. At the interim analysis, 69 subjects in the 4.0 mm arm were to be compared to the angiographic subset subjects enrolled in TAXUS arm of the RCT. Group sequential boundaries based on the Pocock alpha spending function would be applied to the analysis of in-segment LL.

Hypothesis testing of the primary endpoint was based on a per-subject analysis of the analysis lesion. The analysis lesion was defined as the target lesion for subjects with a

single target lesion, and one of the two target lesions, selected at random, for subjects with two target lesions.

*Secondary Endpoints*
Secondary endpoints include Acute Success and ischemia driven TVF at 30 and 180 days. Other endpoints included ischemia driven TLR, TVR, and MACE at 30, 180 and 270 days and stent thrombosis (acute, subacute and late).

***Results***
Although 80 subjects were originally planned to receive the Xience 4.0 mm stent based on the initial sample size, data on 69 subjects was presented at the time of the interim analysis to support approval of the stent. Of these 69 subjects, only 49 evaluable subjects had angiographic data for the primary analysis.

**Table 23. SPIRIT III 4.0mm Arm Baseline Demographics**

| | **XIENCE V 4.0mm N=69** |
|---|---|
| **Subject Demography** | |
| Age (yrs) | 61.93 ± 11.20 (69) |
| Male | 72.5% (50/69) |
| Current Cigarette Use | 27.9% (19/68) |
| Any Diabetes | 30.4% (21/69) |
| Diabetes Req. Insulin | 8.7% (6/69) |
| Hypertension Req. Medication | 65.2% (45/69) |
| Hyperlipidemia Req. Medication | 77.9% (53/68) |
| Prior Myocardial Infarction | 17.4% (12/69) |
| Prior PCI | 18.8%(13/69) |
| Prior CABG | 5.8%(4/69) |
| **Target Vessel** | |
| LAD | 26.1% (18/69) |
| LCX | 17.4% (12/69) |
| RCA | 56.5% (39/69) |
| **Number of diseased vessels >50% stenosed** | |
| Single | 82.6% (57/69) |
| Double | 11.6% (8/69) |
| Triple | 5.8% (4/69) |
| **Indication for PCI** | |
| Stable Angina | 47.8% (32/67) |
| Unstable Angina | 19.4% (13/67) |
| **GP IIb/IIIa inhibitor Use** | 31.9% (22/69) |
| **Lesion Morphology** | |
| Calcification (moderate/severe) | 26.1% (18/69) |
| Thrombus | 1.4% (1/69) |
| Eccentric Lesion | 24.6% (17/69) |
| Lesion Angulation > 45deg | 17.4%(12/69) |

Baseline demographics and risk factors were generally comparable among the angiographic subgroups of the TAXUS RCT arm (dataset for primary endpoint analysis) and XIENCE V RCT arm with the XIENCE V 4.0 mm arm. However, the small sample size of the 4.0mm arm limited robust statistical comparisons.

Target vessel and vessel size differed somewhat between the 4.0mm and RCT arms of the trial; however lesion characteristics were more comparable:

**TABLE 24. Baseline Vessel Characteristics**

| | **XIENCE V 4.0 mm Arm (N=69)(M=69)** | **TAXUS RCT Angiographic Group (N=188) (M=220)** | **XIENCE V RCT Angiographic Group (N=376) (M=427)** |
|---|---|---|---|
| **Target Vessel** | | | |
| LAD | 26.1% (18/69) | 43.6% (96/220) | 40.5% (173/427) |
| Circumflex or Ramus | 17.4% (12/69) | 28.6% (63/220) | 27.9% (119/427) |
| RCA | 56.5% (39/69) | 27.7% (61/220) | 31.6% (135/427) |
| LMCA | 0.0% (0/69) | 0.0% (0/220) | 0.0% (0/427) |
| Pre-Procedure Reference Vessel Diameter (RVD, in mm) Mean ± SD (m) | 3.53± 0.36 (69) | 2.77 ± 0.46 (220) | 2.75 ± 0.44 (427) |
| Pre-Procedure Percent Diameter Stenosis (%DS) Mean ± SD (m) | 71.37± 13.38 (69) | 70.33 ± 13.48 (220) | 70.41 ± 13.32 (427) |
| Lesion Length (mm) Mean ± SD (m) | 15.43 ± 6.21 (69) | 14.99 ± 5.88 (218) | 14.92 ± 5.73 (427) |
| Note: N is the total number of subjects; M is the total number of lesions | | | |

Of the 69 subjects enrolled and treated in XIENCE V 4.0 mm arm 49 (71.0%) subjects had qualifying follow up angiograms; lower than the 77% angiographic follow up in the RCT. In-segment LL in the XIENCE V 4.0 mm arm (0.17 ± 0.38 mm; 49/69 analysis lesions) was comparable to the in-segment LL in the XIENCE V RCT arm (0.14 ± 0.41mm; 301/376 analysis lesions). The difference between the XIENCE V 4.0 mm and XIENCE V RCT arm was 0.03 mm.

### *Primary Endpoint*

**TABLE 25. Comparison of SPIRIT III 4.0 mm arm to TAXUS RCT**

| | XIENCE V 4.0mm Arm (N=69) | TAXUS RCT (N=188) | Non-Inferiority p-Value [1] |
|---|---|---|---|
| **240 Day In-Segment LL Mean ± SD (n)** | 0.17 ± 0.38 (49) | 0.28 ± 0.48 (134) | <0.0001 |
| [1] One-sided by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195mm, compared at a 0.038 significance level. | | | |

### *Secondary Clinical Endpoints*

**TABLE 26. Summary of Secondary Endpoints (Intent-to-Treat)**
**XIENCE V 4.0 mmArm vs. TAXUS RCT vs. XIENCE V RCT**

| Measurements | XIENCE V 4.0 mm Arm (N=69) (M=69) | TAXUS RCT (N=333) (M=383) | XIENCE V RCT (N=669) (M=772) |
|---|---|---|---|
| **Acute Success** | | | |
| Clinical Device Success | 98.5% (67/68) | 98.7% (374/379) | 98.3% (750/763) |
| Clinical Procedure Success | 94.2% (65/69) | 97.3% (322/331) | 98.5% (651/661) |
| **Per-Subject Analysis** | | | |
| Clinical Endpoints to 284 Days[1] | | | |
| TVF-free | 94.2% | 90.5% | 92.4% |
| TLR-free | 98.5% | 95.0% | 97.3% |
| Revascularization[2]-free | 98.5% | 93.5% | 94.7% |
| Cardiac Death-free | 98.5% | 99.4% | 99.4% |
| MACE-free | 94.2% | 91.4% | 95.0% |
| TVF in-hospital[3] | 4.3% (3/69) | 2.4% (8/330) | 0.9% (6/669) |
| TVF through 37 days | 4.3% (3/69) | 3.3% (11/330) | 1.6% (11/667) |
| TVF through 194 days | 5.9% (4/68) | 5.5% (18/326) | 4.1% (27/663) |
| TVF through 284 days | 5.9% (4/68) | 9.7% (31/320) | 7.6% (50/657) |
| **Stent Thrombosis** | | | |
| Acute (< 1 day) | 1.4% (1/69) | 0.0% (0/330) | 0.1% (1/669) |
| Subacute (1 to 30 days) | 0.0% (0/69) | 0.0% (0/330) | 0.3% (2/667) |
| Late (30 to 284 days) | 0.0% (0/67) | 0.0% (0/319) | 0.2% (1/653) |
| Bleeding Complication to 284 days | 6.0% (4/67) | 5.0% (16/319) | 3.1% (20/653) |
| Vascular Complication to 284 days | 0.0% (0/67) | 0.9% (3/319) | 0.9% (6/654) |
| CVA to 284 days | 0.0% (0/67) | 0.6% (2/319) | 0.8% (5/653) |

[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. 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 4.0 mm subjects and those in the RCT 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: N is the total number of subjects; M is the total number of lesions

**Comparison of Clinical Outcomes at 12 months (393 days)**

**TABLE 27. Comparison of Hierarchical Subject Counts of Events at 284 Days and 393 days (ITT Population)**

| | 0-284 days* | | 0-393 days† | |
|---|---|---|---|---|
| | XIENCE V 4.0 mm Arm (N=69) | TAXUS RCT (N=333) | XIENCE V 4.0 mm Arm (N=69) | TAXUS RCT (N=333) |
| MACE (Cardiac Death, MI, TLR) | 5.9% (4/68) | 8.1% (26/321) | 5.9% (4/68) | 10.3% (33/320) |
| TVF (Cardiac Death, MI, TLR, TVR, non-target lesion) | 5.9% (4/68) | 9.0% (29/321) | 5.9% (4/68) | 11.3% (36/320) |
| Cardiac Death | 1.5% (1/68) | 0.6% (2/321) | 1.5% (1/68) | 0.9% (3/320) |
| QMI | 0.0% (0/68) | 0.0% (0/321) | 0.0% (0/68) | 0.0% (0/320) |
| NQMI | 4.4% (3/68) | 2.5% (8/321) | 4.4% (3/68) | 3.8% (12/320) |
| TLR CABG | 0.0% (0/68) | 0.0% (0/321) | 0.0% (0/68) | 0.0% (0/320) |
| TLR PCI | 0.0% (0/68) | 5.0% (16/321) | 0.0% (0/68) | 5.6% (18/320) |
| TVR CABG, non-target lesion | 0.0% (0/68) | 0.3% (1/321) | 0.0% (0/68) | 0.3% (1/320) |
| TVR PCI, non-target lesion | 0.0% (0/68) | 0.6% (2/321) | 0.0% (0/68) | 0.6% (2/320) |

[1] 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.
† Includes events identified after unblinding and that were not included in the 270-day Clinical Report.

**Angiographic Analysis**

**TABLE 28. Angiography Analysis – Per Lesion Analysis (Intent-To-Treat)**

| | XIENCE V 4.0 mm Arm (N=69) (M=69) | TAXUS RCT (N=188) (M=220) | XIENCE V RCT (N=376) (M=427) |
|---|---|---|---|
| **Pre-Procedure RVD (mm)** Mean ± SD (m) | 3.53± 0.36 (69) | 2.77 ± 0.46 (220) | 2.75 ± 0.44 (427) |
| **Pre-Procedure Percent Diameter Stenosis (%DS)** Mean ± SD (m) | 71.37± 13.38 (69) | 70.33 ± 13.48 (220) | 70.41 ± 13.32 (427) |
| **240 day In-Segment** Mean ± SD (m) | 17.92 ± 10.83 (49) | 22.82 ± 16.35 (158) | 18.77 ± 14.43 (344) |
| **In-Stent Late Loss (mm)** Mean ± SD (m) | 0.12 ± 0.34 (49) | 0.30 ± 0.53 (158) | 0.16 ± 0.41 (342) |
| **240 day In-Segment** | 2.0 % (1/49) | 8.9% (14/158) | 4.7% (16/344) |

| | | | |
|---|---|---|---|
| **Angiographic Binary Restenosis (ABR)** | | | |
| Note: N is the total number of subjects; M is the total number of lesions | | | |

**Summary of Results**:

The SPIRIT III 4.0 mm Arm successfully met its primary endpoint of 240-day in-segment late loss. Secondary angiographic endpoints demonstrated lower observed rates of restenosis compared to the Taxus control and were also similar to Xience V data from the SPIRIT III RCT. The SPIRIT III 4.0mm arm was not designed to adequately evaluate clinical outcomes, but for the subjects available for clinical analysis, the results of the Xience V 4.0 mm were comparable to those seen in the SPIRIT III RCT.

***Key Limitations of the SPIRIT III 4.0mm Study:***

- This study was non-randomized
- Only 71% of enrolled subjects had qualifying follow up angiograms
- Study was not to designed to evaluate clinical endpoints, but to establish the effectiveness of the 4.0mm platform by demonstrating comparability in restenosis rates to Taxus in the main RCT

### d. Clinical Pharmacokinetics (PK) Studies

The pharmacokinetics (PK) of Everolimus eluted from the XIENCE™ V EECSS was evaluated in three different sub-studies. Two of the sub-studies were conducted as part of the SPIRIT III trial and the third PK sub-study was conducted OUS as part of the SPIRIT II trial. The PK sub-studies were conducted in three different geographies and the global pharmacokinetic data includes a total of 73 subjects.

**SPIRIT II Pharmacokinetic Sub-study**

The purpose of the SPIRIT II pharmacokinetic sub-study was to determine the pharmacokinetics of everolimus delivered by XIENCE V in the SPIRIT II trial. All subjects were screened per the SPIRIT II protocol inclusion and exclusion criteria. The 39 subjects who volunteered to participate in the pharmacokinetic sub-study 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 used in the SPIRIT II pharmacokinetic study are the same as the US SPIRIT III trial. 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 29 presents the distributions of treatments received.

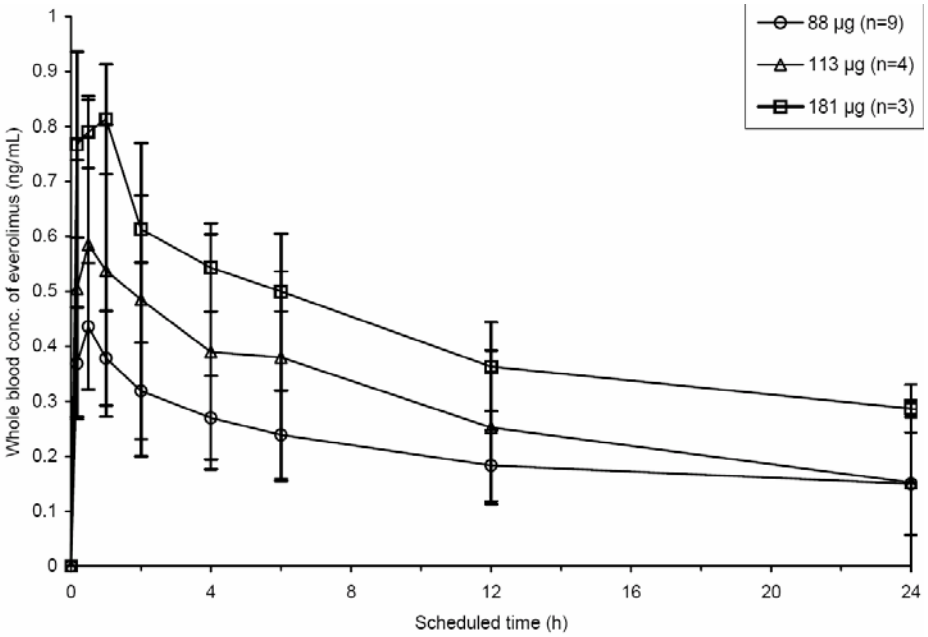
**Table 29. Total Stent Dose of Everolimus received by SPIRIT II Subjects, OUS**

| 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

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. The linear mean whole blood concentration-time profiles of everolimus for the first 24 hours of sampling are presented below for the 88, 113 and 181 µg dosage groups.

**Figure 3: SPIRIT II Linear Mean Whole Blood Concentration-Time Profiles of Everolimus**




The pharmacokinetic parameters for dose levels (88, 113 and 181 µg) to which more than 2 subjects were exposed are listed below in Table 30.

**Table 30. SPIRIT II Pharmacokinetic Parameters of Everolimus**

| (mean ± SD, tmax: median (range)) | **88 µg** | **113 µg** | **181 µg** |
|---|---|---|---|
| n | 13[b] | 4[c] | 4 |
| tmax, h | 0.50 (0.13 - 2.17) | 0.50 (0.50 - 0.50) | 0.46 (0.17 - 1.00) |
| Cmax, ng/mL | 0.4369 ± 0.1507 | 0.5850 ± 0.2630 | 0.7925 ± 0.1406 |
| AUC24h, ng.h/mL | 5.156 ± 1.976 | 6.820 ± 4.373 | 10.27 ± 1.035 |
| AUClast, 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 |
| t1/2term, 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 =1 2 for AUC0-24h; [c]n = 3 for AUC0-inf, t1/2term and CL

Mean and median whole blood concentrations of everolimus increased with increasing total stent dose of everolimus. For most subjects whole blood concentrations first increased to reach a maximum at about 10 to 60 minutes after stent implantation. Thereafter, whole blood concentrations decreased biphasically: an initially fast distribution/elimination phase was followed by a slower elimination phase.

The results of this sub-study demonstrate that whole blood concentrations of everolimus increase proportionally to the total stent dose (ranging from 53 to 588 µg). 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. The terminal half-life could not be characterized accurately due to the rapid disappearance of everolimus from the blood of the subjects studied. This measure is typically difficult to determine in products

containing a small amount of drug that is designed for local delivery. Therefore, the lack of characterization of the terminal half-life is not of concern.

**SPIRIT III Pharmacokinetics US RCT Substudy**

The objective of the SPIRIT III US RCT Sub-study is the same as the SPIRIT II PK sub-study, that is, to determine the pharmacokinetics of everolimus delivered from the XIENCE™ V EECS. All subjects were screened per the SPIRIT III protocol inclusion and exclusion criteria. Enrolled subjects who volunteered to participate in the pharmacokinetic sub-study 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). Table 31 presents the distributions of treatments received.

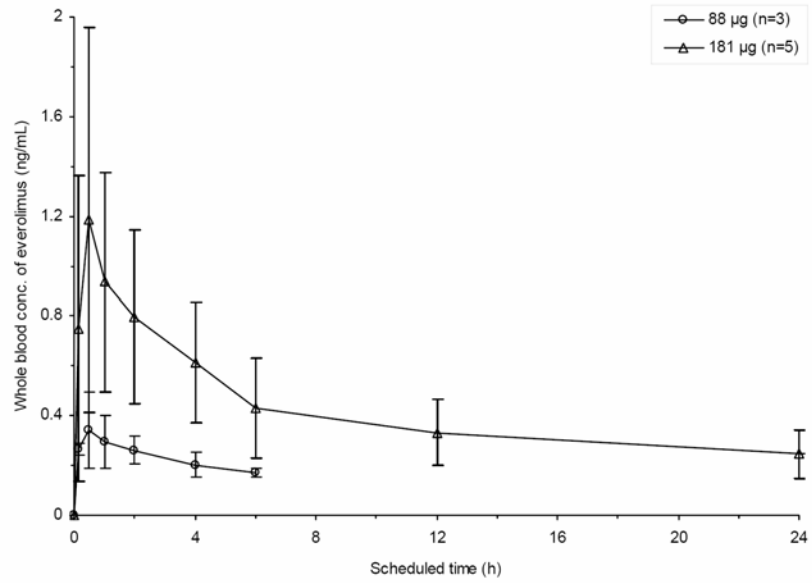
**TABLE 31: Total Stent Dose of Everolimus Received by SPIRIT III Subjects, US***

| 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** |

*Study is currently blinded **One subject was not evaluated at all time points

The pharmacokinetic analysis of the everolimus blood concentration-time data was conducted using non-compartmental methods. Data were summarized by dose based upon the number and size of stents implanted. The results were expressed as means and standard deviations determined for each dose group. Pharmacokinetic correlations were evaluated by linear regression analysis. 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. The linear mean whole blood concentration-time profiles of everolimus for the 88 and 181 µg groups with a sample size greater than two are presented for only the first 24 hours of sampling are plotted below. For the 88 µg dose group, the mean value was below the LLOQ (lower limit of quantification) from 12 hours onwards.

**Figure 4: SPIRIT III Linear Mean Whole Blood Concentration-Time Profiles of Everolimus**




Mean whole blood concentrations of everolimus increased with increasing total dose. For 16 of 17 subjects whole blood concentrations first increased to reach a maximum at about 0.5 to 1 hour after first stent implantation. Thereafter, whole blood concentrations decreased biphasically; an initially fast distribution/elimination phase was followed by a slower elimination phase. For 16 of 17 subjects, the last time point up to which whole blood concentrations could be quantified ranged from 12 to 72 hours after implantation of the first stent. For 1 subject receiving the highest dose (181 µg), a blood concentration of 0.16 ng/ml was detected at 168 hours after the first stent implant time. 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.

Table 32 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.

**TABLE 32. Pharmacokinetic Parameters of Everolimus**

| (mean ± SD, $t_{max}$: median (range)) | **88 µg** | **181 µg** |
|---|---|---|
| n | 3[b] | 6[c] |
| $t_{max}$, hours | 0.50 (0.50 - 1.88) | 0.50 (0.07 - 1.00) |
| $C_{max}$, ng/mL | 0.3867 ± 0.09866 | 1.175 ± 0.6817 |
| $AUC_{0\text{-}24h}$, ng.h/mL | 3.458 ± 0.1981 | 9.601 ± 4.015 |
| $AUC_{0\text{-}t}$, ng.h/mL | 5.319 ± 4.114 | 23.73 ± 13.63 |
| $AUC_{0\text{-}\infty}$, ng.h/mL[a] | - | 44.00 ± 28.67 |
| $t_{1/2term}$, hours[a] | - | 79.08 ± 57.24 |
| CL, L/h[a] | - | 5.130 ± 2.114 |

[a]Accurate determination not possible; [b]n = 2 for $AUC_{0\text{-}24h}$; [c]n = 5 for $AUC_{0\text{-}24h}$ and n = 4 for $AUC_{0\text{-}\infty}$, $t_{1/2term}$ and CL

The results of this sub-study showed 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. $AUC_{0\text{-}24h}$ values ranged from 2.097 to 16.35 ng.h/mL. $AUC_{0\text{-}last}$ 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 very low systemic exposure.

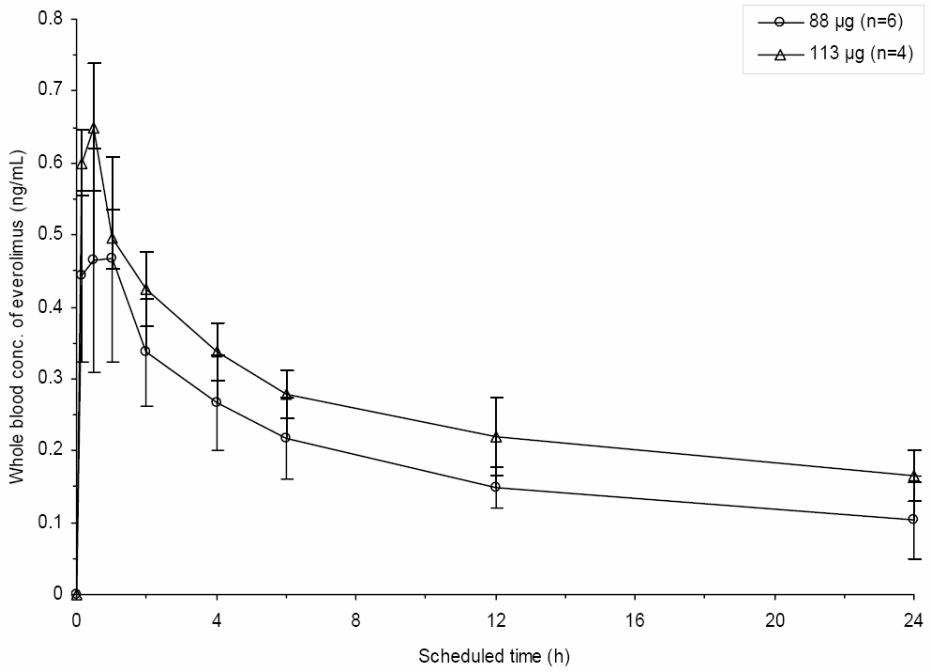
**SPIRIT III Pharmacokinetics Japan Registry Sub-study**

The objective of the SPIRIT III Japan PK sub-study is the same as the SPIRIT II PK and SPIRIT III RCT PK sub-studies. All subjects were screened per the SPIRIT III protocol inclusion and exclusion criteria. The seventeen subjects who volunteered to participate in the pharmacokinetic sub-study 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 for the US trial. Data were summarized by dose based upon the number and size of stents implanted. The results were expressed as means and standard deviations determined for each dose group. Pharmacokinetic correlations were evaluated by linear regression analysis.

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.

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. The linear mean whole blood concentration-time profiles of everolimus for the 88 and 113 µg groups for only the first 24 hours of sampling are plotted below.

**Figure 5: Japanese Arm Linear Mean Whole Blood Concentration-Time Profiles of Everolimus**




Mean whole blood concentrations of everolimus increased with increasing total stent dose of everolimus. For all subjects, whole blood concentrations first increased to reach a maximum at about 0.5 to 1 hour after first stent implantation. Thereafter, whole blood concentrations decreased biphasically; an initially fast distribution/elimination phase was followed by a slower elimination phase. 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 $AUC_{0\text{-}24h}$ values ranged from 2.942 to 19.72 ng.h/mL and individual $AUC_{0\text{-}t}$ values ranged from 2.218 to 54.49 ng.h/mL. Table 33 presents the pharmacokinetic parameters of those subject groups (88 µg and 113 µg) with a sample size greater than two.

**TABLE 33. Pharmacokinetic Parameters of Everolimus in Japanese Patients**

| (mean ± SD, tmax: median (range)) | **88 µg** | **113 µg** |
|---|---|---|
| n | 6 | 4 |
| $t_{max}$, hours | 1.00 (0.50 - 1.02) | 0.51 (0.50 - 0.53) |
| $C_{max}$, ng/mL | 0.5017 ± 0.1398 | 0.6500 ± 0.08756 |
| $AUC_{0\text{-}24h}$, ng.h/mL | 4.476 ± 1.087 | 6.154 ± 0.7523 |
| $AUC_{0\text{-}t}$, ng.h/mL | 5.049 ± 2.138 | 11.02 ± 4.002 |
| $AUC_{0\text{-}\infty}$, ng.h/mL[a] | 12.98 ± 7.078 | 19.97 ± 7.890 |
| $t_{1/2term}$, hours[a] | 45.22 ± 35.08 | 53.57 ± 19.34 |
| CL, L/h[a] | 9.286 ± 6.069 | 6.471 ± 2.807 |

[a] Accurate determination not possible

The results of this sub-study 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 2.11ng/mL. Individual $AUC_{0\text{-}24h}$ values ranged from 2.942 to 19.72ng.h/mL. Individual $AUC_{0\text{-}t}$ values ranged from 2.218 to 54.49ng.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.

**Combined PK Results**

Statistical testing was also performed 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 34.

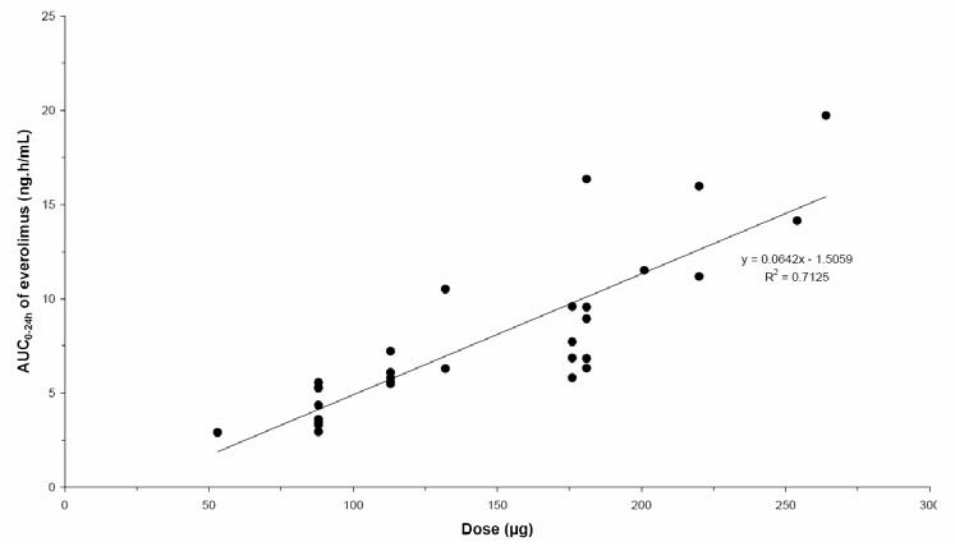
**TABLE 34. Statistical Comparison of the Dose-Normalized Everolimus PK between the US and Japanese populations**

| **Parameter (Dose Normalized)** | **Least Square means[a]** | | **LS means ratio (%)** | **90% CI (%)** | **p-value** |
|---|---|---|---|---|---|
| | **US population (reference)** | **Japanese population (test )** | | | **Country** |
| Cmax, ng/mL | 0.004719 | 0.005530 | 117.2 | 97.16 - 141.3 | 0.1613 |
| AUC0-24h, ng.h/mL | 0.04878 | 0.05276 | 108.2 | 92.05 - 127.1 | 0.4148 |
| AUC0-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 AUC0-24h where n=13 for the US population

The statistical analysis shows that the Japanese population is similar to the US population. 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.

**Figure 6: Linear Regression Analysis on the Combined Primary Pharmacokinetic Results**




**Conclusion:**

These three studies show that whole blood concentrations of everolimus increase proportionally to the total stent dose. The pharmacokinetic parameters associated with the elution of everolimus from the XIENCE™ V EECS were consistent in all three sub-studies. 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 (one subject who was exposed to a total dose of 588 ug from 4 stents). In all sub-studies, the $C_{max}$ value never reached the minimum therapeutic value of 3.0 ng/ml. The therapeutic value of 3.0 ng/ml is the level deemed necessary for effective systemic administration of everolimus to prevent organ rejection. These studies demonstrated that whole blood concentrations of everolimus increase proportionally to the total stent dose (ranging from 53 to 588 µg). These studies have been reviewed by FDA and no outstanding concerns remain. The pharmacokinetic profile for everolimus eluted from the XIENCE V EECSS has been properly characterized.

**e. SPIRIT IV**

Abbott Vascular initiated the SPIRIT IV study to further evaluate XIENCE V EECSS and to potentially contribute additional data to the analysis of the SPIRIT III major secondary endpoint of 270-day TVF. A flexible study design was proposed that would combine SPIRIT IV clinical data with the original SPIRIT III dataset in a manner that would increase the effective sample size of the pivotal cohort. However, after a planned interim analysis of SPIRIT III, an independent statistician that was specifically utilized for the prespecified flexible design strategy determined that data from SPIRIT IV would not be needed to provide sufficient statistical power to evaluate the SPIRIT III RCT co-primary endpoint of 270-day TVF. Following this decision, Abbott decided to continue with SPIRIT IV as a continued access trial. Abbott also decided to increase the sample size of SPIRIT IV to adequately evaluate more complex patients.

**Objective**: To evaluate the safety and efficacy of the XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE V) for the treatment of up to three *de novo* native coronary artery lesions, maximum of two lesions per epicardial vessel.

**Primary endpoint**: The primary endpoint of the SPIRIT IV clinical trial is ischemia driven major adverse cardiac event (MACE) at 1-year follow up.

**Important secondary endpoints:** Key secondary endpoints to examine the safety and efficacy included the following:

- TVF, TLR, TVR, and MACE at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Ischemia driven TVR at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Composite endpoint of cardiac death, MI, and TLR at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Composite endpoint of All death, All MI, and all revascularizations (DMR) at 30, 180, 270 days, and 1, 2, 3, 4, 5 years
- Acute success (clinical device and clinical procedure)
- Definite + Probable Stent Thrombosis rate based on ARC definition through 5 years
- Protocol defined Stent thrombosis rate through 5 years
- All Mortality rate at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- All MI rate at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Cardiac death and all MI rate 30, 180, 270 days, and 1, 2, 3, 4, and 5 years

**Design**: SPIRIT IV is prospective, 2:1 randomized, active-controlled, single-blinded, multicenter, US clinical trial evaluating XIENCE V versus TAXUS in subjects with reference vessel diameters (RVD) ≥ 2.5 mm to ≤ 4.25 mm and lesion lengths ≤ 28 mm; non-inferiority to TAXUS. SPIRIT IV is designed to enroll 3690 subjects at up to 80 sites in the United States.

**Randomization**: Subjects are randomly assigned to a treatment group (randomized 2:1; XIENCE V: TAXUS). Subjects will be stratified by diabetes mellitus (diabetic vs. non-diabetic), and lesion characteristics (complex vs. non-complex). Complex lesion characteristics include triple vessel treatment, or dual lesion per vessel treatment, or lesions involving RCA-aorto-ostial locations, or bifurcations lesions in which the side branch is ≥ 2 mm in diameter, or bifurcation lesions in which the ostium of the side branch is > 50% stenosed.

**Key Inclusion Criteria:**

- Target lesion(s) must be located in a native coronary artery with visually estimated diameter of ≥ 2.5 mm and ≤ 4.25 mm. Treatment of up to three *de novo* target lesions with a maximum of two *de novo* target lesions per epicardial vessel
- The target lesion(s) must be in a major artery or branch with a visually estimated stenosis of ≥ 50% and < 100% with a TIMI flow of ≥1
- Target lesion(s) must measure ≤ 28 mm in length by visual estimation
- If more than one target lesion will be treated, the RVD and lesion length of each must meet the above criteria.
- Non-study, percutaneous intervention for lesions in a target vessel (including side branches) is allowed if done ≥ 9 months prior to the index procedure
- Non-study percutaneous intervention for lesions in a non-target vessel involving:
    - Successful and uncomplicated (visually estimated diameter stenosis < 50%, TIMI Grade-3 flow, no ECG changes, prolonged chest pain, or angiographic complications) bare-metal stent, balloon dilatation, cutting balloon, atherectomy, thrombectomy, and laser treatments are allowed if done ≥ 24 hours prior to the index procedure or during (before randomization) the index procedure. For interventions done within 24 to 48 hours prior to the index procedure, CK and CK-MB must be assessed to be < 2 times the upper limit of normal at the time of the index procedure. NOTE: Procedures within the 24 hour period preceding the index procedure are not permitted
    - Unsuccessful or complicated bare-metal stent, balloon dilatation, cutting balloon, atherectomy, thrombectomy, and laser treatments are allowed if done ≥ 30 days prior to the index procedure
    - Drug-eluting stent treatment is allowed if done ≥ 90 days prior to the index procedure

**Key Exclusion Criteria:**

- The target lesion(s) meets any of the following criteria:
    - Left main coronary artery location including left main ostial 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
    - Involves a bifurcation in which the side branch is ≥ 2 mm in diameter AND the ostium of the side branch is > 50% stenosed by visual estimation
    - Involves a side branch requiring pre-dilatation
    - Total occlusion (TIMI flow 0) prior to wire crossing

    - Excessive tortuosity proximal to or within the lesion
    - Extreme angulation (≥ 90º) proximal to or within the lesion
    - Heavy calcification
    - Restenotic from previous intervention
- Subject has received brachytherapy in any epicardial vessel (including side branches)
- The target vessel contains thrombus
- Another clinically significant lesion in the target vessel is present that requires or has a high probability of requiring PCI during the index procedure
- Another lesion in a target or non-target vessel (including all side branches) is present that requires or has a high probability of requiring PCI within 9 months after the index procedure

**Stent procedure:** The XIENCE V used in the study includes stents 2.5, 3.0, 3.5 and 4.0 mm in diameter, and 8, 18 and 28 mm in length. The XIENCE V has to adequately cover the lesion such that a minimum of 3 mm of healthy vessel on either side of the lesion is covered by the stent. Therefore, the 8 mm stent will be used primarily for bailout purposes but may be used for short (2 mm) lesions as well. Post-dilatation is left to the discretion of the investigator.

**Antiplatelet therapy:** Subjects who are not on chronic antiplatelet or aspirin therapy are 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 are to be maintained on 75 mg clopidogrel bisulfate daily for a minimum of 6 months and all subjects will receive ≥ 80 mg of aspirin daily to be taken throughout the length of the trial (5 years) following the procedure.

**Study sites and dates of enrollment:** The first subject was enrolled August 2006. Enrollment is currently ongoing.

**Follow up schedule:** Subjects are evaluated at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years following the index procedure.

**Statistical Analyses:** The overall sample size for the study was based on the primary endpoint of MACE at 1-year follow-up. MACE is defined as a per-subject hierarchical count of cardiac death, target vessel Q-wave and non-Q wave MI and ischemia driven target lesion revascularization per ARC definition.

The study has an 80% statistical power based on the primary endpoint to demonstrate non-inferiority of XIENCE V to TAXUS with a non-inferiority delta of 2.7% and overall 2.5% alpha (one-tailed).

***Results***

Enrollment for SPIRIT IV is ongoing. No results are available at this time.

### f. Combined SPIRIT II RCT and SPIRIT III RCT

FDA requested that Abbott perform a one-year combined analysis of the SPIRIT II and SPIRIT III randomized clinical trial (RCT) pooled subject population. The primary goal for this analysis was to provide improved estimates of the true rates of stent thrombosis in the Xience and TAXUS DES platforms, primarily by increasing the evaluable sample size in a post-hoc manner.

The combined 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. Since both SPIRIT II and SPIRIT III RCT were randomized with the same active control, and the trials are similar in the distributions of patients' baseline characteristics, no statistical adjustments were made for baseline characteristics in the analyses in which the two studies are combined.

**TABLE 35. 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 36. 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% |

Key design elements of the SPIRIT II and III RCTs were similar.

**TABLE 37. Key Elements of Design**

| | SPIRIT II | SPIRIT III RCT |
|---|---|---|
| **Number, sites** | 300 patients at 31 sites | 1002 patients 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<br>1 per vessel | 1-2 lesions<br>1 per vessel |
| **Clinical visits (First year)** | 1, 6, 9, 12 m | 1, 6, 8, 9, 12 m |

***Results***

Clinical outcomes in the combined population were lower than that observed in the pivotal SPIRIT III RCT, due to the inclusion of SPIRIT II RCT subjects. In the combined population, the trend toward lower clinical event rates in the composite outcomes in Xience V compared to Taxus is again observed. No statistical adjustments were made for baseline characteristics in the combined analysis.

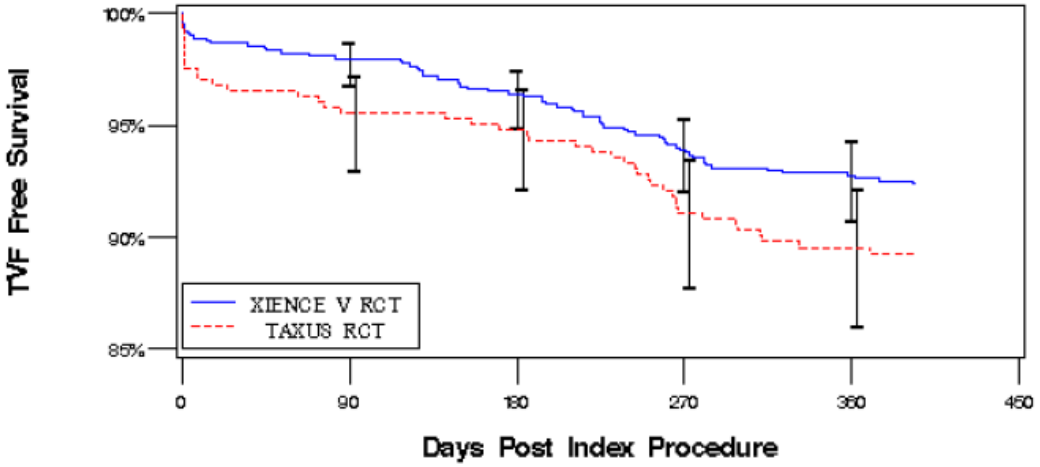
**TABLE 38. Hierarchical Subject Counts of Adverse Events through 393 Days SPIRIT II and SPIRIT III RCT Pooled ITT Population**

| **0 to 393 days** | **XIENCE V (N=892)** | **TAXUS (N=410)** | **Difference [95% CI][1]** |
|---|---|---|---|
| TVF (Cardiac Death, MI, TLR, TVR, non-target lesion) | 7.7% (67/873) | 10.8% (43/397) | -3.16%<br>[-6.69%, 0.37%] |
| MACE (Cardiac Death, MI, TLR) | 5.3% (46/873) | 10.1% (40/397) | -4.81%<br>[-8.12%, -1.50%] |
| Cardiac Death | 0.6% (5/873) | 1.0% (4/397) | -0.43%<br>[**] |
| QMI | 0.2% (2/873) | 0.0% (0/397) | 0.23%<br>[**] |
| NQMI | 1.9% (17/873) | 3.5% (14/397) | -1.58%<br>[-3.61%, 0.45%] |
| TLR CABG | 0.1% (1/873) | 0.0% (0/397) | 0.11%<br>[**] |
| TLR PCI | 2.4% (21/873) | 5.5% (22/397) | -3.14%<br>[-5.61%, -0.67%] |
| TVR CABG, non-target lesion | 0.5% (4/873) | 0.3% (1/397) | 0.21%<br>[**] |
| TVR PCI, non-target lesion | 1.9% (17/873) | 0.5% (2/397) | 1.44%<br>[**] |

[1] By normal approximation
** Assumption of normal approximation is not met due to small sample size or frequency of events
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: 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 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

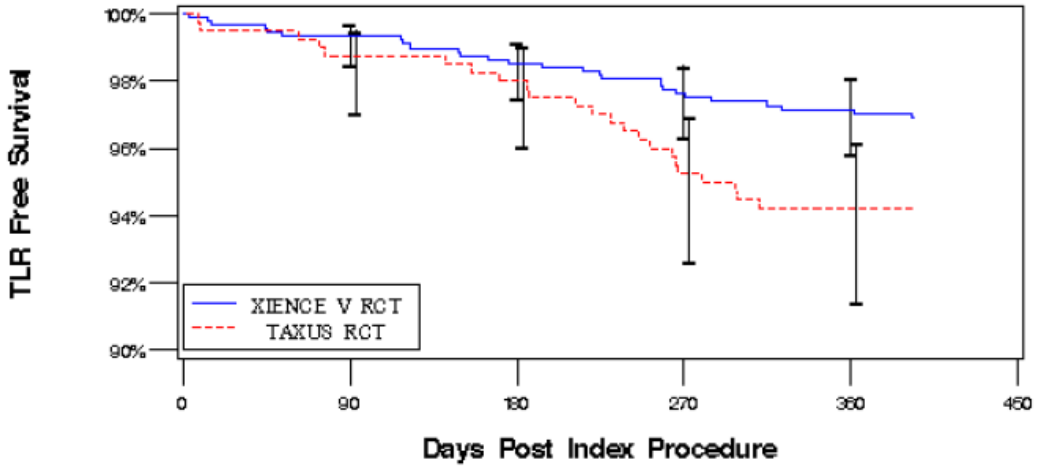
The following Kaplan-Meier curves from the combined SPIRIT II and III trials show the clinically important safety and effectiveness outcomes.

**FIGURE 7. Kaplan-Meier Survival Curve: TVF Free Survival through 393 Days**
(RCT Intent-To-Treat Population)
(SPIRIT II and SPIRIT III RCT Pooled Population)



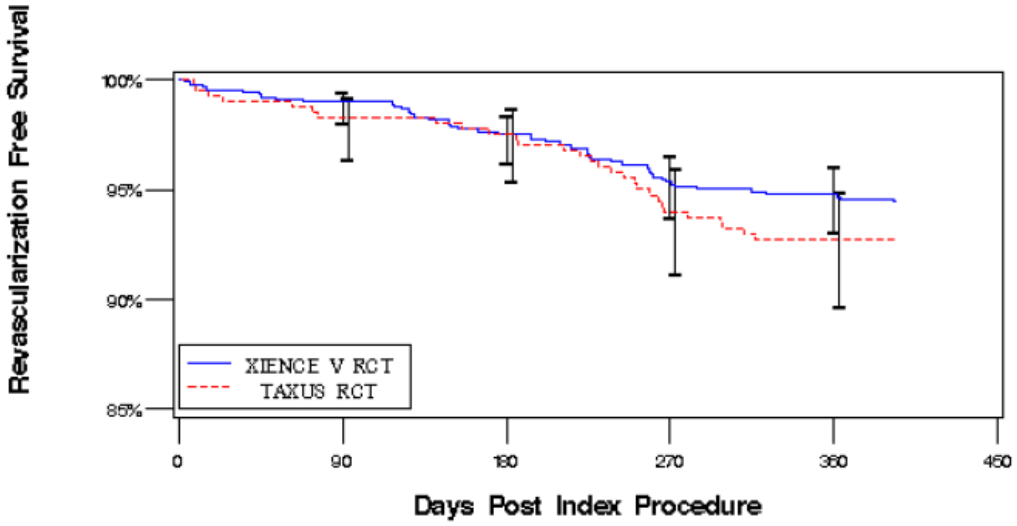

393 Day Number at Risk: Xience V 805, Taxus 351
Log-rank p-value=0.0616

**FIGURE 8. Kaplan-Meier Survival Curve: TLR Free Survival through 393 Days**
(RCT Intent-To-Treat Population)
(SPIRIT II and SPIRIT III RCT Pooled Population)



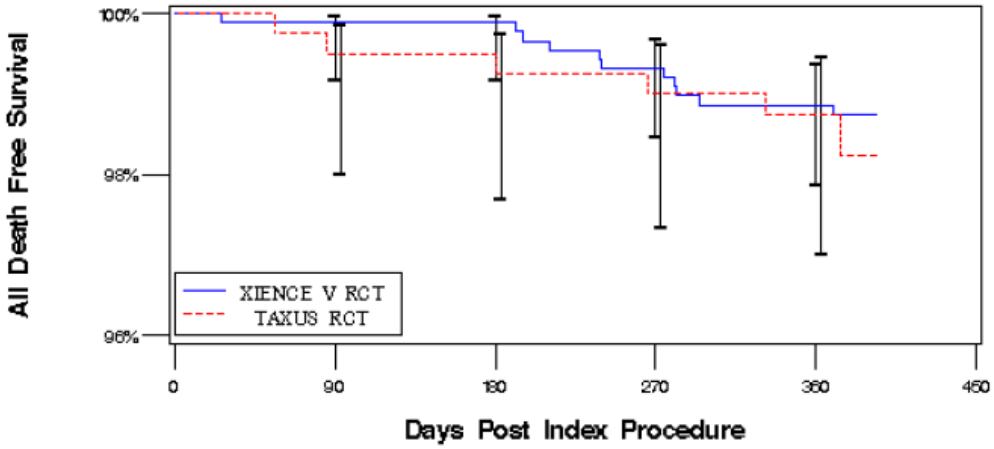

393 Day Number at Risk: Xience V 839, Taxus 367
Log-rank p-value=0.0214

**FIGURE 9. Kaplan-Meier Survival Curve: Revascularization (TLR and non-Target lesion TVR) Free through 393 Days**
(RCT Intent-To-Treat Population)
(SPIRIT II and SPIRIT III RCT Pooled Population)



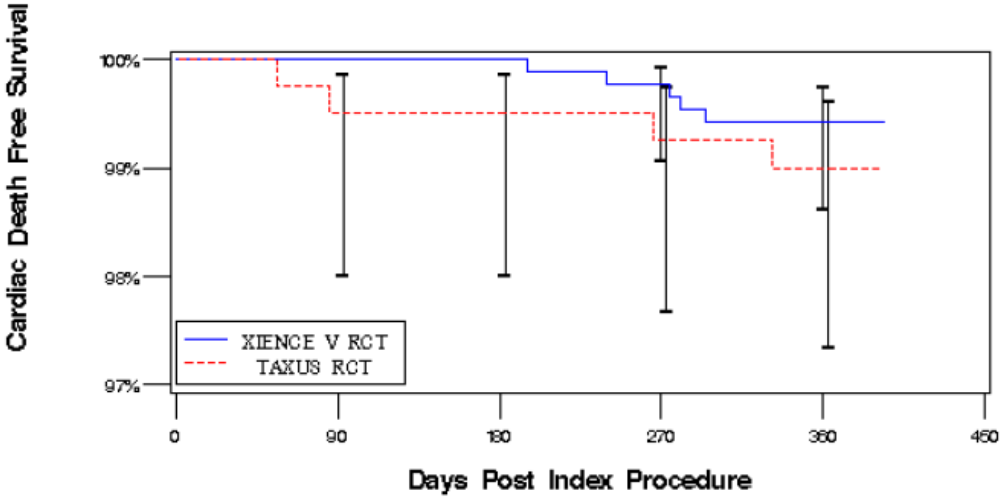

393 Day Number at Risk: Xience V 818, Taxus 362
Log-rank p-value=0.2444

**FIGURE 10. Kaplan-Meier Survival Curve: All Death Free through 393 Days**
(RCT Intent-To-Treat Population)
(SPIRIT II and SPIRIT III RCT Pooled Population)



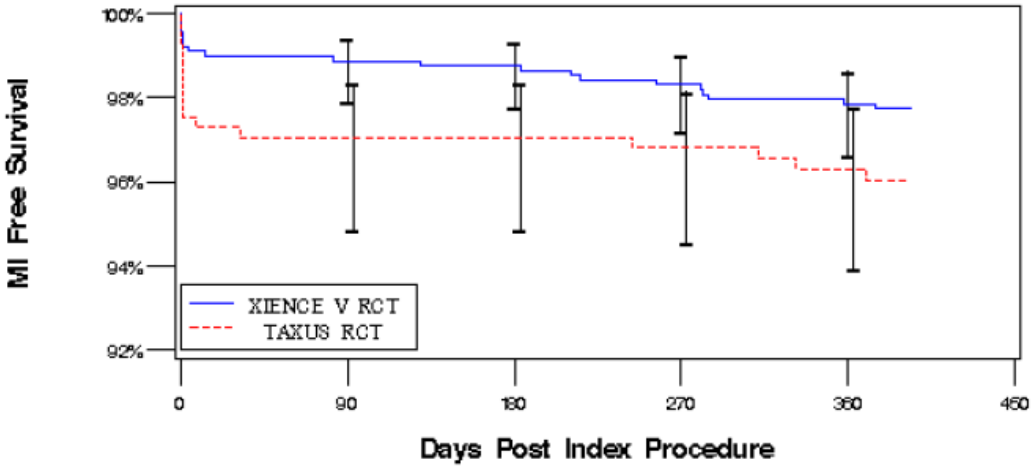

393 Day Number at Risk: Xience V 865, Taxus 389
Log-rank p-value=0.4811

**FIGURE 11. Kaplan-Meier Survival Curve: Cardiac Death Free Survival through 393 Days**
(RCT Intent-To-Treat Population)
(SPIRIT II and SPIRIT III RCT Pooled Population)



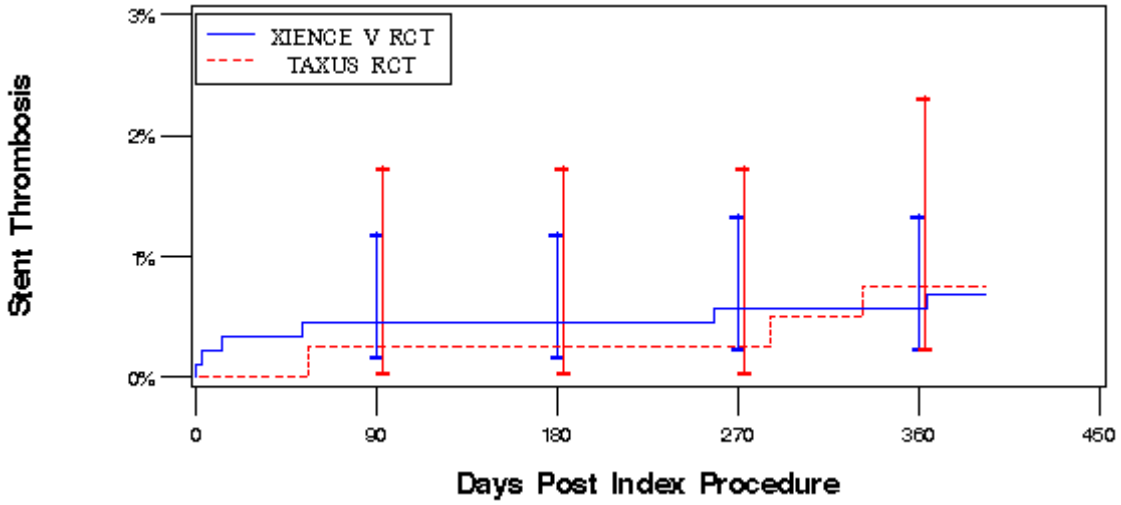

393 Day Number at Risk: Xience V 865, Taxus 389
Log-rank p-value=0.3913

**FIGURE 12. Kaplan-Meier Survival Curve: MI Free Survival through 393 Days**
(RCT Intent-To-Treat Population)
(SPIRIT II and SPIRIT III RCT Pooled Population)



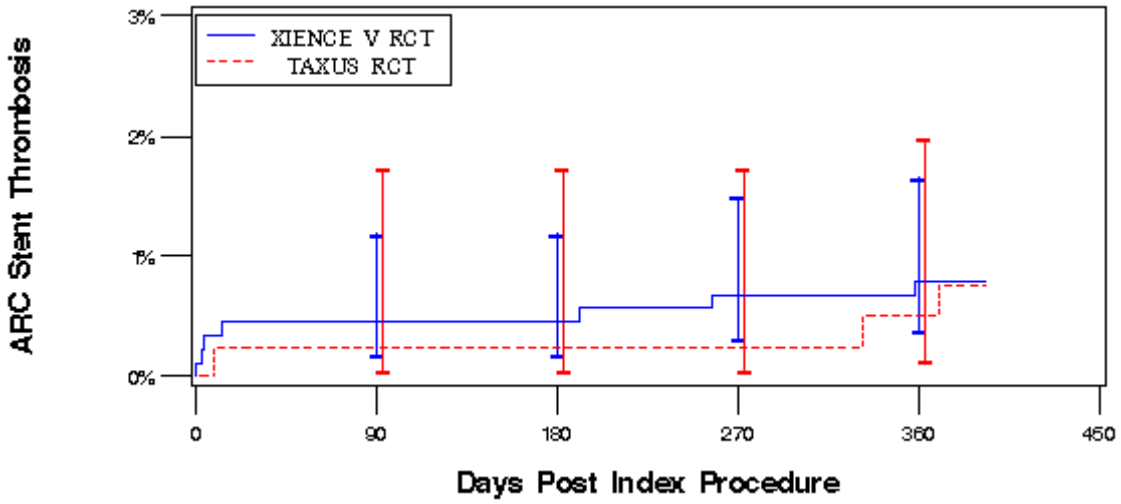

393 Day Number at Risk: Xience V 847, Taxus 376
Log-rank p-value=0.0836

**FIGURE 13. Kaplan-Meier Survival Curve: Estimated Cumulative Incidence Rates Of Stent Thrombosis Through 393 Days**
(RCT Intent-To-Treat Population)
(SPIRIT II and SPIRIT III RCT Pooled Population)




393 Day Number at Risk: Xience V 860, Taxus 388
Log-rank p-value=0.8970

**FIGURE 14. Kaplan-Meier Survival Curve: Estimated Cumulative Incidence Rates of TLR - Uncensored ARC Stent Thrombosis (Definite + Probable) through 393 Days**
(RCT Intent-To-Treat Population, SPIRIT II and SPIRIT III RCT Pooled Population)




393 Day Number at Risk: Xience V 860, Taxus 388
Log-rank p-value=0.9280

### g. Single vs. Dual Vessel Treated Subgroups

SPIRIT II and III represent the first DES studies intended to support a PMA that prospectively included treatment of dual vessel disease. The sponsor has provided the following table of clinical endpoints stratified by dual versus single vessel treatment. Except for rates of stent thrombosis, a consistent trend in treatment effects was observed across single vessel and dual vessel subgroups. That is, clinical endpoints trended lower in both the single vessel and Xience groups. The numerically higher observed stent thrombosis rates noted for Xience dual vessel treated subjects did not translate into higher observed rates of death or MI when compared to the Taxus dual vessel arm.

**TABLE 39. Combined SPIRIT II and II Analyses**

| Events through 393 days (Single and Dual Vessel Treated Subgroup) | | | | |
|---|---|---|---|---|
| | **XIENCE V Dual Vessel Treated** | **TAXUS Dual Vessel Treated** | **XIENCE V Single Vessel Treated** | **TAXUS Single Vessel Treated** |
| **TVF** | 12.3% (17/138) | 23.4% (15/64) | 6.8% (50/735) | 8.4% (28/333) |
| **MACE** | 8.0% (11/138) | 23.4% (15/64) | 4.8% (35/735) | 7.5% (25/333) |
| **All Death** | 0.0% (0/138) | 4.6% (3/65) | 1.5% (11/739) | 1.2% (4/333) |
| Cardiac Death | 0.0% (0/138) | 3.1% (2/64) | 0.7% (5/735) | 0.6% (2/333) |
| **MI** | 4.3% (6/138) | 9.4% (6/64) | 1.9% (14/735) | 3.0% (10/333) |
| **TLR** | 4.3% (6/138) | 12.5% (8/64) | 2.9% (21/735) | 4.5% (15/333) |
| **TVR (CABG/PCI), non Target lesion** | 5.1% (7/138) | 12.5% (8/64) | 2.3% (17/735) | 2.1% (7/333) |
| **Stent Thrombosis** | | | | |
| Protocol defined | 2.9% (4/138) | 1.6% (1/62) | 0.3% (2/729) | 0.6% (2/332) |
| ARC definite + probable (TLR *not* censored) | 2.2% (3/138) | 1.6% (1/62) | 0.5% (4/730) | 0.6% (2/332) |
| ARC definite + probable (TLR censored) | 2.2% (3/138) | 1.6% (1/62) | 0.5% (4/730) | 0.6% (2/332) |

* Stent thromboses rates derived from <u>all</u> target lesion analyses

### h. Stent Thrombosis and Dual Antiplatelet Therapy

Drugs that interrupt the cell cycle such as paclitaxel and sirolimus (and its analogs including zotarolimus and everolimus) have potent antiproliferative and anti-inflammatory properties. Fundamentally, local delivery of these agents via DES prevent restenosis by inhibiting: (1) vascular smooth muscle cell migration and proliferation and synthesis of extracellular matrix, and (2) inflammatory cell production of growth factors and cytokines. Effective suppression of in-stent neointimal growth, however, can result in delayed or incomplete coverage of stent struts by endothelialized neointimal tissue.

Autopsy studies suggest that impaired neointimal healing extends the window of thrombotic risk for DES vs. bare metal stents and is an important mechanism of DES thrombosis. Stent thrombosis, although rare, is often associated with death or MI.

Concurrent with the presentation and publications of reports of DES thrombosis in 2005-6, it became apparent that uniform definitions of stent thrombosis across study protocols were lacking. Reported rates of stent thrombosis are clearly influenced if unequivocal evidence is required (e.g., by angiography or at autopsy) or if any unexplained death is ascribed to stent thrombosis. As part of an effort to devise common clinical outcomes that might be used in DES trials, FDA participated in the Academic Research Consortium (ARC), which produced suggested uniform definitions of stent thrombosis based on the timing of the event post-stent implantation (early, late, and very late) and the level of evidence available (definite, probable, and possible) supporting the diagnosis of stent thrombosis. While recognizing that all proposed stent thrombosis definitions are imperfect, FDA believes the ARC definite + probable category of stent thrombosis provides the optimal balance between clinical sensitivity and specificity. FDA has requested that all DES sponsors apply the ARC stent thrombosis definitions to their datasets for adjudication to supplement stent thrombosis rates per the study protocol definitions.

Concerns regarding DES thrombosis, particularly late stent thrombosis, lead to the convening of an FDA Circulatory Systems Advisory Panel Meeting On December 7 – 8, 2006. Data presented at this meeting and subsequent publications supported the conclusion that compared to bare metal stents, the approved DES are associated with a numerically increased rate of stent thrombosis that emerges after one year post-DES implantation. However, an analysis of pooled DES trials showed no increase in the rates of death or MI in DES-treated patients compared to those receiving bare metal stents. The reasons for discordance between a numerical increase in DES thrombosis and no increase in the rates of death or MI stent are uncertain. It is possible that the sample sizes in the pooled studies were not large enough to permit the detection of a difference between treatment groups. Alternatively, increases in the rate of death or MI among DES patients might have been offset by a reduction in events associated with in-stent restenosis and repeated revascularization. The optimal duration of dual antiplatelet therapy has remained an important area of uncertainty. Early discontinuation or interruption of dual antiplatelet therapy is associated with DES thrombosis, death and MI, and data from some non-randomized studies suggest that more prolonged dual antiplatelet therapy may be beneficial in DES patients. Addressing this issue, the ACC/AHA/SCAI released a consensus statement recommending extending the use of dual antiplatelet therapy to 12 months post-DES implantation in patients who are not at high risk for bleeding.

A tabulation of stent thrombosis rates in combined SPIRIT II and III data, with corresponding 95% confidence intervals, are provided below.

**TABLE 40: Combined SPIRIT II & III Stent Thrombosis Rates**

| Stent Thrombosis Rates<br>Protocol Defined and Definite + Probable Stent Thrombosis (ARC) | | |
|---|---|---|
| | **XIENCE (N=892)<br>% (n/N)<br>[95% CI]** | **TAXUS (N=410)<br>%, (n/N)<br>[95% CI]** |
| **Thrombosis (0 - 30 days)** | | |
| Stent Thrombosis (Protocol) | 0.3% (3/890)<br>[0.07%, 0.98%] | 0.0% (0/407)<br>[0.00%, 0.90%] |
| ARC definite + probable (TLR-uncensored) | 0.4% (4/890)<br>[0.12%, 1.15%] | 0.2% (1/407)<br>[0.01%, 1.36%] |
| ARC definite + probable (TLR-censored) | 0.4% (4/890)<br>[0.12%, 1.15%] | 0.2% (1/407)<br>[0.01%, 1.36%] |
| **Thrombosis (0 - 9 months)** | | |
| Stent Thrombosis (Protocol) | 0.6% (5/874)<br>[0.19%, 1.33%] | 0.3% (1/396)<br>[0.01%, 1.40%] |
| ARC definite + probable (TLR-uncensored) | 0.7% (6/875)<br>[0.25%, 1.49%] | 0.3% (1/396)<br>[0.01%, 1.40%] |
| ARC definite + probable (TLR-censored) | 0.7% (6/875)<br>[0.25%, 1.49%] | 0.3% (1/396)<br>[0.01%, 1.40%] |
| **Thrombosis (0 – 12 months)** | | |
| Stent Thrombosis (Protocol) | 0.7% (6/867)<br>[0.25%, 1.50%] | 0.8% (3/394)<br>[0.16%, 2.21%] |
| ARC definite + probable (TLR-uncensored) | 0.8% (7/868)<br>[0.32%, 1.65%] | 0.8% (3/394)<br>[0.16%, 2.21%] |
| ARC definite + probable (TLR-censored) | 0.8% (7/868)<br>[0.32%, 1.65%] | 0.8% (3/394)<br>[0.16%, 2.21%] |
| *Note: Confidence intervals are calculated by the binomial exact method* | | |

The rare frequency of ST events makes interpretation of the point estimates difficult. However, comparability of the ST rates in Xience and Taxus at 12 months is suggested by very similar observed ST rates (0.8% vs. 0.8%) as well as substantial overlap of 95% confidence intervals. The larger difference in 12-month definite + probable ST rates seen in SPIRIT III (Xience 1.1% vs. Taxus 0.6%) has become negligible with additional data from SPIRIT II and larger effective sample size.

### i. Adherence to Dual Antiplatelet Therapy

In SPIRIT II and III, the mandated duration of dual antiplatelet therapy was a minimum of 6 months. The actual use of dual antiplatelet therapy may be informative in considering the clinical outcomes in the Xience stent program (including stent thrombosis rates of <1%) and recommendations regarding antiplatelet therapy in the Xience label.

**TABLE 41. Subject Adherence to Antiplatelet Therapy**

| | XIENCE V (N=892) | TAXUS (N=410) |
|---|---|---|
| **Number of Subjects:** | | |
| **On Aspirin** | | |
| 180 Days | 97.3% (865/889) | 95.8% (391/408) |
| 270 Days | 96.5% (858/889) | 94.6% (386/408) |
| 365 Days | 95.4% (848/889) | 92.9% (379/408) |
| **On Clopidogrel or Ticlopidine** | | |
| 180 Days | 93.4% (833/892) | 92.9% (379/408) |
| 270 Days | 67.8% (605/892) | 70.6% (288/408) |
| 365 Days | 63.3% (565/892) | 64.5% (263/408) |
| **On Aspirin + Clopidogrel or Ticlopidine** | | |
| 180 Days | 92.2% (820/889) | 90.9% (371/408) |
| 270 Days | 67.4% (599/889) | 69.6% (284/408) |
| 365 Days | 62.5% (556/889) | 62.7% (256/408) |

Adherence rates between the two arms are roughly comparable. The lower adherence to dual anti-platelet therapy to 365 days appears to have been driven primarily by discontinuation of clopidogrel or ticlopidine.

The applicant has tabulated stent thromboses that occurred after (first) discontinuation of clopidogrel or ticlopidine.

**TABLE 42**: **Adverse Events Subsequent to Discontinuation of Clopidogrel / Ticlopidine through 393 Days Per-Subject Analysis (RCT Intent-To-Treat Population)**

| | XIENCE V (N=892) | TAXUS (N=410) | Difference |
|---|---|---|---|
| **First Discontinuation before 180 Days** | | | |
| Stent Thrombosis after the First Discontinuation | 1.8% (2/112)* | 2.0% (1/50)† | -0.21% |
| ARC definite + probable (TLR-uncensored) | 1.8% (2/112)* | 2.0% (1/50)† | -0.21% |
| ARC definite + probable (TLR-censored) | 1.8% (2/112)* | 2.0% (1/50)† | -0.21% |
| **First Discontinuation between 180 Days and 284 Days** | | | |
| Stent Thrombosis after the First Discontinuation | 0.0% (0/221) | 0.0% (0/108) | 0.00% |
| ARC definite + probable (TLR-uncensored) | 0.5% (1/222) | 0.0% (0/108) | 0.45% |
| ARC definite + probable (TLR-censored) | 0.5% (1/222) | 0.0% (0/108) | 0.45% |
| **First Discontinuation between 285 Days and 393 Days** | | | |
| Stent Thrombosis after the First Discontinuation | 0.0% (0/63) | 0.0% (0/19) | 0.00% |
| ARC definite + probable (TLR-uncensored) | 0.0% (0/63) | 0.0% (0/19) | 0.00% |
| ARC definite + probable (TLR-censored) | 0.0% (0/63) | 0.0% (0/19) | 0.00% |

| **First Discontinuation on and before 393 Days** | | | |
|---|---|---|---|
| Stent Thrombosis after the First Discontinuation | 0.5% (2/389)* | 0.6% (1/174) † | -0.06% |
| ARC definite + probable (TLR-uncensored) | 0.8% (3/390) | 0.6% (1/174) | 0.19% |
| ARC definite + probable (TLR-censored) | 0.8% (3/390) | 0.6% (1/174) | 0.19% |

Note: For subjects with multiple discontinuation of clopidogrel or ticlopidine, the earliest discontinuation date is us alysis.
* Patient in XIENCE V arm stopped clopidogrel on day 146 and had stent thrombosis on day 358.Patient in XIENCE V arm stopped clopidogrel on day 10, and had stent thrombosis on day 13. Pati tarted clopidogrel on day 13 after the event and died on day 26.
† Patient in TAXUS arm stopped on day 170 and had stent thrombosis on day 332.

One can see that 4 of the 10 total ARC definite + probable (TLR-uncensored) stent thromboses (both in Xience V and Taxus arms) occurred in subjects who were known to have discontinued dual antiplatelet therapy.

### j. Diabetic Patients

Diabetic patients comprise an important patient subgroup that is at increased risk for cardiovascular morbidity and mortality. Like previous PCI applications for PMA approval, including the currently approved DES, diabetic patients were included in the SPIRIT clinical trials. Although there were no pre-specified hypotheses or trial design features to warrant a specific labeled indication for the use of the Xience stent in diabetic individuals, FDA believes that clinical outcomes in diabetics should be considered in the review of the Xience stent program. Therefore FDA requested that Abbott conduct a post-hoc pooled analysis of outcomes in diabetics from the SPIRIT II and III clinical trials.

The applicant has tabulated clinical outcomes through 270 days in patients pooled from the SPIRIT II and III trials stratified by non-diabetics, all diabetics, insulin-dependent diabetics, and non-insulin dependent diabetics.

**TABLE 43. SPIRIT II and III Combined Analyses**

| **Combined Xience and Taxus Cohort: Clinical Events in Diabetics through 1 year** | | | | |
|---|---|---|---|---|
| | **Non-Diabetics (N=939)** | **All Diabetics (N=359)** | **Insulin-Dependent (N=86)** | **Non-Insulin-Dependent (N=273)** |
| **TVF** | 8.4% (77/919) | 9.5% (33/348) | 9.5% (8/84) | 9.5% (25/264) |
| **MACE** | 6.6% (61/919) | 7.2% (25/348) | 8.3% (7/84) | 6.8% (18/264) |
| **All Death** | 1.4% (13/922) | 1.4% (5/350) | 2.4% (2/85) | 1.1% (3/265) |
| Cardiac Death | 0.7% (6/919) | 0.9% (3/348) | 1.2% (1/84) | 0.8% (2/264) |
| **MI** | 2.4% (22/919) | 4.0% (14/348) | 7.1% (6/84) | 3.0% (8/264) |
| **TLR** | 4.1% (38/919) | 3.4% (12/348) | 4.8% (4/84) | 3.0% (8/264) |
| **TVR** | 3.0% (28/919) | 3.2% (11/348) | 1.2% (1/84) | 3.8% (10/264) |

| | | | | |
|---|---|---|---|---|
| **(CABG/PCI), non Target Lesion** | | | | |
| **Stent Thrombosis** | | | | |
| Protocol defined | 0.7% (6/914) | 0.9% (3/344) | 1.2% (1/83) | 0.8% (2/261) |
| ARC definite + probable (TLR *not* censored) | 0.4% (4/914) | 1.7% (6/345) | 1.2% (1/83) | 1.9% (5/262) |
| ARC definite + probable (TLR censored) | 0.4% (4/914) | 1.7% (6/345) | 1.2% (1/83) | 1.9% (5/262) |

**TABLE 44. Outcomes in Diabetics by Treatment Arm**

| Clinical Events in Diabetics through 1 year | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Non-Diabetics** | | **All Diabetics** | | **Insulin-Dependent** | | **Non-Insulin-Dependent** | |
| | **XIENCE (N=643)** | **TAXUS (N=296)** | **XIENCE (N=249)** | **TAXUS (N=110)** | **XIENCE (N=63)** | **TAXUS (N=23)** | **XIENCE (N=186)** | **TAXUS (N=87)** |
| **TVF** | 6.4% (40/629) | 12.8% (37/290) | 11.1% (27/244) | 5.8% (6/104) | 12.9% (8/62) | 0.0% (0/22) | 10.4% (19/182) | 7.3% (6/82) |
| **MACE** | 4.0% (25/629) | 12.4% (36/290) | 8.6% (21/244) | 3.8% (4/104) | 11.3% (7/62) | 0.0% (0/22) | 7.7% (14/182) | 4.9% (4/82) |
| **All Death** | 1.0% (6/631) | 2.4% (7/291) | 2.0% (5/246) | 0.0% (0/104) | 3.2% (2/63) | 0.0% (0/22) | 1.6% (3/183) | 0.0% (0/82) |
| Cardiac Death | 0.3% (2/629) | 1.4% (4/290) | 1.2% (3/244) | 0.0% (0/104) | 1.6% (1/62) | 0.0% (0/22) | 1.1% (2/182) | 0.0% (0/82) |
| **MI** | 1.4% (9/629) | 4.5% (13/290) | 4.5% (11/244) | 2.9% (3/104) | 9.7% (6/62) | 0.0% (0/22) | 2.7% (5/182) | 3.7% (3/82) |
| **TLR** | 2.5% (16/629) | 7.6% (22/290) | 4.5% (11/244) | 1.0% (1/104) | 6.5% (4/62) | 0.0% (0/22) | 3.8% (7/182) | 1.2% (1/82) |
| **TVR (CABG/PCI), non TL** | 2.5% (16/629) | 4.1% (12/290) | 3.3% (8/244) | 2.9% (3/104) | 1.6% (1/62) | 0.0% (0/22) | 3.8% (7/182) | 3.7% (3/82) |
| **Stent Thrombosis** | | | | | | | | |
| Protocol defined | 0.5% (3/627) | 1.0% (3/287) | 1.3% (3/240) | 0.0% (0/104) | 1.6% (1/61) | 0.0% (0/22) | 1.1% (2/179) | 0.0% (0/82) |
| ARC definite + probable (TLR *not* censored) | 0.3% (2/627) | 0.7% (2/287) | 2.1% (5/241) | 1.0% (1/104) | 1.6% (1/61) | 0.0% (0/22) | 2.2% (4/180) | 1.2% (1/82) |
| ARC definite + probable (TLR censored) | 0.3% (2/627) | 0.7% (2/287) | 2.1% (5/241) | 1.0% (1/104) | 1.6% (1/61) | 0.0% (0/22) | 2.2% (4/180) | 1.2% (1/82) |

Although there were numerical differences in clinical endpoints between the Xience V and Taxus stents in diabetic strata, post-hoc conclusions regarding these subgroups are limited. The clinical effectiveness of the Xience V stent over Taxus in the non-diabetic population, based on observed rates of clinical endpoints, was not seen in the diabetic population. The explanation for this unexpected result remains unclear. There are a number of limitations to the above data that may preclude definitive conclusions regarding outcomes across these subgroups:

- Dividing the data into multiple subgroups makes post-hoc statistical comparisons of limited value
- Very low observed event rates in some Taxus subgroups contradict historical data that demonstrate higher outcomes, suggesting these SPIRIT subgroups may not accurately estimate rates seen in similar populations
- There are likely to be variables associated with diabetes that confound the data presented, which are difficult to control for in small subgroups.

## k. Summary

The Xience stent is the fourth DES PMA to be brought before an FDA Advisory Panel. The safety and effectiveness of the Xience V stent is supported by one large US RCT, the SPIRIT III trial, and a smaller RCT conducted OUS, the SPIRIT II trial. An additional registry concurrent with SPIRIT III investigated larger vessels using a 4.0mm Xience V stent. The SPIRIT FIRST trial provides additional, albeit limited, data on longer term performance of the Xience V platform.

In pivotal DES trials to date, composite primary study endpoints that combine safety and effectiveness components, such as TVF and MACE, have been utilized. The overall benefit of DES vs. bare metal stent trials was predominantly driven by significant reductions in the need for revascularizations (effectiveness) with no demonstrable differences in the rates of death or MI (safety) between treatment groups.

Over the past 12 to 18 months, concerns have emerged regarding late DES thrombosis that continues to raise question about their long-term safety profile. Although pivotal DES trials have been large by historical standards for cardiac devices, they have been underpowered to detect significant differences in infrequent but clinically important events between treatment groups. Composite clinical endpoints remain appropriate as primary endpoints in pivotal studies, but DES safety (rates of death, MI, and stent thrombosis) continues to warrant close scrutiny and will require pooling of data across pre-market trials and post-market studies.

***Revascularization***

For the combined SPIRIT II and III data, revascularization events had a substantial contribution to the overall TVF component endpoint. Revascularizations were classified by target vessel or lesion and also by PCI versus CABG. Of these, target lesion revascularization by PCI was the most frequent event.

Non-hierarchical event rates (total events) for the combined SPIRIT II and III populations are reviewed below:

**TABLE 45. SPIRIT II and SPIRIT III RCT Combined ITT Population**
***Non-Hierarchical* Subject Counts of Revascularization Events through 393 Days**

| | XIENCE V (N=892) | TAXUS (N=410) |
|---|---|---|
| **Any Revascularization** | **5.6% (49/873)** | **7.3% (29/397)** |
| CABG | 0.8% (7/873) | 0.5% (2/397) |
| PCI | 4.8% (42/873) | 7.1% (28/397) |
| **TLR** | **3.1% (27/873)** | **5.8% (23/397)** |
| CABG | 0.2% (2/873) | 0.0% (0/397) |
| PCI | 2.9% (25/873) | 5.8% (23/397) |
| **TVR, non-target lesion** | **2.7% (24/873)** | **3.8% (15/397)** |
| CABG | 0.6% (5/873) | 0.5% (2/397) |
| PCI | 2.2% (19/873) | 3.3% (13/397) |

In terms of effectiveness, the Xience V had favorable revascularization outcomes comparable to the Taxus control.

***Myocardial Infarction***

Q-wave and non-Q-wave myocardial infarctions have been important components of the clinical composite endpoint given their relatively strong contribution to the overall event rate.

**TABLE 46. SPIRIT II and SPIRIT III RCT Combined ITT Population**
***Non-Hierarchical* Subject Counts of MIs through 393 Days**

| | XIENCE V (N=892) | TAXUS (N=410) |
|---|---|---|
| **0 to 393 days** | | |
| Myocardial Infraction (MI) | 2.3% (20/873) | 4.0% (16/397) |
| QMI | 0.2% (2/873) | 0.3% (1/397) |
| NQMI | 2.1% (18/873) | 3.8% (15/397) |

As reviewed in the table below, a large portion of the overall MI events can be attributed to NQMIs occurring peri-procedurally or soon after the index stenting procedure:

**TABLE 47. SPIRIT II and SPIRIT III RCT Combined ITT Population**
***Non-Hierarchical* Subject Counts of MI's through 37 Days**

| | XIENCE V (N=892) | TAXUS (N=410) |
|---|---|---|
| **0 to 37 days** | | |
| Myocardial Infraction (MI) | 1.0% (9/890) | 2.9% (12/407) |
| QMI | 0.0% (0/890) | 0.0% (0/407) |
| NQMI | 1.0% (9/890) | 2.9% (12/407) |

***Death***

As endpoints of paramount importance, both overall death and cardiac death have been incorporated into clinical composite endpoints such as TVF and MACE. However, due to historically low event rates in DES randomized controlled trials; the contribution of death to the overall composite has been low. In the combined analysis of SPIRIT II and III subjects, cardiac deaths rates at 12 months were comparable between Xience V, 0.6% (5/873) and Taxus, 1.0% (4/397).

***Restenosis***

The primary endpoint of SPIRIT II and III, in-segment late loss (LL) at 240 days, was 0.14 ± 0.41 mm (N = 301) for the XIENCE V arm and 0.28 ± 0.48 mm (N = 134) for the TAXUS arm.

Similar secondary angiographic endpoints demonstrated an *in-stent* LL of 0.16 mm for the XIENCE V arm and 0.31 mm for the TAXUS arm. Per analysis lesion, in-stent % diameter stenosis (%DS) at 240 days was 6.26% for the XIENCE V arm and 10.61% for the TAXUS arm. In-segment %DS was 18.82% for the XIENCE V arm and 23.22% for the TAXUS arm.

The value added of using angiographic late loss as an adequate metric of effectiveness is open to debate. However, the angiographic results noted for Xience V appear to correlate reasonably well with the clinical revascularization results noted in this trial.

***Stent Thrombosis***

Stent thromboses rates were low in both the per-protocol and ARC defined analyses. However, presently there are insufficient data available to adequately evaluate rates of very late stent thromboses after one year post-implantation. Longer term follow-up of pre-market patient cohorts may provide additional ST data, but larger cohorts of subjects enrolled into post-market studies will be needed to properly evaluate this rare event.

## 8. POST-APPROVAL STUDY

The FDA review team, which includes an epidemiologist, recommends that if the XIENCE V Everolimus Eluting Coronary Stent System is approved, a post-approval study should be conducted as a condition of approval. It should be noted that the presence or content of a post-approval study cannot substitute for the requirement of a demonstration of a reasonable assurance of safety and effectiveness prior to approval for marketing.

### a. FDA Views on Post-Approval Studies for Drug-Eluting Stents

As discussed in the December 2006 DES Thrombosis meeting of the Circulatory System Advisory Panel, post-approval data collected on currently approved DES have signaled a potential increase in late stent thrombosis after one year compared to bare metal stents. However, it is not known if this rate plateaus or continues to increase over time, nor is the impact of stent thrombosis on the cumulative rates of cardiac death and MI completely understood. Therefore, FDA currently recommends that postmarket data be collected on a series of consecutively enrolled patients. FDA suggests that the cohort of patients enrolled in accordance with the labeled indications be pooled with the preapproval pivotal trial to reach a sample size sufficiently large to provide adequate power to evaluate a hypothesis comparing the rates of cardiac death and target vessel MI between

the new DES and the control stent used in the pivotal study. This cohort of post-approval patients may be in a single-arm or randomized study, and data pooling may be approached from either a frequentist or Bayesian perspective.

DES post-approval studies to date have demonstrated that routine clinical use of DES typically includes treatment outside of the labeled indications to include higher risk patient and lesion subsets. Based on this previous experience, FDA recognizes that a post-approval study of consecutively enrolled patients will likely include patients representing a broader use of the product and recommends that data from such patients be analyzed to better understand whether significant safety issues exist in the treatment of these patients.

FDA recommends that a sufficient number of patients treated in accordance with the labeled indication be enrolled to confirm that the upper bound of the one-sided 95% confidence interval around the observed rate of stent thrombosis between 12 and 24 months, 24 and 36 months, 36 and 48 months, and 48 and 60 months is < 1% with at least 80% probability. Depending on how the study is designed, it may be appropriate to include an adjustment for multiple comparisons in the statistical analysis plan.

FDA suggests that all patients be consented for 5 years of follow-up. If stent thrombosis rates are demonstrated to plateau or decrease in prior to 5 years, shorter follow-up may be sufficient. Alternatively, if stent thrombosis rates continue to increase, longer term follow-up or specific labeling changes may be appropriate.

FDA recommends that the statistical plan include planned descriptive statistics on certain subgroups of interest including:

- Demographics (age, sex, race and ethnicity)
- Patient characteristics (diabetes, renal insufficiency, left ventricular dysfunction, 3 vessel disease, and 2 vessel disease including proximal LAD disease)
- Lesion characteristics (acute ST elevation MI (STEMI), PCI within 36 hours of non-STEMI ACS, long lesions, small vessel diameters, ostial lesions, bifurcation lesions, trifurcation lesions, thrombus-containing lesions, left main lesions, chronic total occlusions, saphenous vein grafts, arterial grafts, post-brachytherapy, in-stent restenosis, overlapping stents, non-overlapping stents in the same or different vessels, IVUS-guided stent deployment)

**b. Overview of Abbott's Approach**

Abbott has proposed to address FDA's concerns outlined above by conducting a prospective, open-label, multi-center, observational, single-arm registry designed to evaluate XIENCE V EECSS continued safety and efficacy during commercial use in real world settings. Approximately 5,000 patients will be consecutively enrolled at up to 275 sites in the U.S. Clinical follow-up will occur at 14, 30, 180 days and 1, 2, 3, 4, and 5 years.

The Abbott post-approval registry protocol, along with statistical analysis plan, is summarized below.

**c. Protocol summary**

**Objectives**:

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

**Primary endpoint:** Stent thrombosis at 1 year as defined by the Academic Research Consortium (ARC).

**Secondary endpoints:**

- Stent thrombosis at 24 hours, 30, 180 days and at 2, 3, 4 and 5 years
- Composite rate of death, myocardial infarction (MI), and revascularization (percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG]) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Composite rate of cardiac death, MI attributed to the target vessel, and target lesion revascularization (TLR) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Death (cardiac death, vascular death, non-cardiovascular death) at 30, 180, days and at 1, 2, 3, 4 and 5 years
- MI (both Q-wave and non Q-wave) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Revascularization (both PCI and CABG) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Target vessel revascularization (both PCI and CABG) (TVR) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- TLR (both PCI and CABG) at 30, 180 days and at 1, 2, 3, 4 and 5 years
- Compliance and therapy interruptions with prescribed adjunctive antiplatelet therapy at 14, 30, 180 days and at 1, 2, 3, 4 and 5 years
- Major bleeding complications at 14, 30, 180 days and at 1, 2, 3, 4 and 5 years
- Clinical device and procedural success
- Patient health status (symptoms, physical function, and quality of life) at baseline, 180 days, and 1 year as assessed by the Seattle Angina Questionnaire

**Design**: Non-randomized, prospective, multi-center, single arm trial.

**Randomization**: none

**General Inclusion Criteria:** The patient agrees to participate in this study by signing the IRB approved informed consent form. Alternatively, the patient's legally authorized representative agrees to the patient's participation in this study and signs the informed consent form.

**Antiplatelet therapy:** Enrolled patients will be encouraged to receive adjunctive antiplatelet therapy consisting of an indefinite duration of aspirin, along with 6 months of clopidogrel. Clopidogrel will be extended to 12 months in patients who are not at high bleeding risk as recommended by ACC/AHA/SCAI and others.

**Patient enrollment:** Approximately 5,000 patients will be consecutively enrolled in this study at up to 275 sites across the USA. Data from all study sites will be pooled for analyses.

**Follow up schedule:** Clinical follow-up will occur at 14, 30, 180 days and 1, 2, 3, 4, and 5 years. The investigator or designee may conduct follow-up as telephone contacts or office visits.

If available, the following data should be collected at the specified time points:

- Clinical events including death, MI, revascularization, and stent thrombosis at 30, 180 days and 1, 2, 3, 4, and 5 years. Also, AE related data including laboratory test results, ECG, and subsequent repeat coronary angiography results
- Patient compliance and therapy interruptions with adjunctive antiplatelet therapy and major bleeding complications at 14, 30, 180 days and 1, 2, 3, 4, and 5 years
- Patient health status (symptoms, physical function, and quality of life) using the Seattle Angina Questionnaire at 180 days and 1 year
- Chronic concomitant medication at 14, 30, 180 days and 1, 2, 3, 4, and 5 years

**d. Statistical Analysis Plan**

**Sample size calculations and assumptions**:

The 5,000 patient sample size for this study was derived using the anticipated stent thrombosis rate and the precision of this estimate based on the following:

- A 1-year cumulative ARC defined stent thrombosis rate of 1.7% derived from past XIENCE V EECSS trials,
- A standard error of 0.18% for the stent thrombosis rate estimate
- A 2% dropout rate for the overall population at 1-year follow-up (based on ARRIVE study result data)

The estimated stent thrombosis rate and standard error correspond to an approximate 95% confidence interval from 1.35% to 2.05%.

Primary analysis: Stent thrombosis rates and confidence intervals will be summarized at 24 hours, 30, 180 days and 1, 2, 3, 4 and 5 years.

Secondary Analysis: Secondary endpoints will be summarized for the analytical population and certain subpopulations. Two-sided 95% confidence intervals will be calculated for event rates. Descriptive analyses will be provided for patient demographics, clinical device/procedural success, antiplatelet therapy compliance, bleeding complications, medical histories, and co-morbidities. Logistic regression analyses may be used to screen a wide range of parameters for their association with some endpoints. Health status will be assessed by including predetermined categories from the Seattle Angina Questionnaire. Each patient will serve as their own control. Correlation analyses will be conducted for several parameters including, but not limited to, adjunctive dual antiplatelet therapy use, bleeding complications, and late stent thrombosis incidence.

**Comments**

FDA does not agree with the endpoint of stent thrombosis at 1 year. There is not enough data from the pivotal trials or the literature to determine whether the stent thrombosis rate increase, decreases, or plateaus after 1 year. We suggest the primary endpoint be the evaluation of stent thrombosis rates through to 5 years. We also suggest the sponsor study a co-primary endpoint of death and MI at 1 year, and through 5 years, since this is a critical clinical outcome of interest. FDA will continue to work with the sponsor on the postapproval protocol, as appropriate.

## ISSUES FOR PANEL MEMBERS DISCUSSION

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

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

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

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

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

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

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