The PROMUS® Everolimus Eluting Coronary Stent System
Instructions for Use

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Rx ONLY

1.0 PRODUCT DESCRIPTION

The PROMUS® (2.25 – 4.0 mm) Everolimus-Eluting Coronary Stent System (hereinafter referred to as PROMUS EECSS or PROMUS stent system) is a private-labeled XIENCE V® Everolimus Eluting Coronary Stent System (XIENCE V EECSS or XIENCE V stent system) manufactured by Abbott and distributed by Boston Scientific Corporation. The PROMUS EECSS is a device/drug combination product consisting of either the MULTI-LINK VISION® Coronary Stent System or the MULTI-LINK MINI VISION® Coronary Stent System coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer.

1.1 Device Component Description

The device component consists of the MULTI-LINK MINI VISION or MULTI-LINK VISION stent mounted onto the MULTI-LINK MINI VISION or MULTI-LINK VISION stent delivery system (SDS), respectively. The device component characteristics are summarized in Table 1.1-1.

Table 1.1-1: PROMUS Stent System Product Description

	PROMUS Rapid-Exchange (RX) EECSS	PROMUS Over-the-Wire (OTW) EECSS
Available Stent Lengths (mm)	8, 12, 15, 18, 23, 28	8, 12, 15, 18, 23, 28
Available Stent Diameters (mm)	2.25*, 2.5, 2.75, 3.0, 3.5, 4.0	2.5, 2.75, 3.0, 3.5, 4.0
Stent Material	A medical grade L-605 cobalt chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent	
Drug Component	A conformal coating of a non-erodible polymer loaded with 100 µg/cm^2 of everolimus with a maximum nominal drug content of 181 µg on the large stent (4.0 x 28 mm)	
Delivery System Working Length	143 cm	143 cm
Delivery System Design	Single access port to inflation lumen. Guide wire exit notch is located 30 cm from tip. Designed for guide wires ≤ 0.014”.	Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen. Designed for guide wires ≤ 0.014”.
Stent Delivery System Balloon	A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length.	
Balloon Inflation Pressure	Nominal inflation pressure: 8 atm (811 kPa) for 2.25, 2.5 and 2.75 mm diameters; 9 atm (912 kPa) for 3.0, 3.5, and 4.0 mm diameters Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes	
Guiding Catheter Inner Diameter	≥ 5 F (0.056”)	
Catheter Shaft Outer Diameter (nominal)	2.25 – 3.0 mm / 3.5 – 4.0 mm Distal: 0.032” / 0.035” Proximal: 0.026” / 0.026”	2.5 mm / 2.75 x 8 – 3.5 x 18 / 3.5 x 23 – 4.0 x 28 Distal: 0.032” / 0.034” / 0.036” Proximal: 0.042” / 0.042” / 0.042”

*The 2.25 mm diameter PROMUS EECSS is only available on the RX platform.

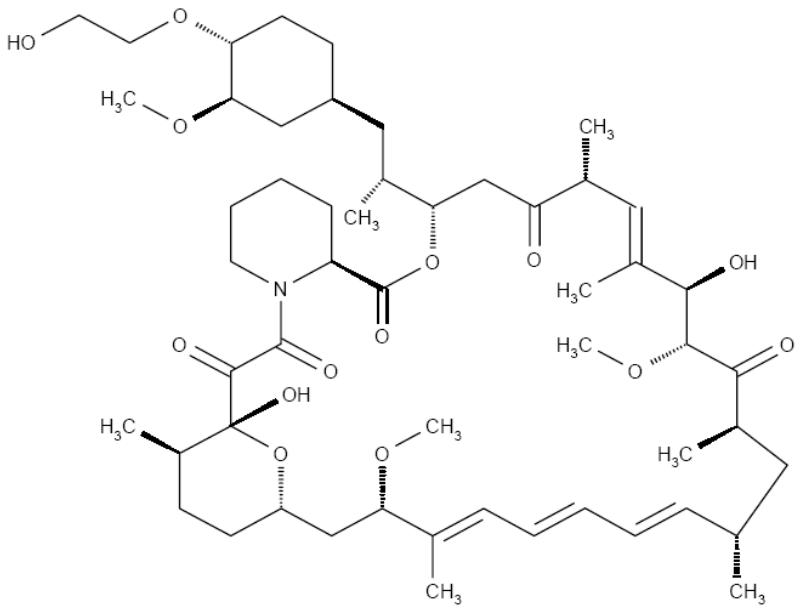
1.2 Drug Component Description

The PROMUS Everolimus Eluting Coronary Stent (PROMUS stent) is coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

1.2.1 Everolimus

Everolimus is the active pharmaceutical ingredient in the PROMUS stent. It is a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin (sirolimus). The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in Figure 1.2.1-1 below.

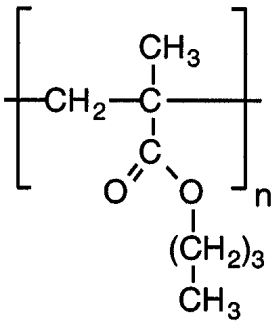
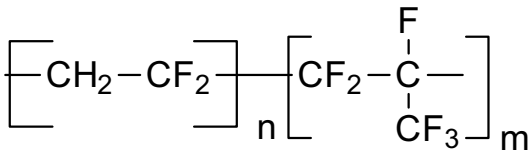
Figure 1.2.1-1: Everolimus Chemical Structure



1.2.2 Inactive Ingredients – Non-erodible Polymer

The PROMUS stent contains inactive ingredients including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA coated stent surface. The drug load is 100 µg/cm^2 for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in Figure 1.2.2-1 below.

Figure 1.2.2-1: Non-erodible Polymer Chemical Structures

PBMA	PVDF-HFP
	

1.2.3 Product Matrix and Everolimus Content

Table 1.2.3-1: PROMUS EECSS Product Matrix and Everolimus Content

Model Number (RX)	Model Number (OTW)	Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (μg)
1009544-08B	-	2.25	8	37
1009539-08B	1009545-08B	2.5	8	37
1009540-08B	1009546-08B	2.75	8	37
1009541-08B	1009547-08B	3.0	8	37
1009542-08B	1009548-08B	3.5	8	53
1009543-08B	1009549-08B	4.0	8	53
1009544-12B	-	2.25	12	56
1009539-12B	1009545-12B	2.5	12	56
1009540-12B	1009546-12B	2.75	12	56
1009541-12B	1009547-12B	3.0	12	56
1009542-12B	1009548-12B	3.5	12	75
1009543-12B	1009549-12B	4.0	12	75
1009544-15B	-	2.25	15	75
1009539-15B	1009545-15B	2.5	15	75
1009540-15B	1009546-15B	2.75	15	75
1009541-15B	1009547-15B	3.0	15	75
1009542-15B	1009548-15B	3.5	15	98
1009543-15B	1009549-15B	4.0	15	98
1009544-18B	-	2.25	18	88
1009539-18B	1009545-18B	2.5	18	88
1009540-18B	1009546-18B	2.75	18	88
1009541-18B	1009547-18B	3.0	18	88
1009542-18B	1009548-18B	3.5	18	113
1009543-18B	1009549-18B	4.0	18	113
1009544-23B	-	2.25	23	113
1009539-23B	1009545-23B	2.5	23	113
1009540-23B	1009546-23B	2.75	23	113
1009541-23B	1009547-23B	3.0	23	113
1009542-23B	1009548-23B	3.5	23	151
1009543-23B	1009549-23B	4.0	23	151
1009544-28B	-	2.25	28	132
1009539-28B	1009545-28B	2.5	28	132
1009540-28B	1009546-28B	2.75	28	132
1009541-28B	1009547-28B	3.0	28	132
1009542-28B	1009548-28B	3.5	28	181
1009543-28B	1009549-28B	4.0	28	181

2.0 INDICATIONS

The PROMUS Everolimus-Eluting Coronary Stent System (PROMUS stent) 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 2.25 mm to 4.25 mm.

3.0 CONTRAINDICATIONS

The PROMUS stent is contraindicated for use in patients:

- Who cannot receive antiplatelet and/or anticoagulant therapy (see Section 5.2 – Pre- and Post-Procedure Antiplatelet Regimen for more information)
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic-polymers or fluoropolymers

4.0 WARNINGS

- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Judicious patient selection is necessary because device use has been associated with stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy (see Section 5.2 – Pre- and Post-Procedure Antiplatelet Regimen for important information regarding antiplatelet therapy).

5.0 PRECAUTIONS

5.1 General Precautions

- Stent implantation should only be performed by physicians who have received appropriate training.
- Stent placement should be performed at hospitals where emergency coronary artery bypass graft surgery is accessible.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent are presently unknown.
- Risks and benefits should be considered in patients with severe contrast agent allergies.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death. Data from the SPIRIT family of clinical trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (see Section 8.2 – Stent Thrombosis Definitions and Section 9.6 – Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Analysis for more information). In the XIENCE V SPIRIT family of clinical trials analyzed to date, the differences in the incidence of stent thrombosis observed with the XIENCE V stent compared to the control stent TAXUS® Express® Paclitaxel-Eluting Coronary Stent System (TAXUS stent)[1] have not been associated with an increased risk of cardiac death, MI, or all-cause mortality. Additional data from longer-term follow-up in the XIENCE V SPIRIT family of trials and analyses of stent thrombosis related to drug-eluting stents (DES) are expected and should be considered in making treatment decisions.

[1] In the SPIRIT II and SPIRIT IV study, there were 17 and 1 patient(s), respectively, who received TAXUS® Liberté® stent.

- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the SPIRIT family of clinical trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.
- Orally administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglyceride levels.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In the SPIRIT FIRST clinical trial, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 3 months post-procedure (75 mg per day). In the XIENCE V SPIRIT II, SPIRIT III and SPIRIT IV clinical trials, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 6 months post-procedure (75 mg per day for clopidogrel bisulfate). Additionally, in the SPIRIT IV trial, it was strongly recommended that subjects should be treated with clopidogrel bisulfate up to 12 months if they were not at high risk for bleeding, per the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) guidelines. Aspirin (a minimum of 75 mg per day) was administered pre-procedure and continued for 1 to 5 years (depending on the study). In the SPIRIT Small Vessel Registry, clopidogrel bisulfate (75 mg per day) or ticlopidine hydrochloride (per site standard of care) was administered for at least 12 months post-procedure, while aspirin (≥ 80 mg per day) was administered indefinitely post-procedure.
- In the SPIRIT II and III clinical trials, approximately 92% of patients remained on dual antiplatelet therapy at 6 months and 62% at 1 year. In the SPIRIT IV clinical trial, approximately 98% of patients remained on dual antiplatelet therapy at 6 months and 93% at 1 year. In the SPIRIT Small Vessel Registry, 86.8% of subjects were on clopidogrel bisulfate or ticlopidine hydrochloride at 1 year. See Section 9.0 – SPIRIT Family of Clinical Trials, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically thienopyridines, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies on sirolimus-eluting or paclitaxel-eluting stents suggest that a longer duration of clopidogrel than was recommended post-procedurally in DES pivotal trials may be beneficial. Current ACC/AHA/SCAI PCI practice guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be given for at least 12 months in patients who are not at high risk of bleeding.[2,3].
- It is very important that the patient comply with post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medications could result in a higher risk of stent thrombosis, MI, or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy. Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for

[2] Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121
[3] King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209

cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

5.3 Multiple Stent Use

A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. In the SPIRIT II and III clinical trials, treatment was limited to 36 mm of total stent length in up to two lesions in different epicardial coronary arteries. In the SPIRIT IV trial, treatment was limited to 36 mm of total stent length in up to three lesions, with a maximum of two lesions per epicardial artery. Use of more than two stents to treat lesions longer than 28 mm has not been evaluated and may increase the risk of complications. Studies evaluating the effects of higher everolimus doses have not been conducted.

In the SPIRIT II, SPIRIT III, and SPIRIT IV clinical trials, lesions > 22 mm in length and ≤ 28 mm in length were treated with planned overlapping XIENCE V stents in the XIENCE V arm, or a single 32 mm TAXUS stent or planned overlapping TAXUS stents in the TAXUS arm. The PROMUS Everolimus-Eluting Coronary Stent System is a private-labeled XIENCE V Everolimus Eluting Coronary Stent System manufactured by Abbott and distributed by Boston Scientific Corporation.

In the SPIRIT IV clinical trial, there were 239 patients in the planned overlapping XIENCE V stent subgroup, 55 patients in the single 32 mm TAXUS stent subgroup, and 99 patients in the planned overlapping TAXUS subgroup (with 6 patients in the TAXUS arm receiving both single 32 mm and overlapping TAXUS stents). At one year, the target lesion failure (TLF) rate was 6.8% in the planned overlapping XIENCE V stent subgroup, 9.4% in the single 32 mm TAXUS stent subgroup, and 9.6% in the planned overlapping TAXUS stent subgroup.

In the pooled SPIRIT II, SPIRIT III, and SPIRIT IV analysis, there were a total of 317 patients in the planned overlapping XIENCE V stent subgroup, 86 patients in the single 32 mm TAXUS stent subgroup, and 113 patients in the planned overlapping TAXUS stent subgroup. At one year, the all cause mortality rate was 1.3% in the planned overlapping XIENCE V stent subgroup, 3.6% in the single 32 mm TAXUS stent subgroup, and 0.0% in the planned overlapping TAXUS stent subgroup. The cardiac death rate was 0.3% in the planned overlapping XIENCE V stent subgroup, 1.2% in the single 32 mm TAXUS stent subgroup, and 0.0% in the planned overlapping TAXUS stent subgroup. At one year, the rate of target vessel MI was 2.6% in the planned overlapping XIENCE V stent subgroup, 6.0% in the single 32 mm TAXUS stent subgroup, and 2.8% in the planned overlapping TAXUS stent subgroup. The Academic Research Consortium (ARC)-defined definite plus probable stent thrombosis rate at one year was 0.3% in the planned overlapping XIENCE V stent subgroup 1.3% in the single 32 mm TAXUS stent subgroup, and 0.9% in the planned overlapping TAXUS stent subgroup.

The effects of stent implantation of PROMUS stents combined with other drug-eluting stents are unknown. When multiple drug-eluting stents are required, use only PROMUS stents in order to avoid potential interactions with other drug-eluting or coated stents.

In addition, only stents composed of similar materials should be implanted in consecutive stent-to-stent contact to avoid corrosion potential between unrelated materials.

5.4 Brachytherapy

PROMUS stent safety and effectiveness have not been evaluated in patients with prior target lesion or in-stent restenosis-related brachytherapy.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (such as directional atherectomy catheters and rotational atherectomy catheters), or laser angioplasty catheters in conjunction with PROMUS stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

Pregnancy Category C. See Section 6.5 – Drug Information, Pregnancy. The PROMUS stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a PROMUS stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

5.6.2 Lactation

See Section 6.6 – Drug Information, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation considering the importance of the stent to the mother.

5.6.3 Gender

See Section 9.7 for an analysis (from pooled data from the SPIRIT II, SPIRIT III, and SPIRIT IV trials) of gender-specific outcomes associated with the XIENCE V stent.

5.6.4 Ethnicity

Insufficient subject numbers prevent ethnicity-related analyses of PROMUS stent safety and effectiveness.

5.6.5 Pediatric Use

The safety and effectiveness of the PROMUS stent in pediatric subjects have not been established.

5.6.6 Geriatric Use

Clinical studies of the XIENCE V stent did not have an upper age limit. Among the 3350 subjects in the XIENCE V stent group from the pooled SPIRIT II, SPIRIT III and SPIRIT IV trials, there were 1470 subjects who were age 65 or older and 160 subjects who were over 80 years of age. A post hoc analysis showed no clinically significant differences in outcomes between patients under 65 and over 65 years of age in the XIENCE V stent group.

5.7 Lesion/Vessel Characteristics

Safety and effectiveness of the PROMUS stent have not been established for subject populations in the following clinical settings:

- Unresolved vessel thrombus at the lesion site
- Coronary artery reference vessel diameters < 2.25 mm or > 4.25 mm
- Lesion length > 28 mm
- Lesions located in saphenous vein grafts
- Lesions located in an unprotected left main coronary artery, ostial lesions, chronic total occlusions, and lesions located at a bifurcation
- Previously stented lesions
- Diffuse disease or poor flow (TIMI < 1) distal to the identified lesions
- Excessive tortuosity proximal to or within the lesion
- Recent acute myocardial infarction (AMI) or evidence of thrombus in the target vessel
- Moderate or severe lesion calcification
- Multivessel disease
- In-stent restenosis

5.8 Drug Interactions

See Section 6.3 – Drug Information, Interactions with Drugs or Other Substances. Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein. Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the PROMUS stent because of limited systemic exposure to everolimus eluted from the stent used in SPIRIT clinical trials (see Section 6.2 – Drug Information, Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Therefore, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to implant a PROMUS stent in a patient taking a drug with a known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a PROMUS stent.

5.9 Immune Suppression Potential

Everolimus, the PROMUS stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the SPIRIT clinical trials. However, for patients who receive several PROMUS stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

5.10 Lipid Elevation Potential

Oral everolimus use in renal transplant patients and in patients treated for advanced renal cell carcinoma was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low- and high-dose prolonged oral

therapy in a dose-related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the PROMUS stent is expected to be significantly lower than concentrations usually observed in transplant patients. Increased serum cholesterol and triglycerides were not observed in the SPIRIT family of clinical trials.

5.11 Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated that the PROMUS stent, in single and in overlapped configurations up to 68 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for each duration of a sequence

The PROMUS stent should not migrate in this MRI environment. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the PROMUS stent.

Stent heating was derived by using the measured non-clinical, *in vitro* temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil in combination with the local specific absorption rates (SARs) in a digitized human heart model. The temperature rise was derived by validated calculation. At overlapped lengths up to 68 mm, the PROMUS stent produced a non-clinical maximum local temperature rise of 3ºC at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for one sequence of 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stents greater than 68 mm in length or stents with fractured struts are unknown.

As demonstrated in non-clinical testing, an image artifact can be present when scanning the PROMUS stent. MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the PROMUS stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of PROMUS stents.

5.12 Stent Handling

- **Each stent is for single use only.** Do not resterilize or reuse this device. Note the "Use by" (expiration) date on the product label.
- **The foil pouch is not a sterile barrier.** The inner header bag (pouch) within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.**
- **Do not remove the stent from the delivery system.** Removal may damage the stent and/or lead to stent embolization. These components are intended to perform together as a system.
- The delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or disrupt the stent on the balloon, especially during delivery system removal from packaging, placement over the guide wire, and advancement through the rotating hemostatic valve adapter and guiding catheter hub.

- **Do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.
- Use only the appropriate balloon inflation media (see Section 13.3.3 – Operator's Instructions, Delivery System Preparation). Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in stent deployment.

5.13 Stent Placement

5.13.1 Stent Preparation

- **Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed.** Use the balloon purging technique described in Section 13.3.3 – Operator's Instructions, Delivery System Preparation.
- **While introducing the delivery system into the vessel, do not induce negative pressure on the delivery system prior.** This may cause dislodgement of the stent from the balloon.
- Use guiding catheters which have lumen sizes that are suitable to accommodate the stent delivery system (see Section 1.1 – Product Description, Device Component Description).

5.13.2 Stent Implantation

- The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the difficulty of stent placement and cause procedural complications.
- Do not expand the stent if it is not properly positioned in the vessel (see Section 5.14 – Precautions, Stent System Removal).
- Implanting a stent may lead to vessel dissection and acute closure requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- Although the safety and effectiveness of treating more than one vessel per coronary artery with PROMUS stents have not been established, if this is performed, place the stent in the distal lesion before the proximal lesion in order to minimize dislodgement risk incurred by traversing through deployed stents.
- Stent placement may compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** (See Table 14-1 – Typical PROMUS EECSS Compliance.) Balloon pressures should be monitored during inflation. Applying pressures higher than specified on the product label may result in a ruptured balloon with possible arterial damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- An unexpanded stent may be retracted into the guiding catheter one time only. An unexpanded stent should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter should not be performed as the stent may be damaged when retracting the undeployed stent back into the guiding catheter.
- Should **any resistance** be felt **at any time** during coronary stent system withdrawal, the stent delivery system and guiding catheter should be **removed as a single unit** (see Section 5.14 – Precautions, Stent System Removal).
- Stent retrieval methods (i.e., using additional wires, snares, and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Although the stent delivery system balloon is strong enough to expand the stent without rupture, a circumferential balloon tear distal to the stent and prior to complete stent

expansion, could cause the balloon to become tethered to the stent, requiring surgical removal. In case of balloon rupture, it should be withdrawn and, if necessary, a new dilatation catheter exchanged over the guide wire to complete the expansion of the stent.
- Ensure the stented area covers the entire lesion/dissection site and that no gaps exist between stents.

5.14 Stent System Removal

Should **any resistance** be felt **at any time** during either lesion access or removing the delivery system post-stent implantation, the stent delivery system and the guiding catheter should be **removed as a single unit.**

When removing the delivery system and guiding catheter as a single unit, the following steps should be executed under direct visualization using fluoroscopy:

- Confirm complete balloon deflation. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position. In some cases it may be necessary to slightly retract the guiding catheter in order to prevent unplanned guiding catheter movement and subsequent vessel damage. In cases where unplanned guiding catheter movement has occurred, a coronary tree angiographic assessment should be undertaken to ensure that there is no damage to the coronary vasculature.
- DO NOT retract the delivery system into the guiding catheter.
- Position the proximal balloon marker just distal to the guiding catheter tip.
- Advance the guide wire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter, and remove the guiding catheter and delivery system as a **single unit.**

Failure to follow these steps and/or applying excessive force to the delivery system can potentially result in loss or damage to the stent and/or delivery system components and/or vasculature.

If it is necessary to retain guide wire position for subsequent artery/lesion access, leave the guide wire in place and remove all other system components.

Stent retrieval methods (i.e., additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include, but are not limited to, bleeding, hematoma, or pseudoaneurysm.

5.15 Post-Procedure

- When **crossing a newly deployed stent** with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter or delivery system, exercise care to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Antiplatelet therapy should be administered post-procedure (see Section 5.2 – Pre- and Post-Procedure Antiplatelet Regimen and Section 9.0 - SPIRIT Family of Clinical Trials). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.
- If the patient requires imaging, see Section 5.11 – Precautions, Magnetic Resonance Imaging (MRI).

6.0 DRUG INFORMATION

6.1 Mechanism of Action

The mechanism by which the PROMUS stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent

The PROMUS Everolimus-Eluting Coronary Stent System is a private-labeled XIENCE V Everolimus Eluting Coronary Stent System manufactured by Abbott and distributed by Boston Scientific Corporation. Everolimus elution from the XIENCE V stent (used in the SPIRIT clinical trials) post-implantation has been evaluated in three pharmacokinetic (PK) substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the United States (US) randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The third PK substudy was conducted as part of the SPIRIT II clinical trial at sites in Europe, India, and New Zealand. Whole blood everolimus PK parameters determined from subjects receiving the XIENCE V stent are provided in Table 6.2-1.

Table 6.2-1: Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation

SPIRIT III RCT and 4.0 Arm							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t}[a] (ng.h mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n = 3[b])	88 µg	0.050 (0.50-1.88)	0.3867 ± 0.09866		5.31 ± 4.114		
3.5-4.0 x 28 mm (n = 6[c])	181 µg	0.50 (0.07-1.00)	1.175 ± 0.6817	79.08 ± 57.24	23.73 ± 13.63	44.00 ± 28.67	5.130 ± 2.114
SPIRIT III Japanese Arm							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n = 6)	88 µg	1.00 (0.50-1.02)	0.5017 ± 0.1398	45.22 ± 35.08	5.049 ± 2.138	12.98 ± 7.078	9.286 ± 6.069
3.5-4.0 x 18 mm (n = 4[b])	113 µg	0.51 (0.50-0.53)	0.6500 ± 0.08756	53.57 ± 19.34	11.02 ± 4.002	19.97 ± 7.890	6.471 ± 2.807
SPIRIT II Clinical Trial							
	Dose (µg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)[a]	AUC_{last} (ng.h/mL)	$AUC_{0-\infty}$[a] (ng.h/mL)	CL (L/h)[a]
		median (range)	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
2.5-3.0 x 18 mm (n = 13)	88 µg	0.50 (0.13-2.17)	0.4369 ± 0.1507	54.08 ± 35.78	8.255 ± 5.863	19.60 ± 15.30	8.066 ± 6.443
3.5-4.0 x 18 mm (n = 4[c])	113 µg	0.50 (0.50-0.50)	0.5850 ± 0.2630	47.60 ± 62.13	42.54 ± 58.83	22.79 ± 31.47	16.96 ± 13.07
3.5-4.0 x 28 mm (n = 4)	181 µg	0.46 (0.17-1.00)	0.7925 ± 0.1406	103.4 ± 64.17	28.07 ± 13.18	52.71 ± 27.40	5.332 ± 5.048

[a] Accurate determination not possible due to rapid disappearance of everolimus from the blood
[b] n = 5 for $t_{1/2}$ and CL.
[c] n = 3 for $t_{1/2}$ and CL.
t_{max}(h) = time to maximum concentration.
C_{max} = maximum observed blood concentration.
$t_{1/2}$ (h) = terminal phase half-life.
AUC_{0-t} or AUC_{last} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
$AUC_{(0-\infty)}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL = total blood clearance.

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, 1 subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all 3 studies, the C_{max} value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination; $t_{½}$, AUC_{0-t}, AUC_{last}, AUC_{∞}, and CL could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

Everolimus disappearance from circulation following XIENCE V stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies.

6.3 Interactions with Drugs or Other Substances

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the liver and to some extent in the intestinal wall, and is a substrate for the multidrug efflux pump P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of everolimus may be influenced by medicinal products that also affect CYP3A4 and PgP pathways. 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 the PROMUS stent because of limited systemic exposure to everolimus eluted from the stent used in the SPIRIT clinical trials, (see Section 6.2 – Drug Information, Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to implant the PROMUS stent in a subject taking a drug with a known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods listed below [4]. Medications that are strong inhibitors of CYP3A4 or PgP might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 or PgP may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers [verapamil and diltiazem], aprepitant, atazanavir, nefazodone, amprenavir, indinavir, nelfinavir, delavirdine, fosamprenavir, saquinavir and telithromycin)
- Inducers of CYP3A4 isozyme (St. John's Wort, rifampin, rifabutin, carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, dexamethasone)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- PgP inhibitors (Digoxin, cyclosporine)
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit/grapefruit juice

Everolimus is approved in the United States under the name of Zortress® for the prophylaxis of organ rejection in adult kidney transplant recipients at low-moderate immunologic risk, at the dose of 1.5 mg/day when taken by mouth. Outside the United States, Zortress® is sold under the brand name Certican® in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor® for the treatment of patients with advanced renal cell carcinoma (cancer) after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The amount of drug that circulates in the bloodstream following implantation of a PROMUS stent is several fold lower than that obtained with oral doses (1.5 mg to 20 mg/day).

[4] Certican® Investigator's Brochure and Novartis Pharmaceutical Corporation; Afinitor® Prescribing Information; Zortress® Prescribing Information.

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of PROMUS stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group (PROMUS stent). The test group did not demonstrate an increased incidence of neoplastic lesions, when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. Based on the results of this study, the PROMUS stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies were conducted on the PROMUS stent in mammalian cells and bacteria. These studies included gene mutations in bacteria (Ames Test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. Based on the results of these studies, the PROMUS stent is not genotoxic.

A reproductive toxicity (teratology) study was conducted in female Sprague-Dawley rats. The PROMUS stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (PROMUS stent) and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of *in utero* mortality. Additionally, the PROMUS stent did not cause any reproductive toxicity in the offspring in this study.

6.5 Pregnancy

Pregnancy Category C: There are no adequate everolimus or PROMUS stent related studies in pregnant women. Effects of the PROMUS stent on prenatal and postnatal rat development were no different than the controls. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.

Effective contraception should be initiated before implanting a PROMUS stent and continued for one year post-implantation. The PROMUS stent should be used in pregnant women only if potential benefits justify potential risks.

The safety of the PROMUS stent has not been evaluated in males intending to father children.

6.6 Lactation

It is unknown whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to PROMUS stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

7.0 OVERVIEW OF CLINICAL STUDIES

The PROMUS Everolimus-Eluting Coronary Stent System is a private-labeled XIENCE V Everolimus Eluting Coronary Stent System manufactured by Abbott and distributed by Boston Scientific Corporation. Principal XIENCE V safety and effectiveness information is derived from the SPIRIT III clinical trial, confirmed by the SPIRIT IV clinical trial, and supported by the SPIRIT FIRST and SPIRIT II clinical trials. The safety and effectiveness of the 2.25 mm diameter XIENCE V stent is derived from the SPIRIT Small Vessel Registry. These studies evaluated the performance of the XIENCE V stent in subjects with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in Table 7-1.

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS® Express® stent (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consisted of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy (see Section 6.2 – Drug Information, Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Enrollment is complete in the RCT, the 4.0 mm diameter stent arm, and the Japan arm.

The SPIRIT III RCT was a prospective, randomized (2:1; XIENCE V:TAXUS), active-controlled, single-blinded, multi-center, clinical trial in the US designed to evaluate the safety and efficacy of the XIENCE V stent 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 study was designed to enroll 1,002 subjects at up to 80 sites in the US. The primary endpoint in the RCT was in-segment late loss at 240 days, and the co-primary endpoint was ischemia-driven target vessel failure (TVF, defined as the composite of cardiac death, MI, or ischemia-driven TVR) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and annually from 1 to 5 years), as well as angiographic results and intravascular ultrasound (IVUS) results at 240 days. Follow-up through 3 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III 4.0 mm arm was a prospective, multi-center, single-arm registry designed to evaluate the XIENCE V stent 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. This study was designed to enroll up to 80 subjects at up to 80 sites in the US. Enrolled subjects were scheduled for clinical follow-up at 30, 180, 240, and 270 days and annually from 1 to 5 years, with angiographic follow-up at 240 days. The primary endpoint was in-segment late loss at 240 days compared to the TAXUS arm from the SPIRIT III RCT. Follow-up through 2 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subset derived from the RCT[5] and Japan non-randomized arm. Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan).

The SPIRIT IV trial was a prospective, randomized, active-controlled, single-blinded, multi-center evaluation of the XIENCE V stent compared to the TAXUS® Express® stent[6] (TAXUS stent) in the treatment of up to three *de novo* lesions ≤ 28 mm in length in native coronary

[5] Includes one subject from the 4.0 mm non-randomized arm.
[6] In the TAXUS stent arm, there was 1 subject who received 1 TAXUS Liberté® stent.

arteries with RVD ≥ 2.5 mm to ≤ 4.25 mm. The SPIRIT IV trial was randomized 2:1 (XIENCE V: TAXUS) and designed to enroll 3,690 subjects at up to 80 sites in the US. Subjects were stratified by diabetes mellitus (diabetic vs. non-diabetic) and lesion characteristics (complex vs. non-complex). Complex lesion characteristics included triple vessels treatment, or dual lesions per vessel treatment, or lesions involving RCA-aorto-ostial locations, or bifurcations lesions. The primary endpoint was target lesion failure (TLF, defined as the composite of cardiac death, target vessel myocardial infarction and ischemia-driven target lesion revascularization) at 1 year. The major secondary endpoints were ischemic driven target lesion revascularization (ID-TLR) at 1 year and the composite of cardiac death or target vessel MI at 1 year. Formal non-inferiority and superiority testing were planned for the primary and the two major secondary endpoints following a fixed sequence. Secondary endpoints included clinical outcomes at 30, 180, 270 days and annually from 1 to 5 years. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT II clinical trial was a randomized, single-blinded, active-control, multi-center clinical evaluation. Subject eligibility criteria were similar to the SPIRIT III clinical trial and enrollment duration overlapped between studies. In this study, 300 subjects (3:1 randomization XIENCE V: TAXUS® Express® or TAXUS® Liberté®) were enrolled at 28 sites outside the United States. The primary endpoint was in-stent late loss at180 days. Secondary endpoints included clinical outcomes at 30, 180, 270 days and annually from 1 to 5 years; angiographic results at 180 days and 2 years; and IVUS results at 180 days and 2 years. Clinical follow-up through 4 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT FIRST clinical trial was a randomized, single-blinded, controlled, multi-center first-in-man study. This trial was the first human study to evaluate the XIENCE V stent safety and performance. Sixty subjects (XIENCE V stent [n = 28] and MULTI-LINK VISION bare metal control stent [n = 32]) were enrolled at 9 sites in Europe. The primary endpoint was in-stent late loss at 180 days on the per-treatment evaluable population, and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 180 days based on IVUS analysis of the per-treatment evaluable population. Follow-up through 5 years is currently available.

The SPIRIT Small Vessel (SV) Registry was a prospective, single-arm, open-label, US multi-center registry study using 2.25 mm diameter XIENCE V EECSS. The trial enrolled a total of 150 subjects, of which 69 subjects were included in an angiographic follow-up cohort, at 33 sites. The SPIRIT SV trial allowed for target and non-target lesion treatment. The target lesion was identified as that lesion intended to be treated by the 2.25 mm XIENCE V EECSS and the non-target lesion was identified as that lesion intended to be treated by the commercial XIENCE V EECSS. The SPIRIT SV trial allowed for single target lesion or two lesion treatment (two target lesions or one target and one non-target lesion) in separate epicardial vessels. The primary endpoint was target lesion failure (TLF, defined as the composite of cardiac death, target vessel myocardial infarction and clinically indicated target lesion revascularization) at 1 year. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

Table 7-1 summarizes the clinical trial designs for the SPIRIT family of trials.

Table 7-1: XIENCE V SPIRIT Clinical Trial Designs

	SPIRIT IV Clinical Trial	SPIRIT III Clinical Trial		SPIRIT II Clinical Trial	SPIRIT FIRST Clinical Trial	SPIRIT Small Vessel Registry
		RCT	Registries			
Study Type/Design	• Multi-center • Randomized • Single-blinded • Active-control	• Multi-center • Randomized • Single-blinded • Active-control	• Multi-center • Single-arm • Open-label	• Multi-center • Randomized • Single-blinded • Active-control	• Multi-center • Randomized • Single-blinded • Control	• Multi-center • Non-randomized • Open-label • Non-blinded • Single-arm
Number of Subjects Enrolled	Total: 3,690 XIENCE V: 2,460 TAXUS® Express® Control: 1,230**	Total: 1,002 XIENCE V: 668 TAXUS® Express® Control: 334	Total: 168 4.0 mm: 80 Japan: 88*	Total: 300 XIENCE V: 225 TAXUS® Express® or TAXUS® Liberté® Control: 75Δ	Total: 60 XIENCE V: 30 VISION Control: 30	2.25 mm XIENCE V Total : 150 No control
Treatment	Up to three *de novo* lesions, maximum of two lesions per epicardial vessel	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	Single *de novo* lesion	Up to two *de novo* lesions in different epicardial vessels
Lesion Size	RVD: ≥ 2.5 ≤ 4.25§ mm Length: ≤ 28 mm	RVD: ≥ 2.5 ≤ 3.75 mm Length: ≤ 28 mm	4.0 mm RVD: > 3.75 ≤ 4.25 mm Length: ≤ 28 mm Japan RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm	RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm	RVD: 3 mm Length: ≤ 12 mm	RVD: ≥ 2.25 < 2.50 mm Length: ≤ 28 mm
Stent Sizes (XIENCE V)	Diameter: 2.5, 3.0, 3.5, 4.0§ mm Length: 8, 18, 28 mm	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm	4.0 mm Diameter: 4.0 mm Length: 8, 18, 28 mm Japan Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 3.0 mm Length: 18 mm	Diameter: 2.25 mm Length: 8, 18, 28 mm
Post-Procedure Antiplatelet Therapy	Clopidogrel 12 months minimum(or ticlopidine per site standard),# Aspirin 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), aspirin 5 years	4.0 mm: same as RCT Japan: ticlopidine 3 months, aspirin 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), aspirin 1 year	Clopidogrel 3 months minimum (or ticlopidine per site standard), aspirin 1 year	Clopidogrel 12 months minimum (or ticlopidine per site standard), aspirin indefinitely
Primary Endpoint	Ischemia-driven target lesion failure at 1-year (composite of cardiac death, target vessel MI or ischemia driven TLR)	In-segment late loss at 240 days	In-segment late loss at 240 days	In-stent late loss at 180 days	In-stent late loss at 180 days	Clinically indicated target lesion failure at 1-year (composite of cardiac death, target vessel MI and clinically indicated TLR)
Co-Primary Endpoint	None	TVF at 270 days	None	None	None	None
Major Secondary Endpoint	1. Ischemia-driven TLR at 1-year 2. Composite endpoint of cardiac death or target vessel MI at 1-year	None	None	None	In-stent %VO at 180 days	None

	SPIRIT IV Clinical Trial	SPIRIT III Clinical Trial		SPIRIT II Clinical Trial	SPIRIT FIRST Clinical Trial	SPIRIT Small Vessel Registry
		RCT Registri	es			
Clinical Follow-up	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, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30 days, 240, days, 1 to 5 years
Angiographic Follow-up	None	240 days (N = 564)	240 days (All registry)	180 day (all), 2 years (N = 152)	180 days, 1 year (all)	240 days (n = 69)
IVUS Follow-up	None	240 days (N = 240)	240 days (Japan only)	180 day, 2 years (N = 152)	180 days, 1 year (all)	None
PK Study	None	US: Minimum 15 subjects with single lesion, maximum 20 with dual lesions Japan: Minimum 10 subjects with single lesion, maximum 20 with dual lesions		Minimum 15 subjects with single lesion, maximum 20 with dual lesions	None	None
Status	One year reported; 2, 3, 4 and 5 years planned	One, 2, and 3 years reported; 4 and 5 years planned		One, 2, 3 and 4 years reported; 5 years planned	One, 2, 3, 4 and 5 years reported	One year reported

*Only pharmacokinetic substudy results included (see Section 6.2 – Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent)

** In the TAXUS arm, there was 1 patient who received 1 TAXUS® Liberté® stent.

§ RVD ≥ 2.5 mm to ≤ 3.75 mm and stent sizes up to 3.5 mm until 4.0 mm TAXUS is commercially available

All subjects receiving a study stent were to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of 6 months. Per the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) guidelines, it was strongly recommended that subjects should be treated with clopidogrel bisulfate up to 12 months if they are not at high risk for bleeding.

Δ Of the 300 subjects enrolled, 223 received XIENCE V, 59 received TAXUS® Express®, and 17 received TAXUS® Liberté®. One patient received a non-study stent.

8.0 ADVERSE EVENTS

8.1 Observed Adverse Events

Principal adverse event information is derived from the SPIRIT IV, SPIRIT III, SPIRIT II, SPIRIT FIRST and SPIRIT Small Vessel clinical trials and is shown in Table 8.1-1 and 8.1-2. Within these tables, the intent-to-treat population includes all subjects randomized, while the per-treatment evaluable population includes only those subjects who received a study device at the target lesion with no major procedure protocol deviations except deviations relating to the treatment arm, for whom follow-up data are available. See also Section 8.3 – Adverse Events, Potential Adverse Events. See Section 9.0 – SPIRIT Family of Clinical Trials for more complete study design descriptions and results.

Table 8.1-1: SPIRIT Family of Trials
Principal Adverse Events from Post-Procedure to 1 Year

	SPIRIT IV		SPIRIT III			SPIRIT II		SPIRIT FIRST		SPIRIT Small Vessel
	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	XIENCE V (N = 223)	TAXUS (N = 77)	XIENCE V (N = 27)	VISION (N = 29)	2.25 mm XIENCE V (N = 144)
In-Hospital										
TVF[1]	1.5% (36/2451)	2.0% (24/1224)	0.9% (6/669)	2.4% (8/330)	4.1% (3/73)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)	1.4% (2/143)
MACE[2]	1.4% (35/2451)	1.9% (23/1224)	0.9% (6/669)	2.4% (8/330)	4.1% (3/73)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)	1.4% (2/143)
All Death	0.0% (0/2451)	0.0% (0/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)	0.0% (0/143)
Cardiac Death	0.0% (0/2451)	0.0% (0/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)	0.0% (0/143)
Non-Cardiac Death	0.0% (0/2451)	0.0% (0/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)	0.0% (0/143)
MI	1.4% (35/2451)	1.8% (22/1224)	0.7% (5/669)	2.4% (8/330)	4.1% (3/73)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)	1.4% (2/143)
QMI	0.1% (3/2451)	0.2% (2/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)	0.7% (1/143)
NQMI	1.3% (32/2451)	1.6% (20/1224)	0.7% (5/669)	2.4% (8/330)	4.1% (3/73)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)	0.7% (1/143)
Cardiac Death or MI	1.4% (35/2451)	1.8% (22/1224)	0.7% (5/669)	2.4% (8/330)	4.1% (3/73)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)	1.4% (2/143)

	SPIRIT IV		SPIRIT III			SPIRIT II		SPIRIT FIRST		SPIRIT Small Vessel
	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	XIENCE V (N = 223)	TAXUS (N = 77)	XIENCE V (N = 27)	VISION (N = 29)	2.25 mm XIENCE V (N = 144)
Ischemia-Driven Revascularization	0.4% (9/2451)	0.5% (6/1224)	0.1% (1/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)	0.7% (1/143)
Ischemia-Driven TLR	0.3% (8/2451)	0.4% (5/1224)	0.1% (1/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)	0.0% (0/143)
Ischemia-Driven TVR, Non TL	0.1% (3/2451)	0.2% (2/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)	0.7% (1/143)
Stent Thrombosis[3] (Per Protocol)	0.1% (3/2451)	0.4% (5/1224)	0.3% (2/669)	0.0% (0/330)	1.4% (1/73)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)	0.0% (0/143)
9 Months[4]										
TVF[1]	4.6% (111/2419)	7.1% (85/1201)	7.6% (50/660)	9.7% (31/320)	6.8% (5/73)	4.5% (10/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)	9.4% (13/139)
MACE[2]	3.3% (80/2419)	6.2% (74/1201)	5.0% (33/660)	8.8% (28/320)	6.8% (5/73)	2.7% (6/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)	7.2% (10/139)
All Death	0.7% (18/2419)	0.9% (11/1201)	1.1% (7/661)	0.9% (3/321)	1.4% (1/73)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)	1.4% (2/139)
Cardiac Death	0.3% (8/2419)	0.2% (3/1201)	0.6% (4/661)	0.6% (2/321)	1.4% (1/73)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)	1.4% (2/139)
Non-Cardiac Death	0.4% (10/2419)	0.7% (8/1201)	0.5% (3/661)	0.3% (1/321)	0.0% (0/73)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)	0.0% (0/139)
MI	1.8% (43/2419)	3.0% (36/1201)	2.3% (15/660)	3.1% (10/320)	4.1% (3/73)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)	1.4% (2/139)
QMI	0.1% (3/2419)	0.3% (4/1201)	0.2% (1/660)	0.0% (0/320)	0.0% (0/73)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)	0.7% (1/139)
NQMI	1.7% (40/2419)	2.7% (33/1201)	2.1% (14/660)	3.1% (10/320)	4.1% (3/73)	0.9% (2/220)	3.9% (3/77)	0.0% (0/26)	0.0% (0/28)	0.7% (1/139)
Cardiac Death or MI	2.1% (51/2419)	3.1% (37/1201)	2.9% (19/660)	3.8% (12/320)	5.5% (4/73)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)	2.9% (4/139)
Ischemia-Driven Revascularization	3.0% (72/2419)	5.2% (62/1201)	5.3% (35/660)	6.6% (21/320)	2.7% (2/73)	3.6% (8/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)	11.5% (16/139)
Ischemia-Driven TLR	1.7% (40/2419)	4.1% (49/1201)	2.7% (18/660)	5.0% (16/320)	2.7% (2/73)	1.8% (4/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)	4.3% (6/139)
Ischemia-Driven TVR, Non TL	1.9% (45/2419)	2.2% (27/1201)	3.0% (20/660)	4.1% (13/320)	0.0% (0/73)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	3.6% (1/28)	5.0% (7/139)
Stent Thrombosis[3]										

	SPIRIT IV		SPIRIT III			SPIRIT II		SPIRIT FIRST		SPIRIT Small Vessel
	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	XIENCE V (N = 223)	TAXUS (N = 77)	XIENCE V (N = 27)	VISION (N = 29)	2.25 mm XIENCE V (N = 144)
Protocol	0.17% (4/2398)	0.84% (10/1191)	0.6% (4/657)	0.0% (0/319)	1.4% (1/72)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)	2.2% (3/139)
1 Year[5]										
TVF[1]	5.5% (134/2416)	7.7% (92/1195)	8.5% (56/655)	11.6% (37/319)	6.8% (5/73)	4.5% (10/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)	11.0% (15/136)
MACE[2]	4.1% (98/2416)	6.9% (82/1195)	6.0% (39/655)	10.3% (33/319)	6.8% (5/73)	2.7% (6/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)	8.1% (11/136)
All Death	1.0% (25/2416)	1.3% (15/1195)	1.2% (8/657)	1.3% (4/320)	1.4% (1/73)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)	1.5% (2/136)
Cardiac Death	0.4% (10/2416)	0.4% (5/1195)	0.8% (5/657)	0.9% (3/320)	1.4% (1/73)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)	1.5% (2/136)
Non-Cardiac Death	0.6% (15/2416)	0.8% (10/1195)	0.5% (3/657)	0.3% (1/320)	0.0% (0/73)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)	0.0% (0/136)
MI	1.9% (45/2416)	3.1% (37/1195)	2.7% (18/655)	4.1% (13/319)	4.1% (3/73)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)	1.5% (2/136)
QMI	0.1% (3/2416)	0.4% (5/1195)	0.3% (2/655)	0.3% (1/319)	0.0% (0/73)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)	0.7% (1/136)
NQMI	1.7% (42/2416)	2.8% (33/1195)	2.4% (16/655)	3.8% (12/319)	4.1% (3/73)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)	0.7% (1/136)
Cardiac Death or MI	2.2% (54/2416)	3.3% (39/1195)	3.4% (22/655)	4.7% (15/319)	5.5% (4/73)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)	2.9% (4/136)
Ischemia-Driven Revascularization	3.8% (93/2416)	5.7% (68/1195)	6.1% (40/655)	7.8% (25/319)	2.7% (2/73)	3.6% (8/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)	13.2% (18/136)
Ischemia-Driven TLR	2.3% (56/2416)	4.6% (55/1195)	3.4% (22/655)	5.6% (18/319)	2.7% (2/73)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)	5.1% (7/136)
Ischemia-Driven TVR, Non TL	2.2% (54/2416)	2.4% (29/1195)	3.2% (21/655)	4.7% (15/319)	0.0% (0/73)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	3.6% (1/28)	5.9% (8/136)
Stent Thrombosis[3]										
Per Protocol	0.17% (4/2389)	0.85% (10/1181)	0.8% (5/649)	0.6% (2/316)	1.4% (1/72)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)	2.2% (3/136)
ARC (Definite+Probable)	0.29% (7/2391)	1.10% (13/1181)	0.9% (6/650)	0.6% (2/316)	0.0% (0/72)	0.0% (0/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)	1.5% (2/136)

Notes:

- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels/lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- SPIRIT II, III and IV based on intent-to-treat population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population (a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm [randomized versus actually received]).
- SPIRIT III 4.0 mm arm clinical data with 73 subjects are available for 2-year follow-up.
- Revascularization includes TLR and non-TLR TVR; except for in SPIRIT SV where revascularization includes TVR and non-TVR, and non-treated vessel revascularization.
- Q wave MI for all SPIRIT Trials is defined as the development of new pathological Q wave on the ECG.
- Non-Q wave MI for SPIRIT IV and SPIRIT III is defined as the elevation of CK levels to greater than or equal to 2 times the upper limit of normal with elevated CKMB in the absence of new pathological Q waves.
- Non-Q wave MI for SPIRIT II is defined as a typical rise and fall of CKMB with at least one of the following: Ischemia symptoms, ECG changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention.
  - If non procedural/spontaneous MI, CKMB is greater than or equal to 2 times upper limit of normal
  - If post PCI, CKMB is greater than or equal to 3 times upper limit of normal
  - If post CABG, CKMB is greater than or equal to 5 times upper limit of normal
- Non-Q wave MI for SPIRIT FIRST is defined (WHO definition) as the elevation of post-procedure CK levels to greater than or equal to 2 times the upper normal limit with elevated CKMB in the absence of new pathological Q waves.
- Non-Q wave MI for SPIRIT FIRST is defined (ESC/ACC definition) as for non procedural, CKMB elevation greater than or equal to 2 times the upper normal limit, for post PCI, CKMB elevation greater than or equal to three times the upper normal limit, and for post CABG, CKMB elevation greater than or equal to five times the upper normal limit.

[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion. SPIRIT SV used clinically indicated TLR and TVR definition rather than ischemia driven TLR and TVR definition, which was used for SPIRIT II, SPIRIT III, and SPIRIT IV. [Clinically indicated TLR and TVR (SPIRIT SV) was defined as a revascularization with %DS (percent diameter stenosis) ≥50% by core lab QCA assessment with one of the following: 1) a positive history of recurrent angina pectoris, presumably related to the target vessel, 2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel, 3) abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve), or 4) a TLR or TVR with %DS ≥70% even in the absence of the above-mentioned ischemic signs or symptoms. Ischemia driven TLR and TVR (SPIRIT II, SPIRIT III, SPIRIT IV) was defined as revascularization with a positive functional ischemia study, ischemic symptoms and angiographic %DS ≥ 50% by core laboratory QCA, or angiographic %DS ≥70% by core laboratory QCA without angina or positive functional study.]

[2] MACE includes cardiac death, MI and ischemia-driven TLR.

[3] See Section 8.2 – Stent Thrombosis Definitions.

[4] SPIRIT IV, SPIRIT III and SPIRIT FIRST includes 14 day window. SPIRIT SV 8 month data is presented, as follow-up was not required at 9 months.

[5] SPIRIT IV, SPIRIT III, SPIRIT FIRST and SPIRIT SV include 28 day window.

Table 8.1-2: SPIRIT Family of Trials: Principal Adverse Events from Latest Follow-up

	SPIRIT IV *1 Year*[4]		SPIRIT III			SPIRIT II *4 Years*[4]		SPIRIT FIRST *5 Years*[4]		SPIRIT Small Vessel *1 Year*
			RCT *3 Years*[4]		4.0 mm XIENCE V Arm 2 Years[4]					
	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V (N = 73)	XIENCE V (N = 223)	TAXUS (N = 77)	XIENCE V (N = 27)	VISION (N = 29)	2.25 mm XIENCE V (N = 144)
TVF[1]	5.5% (134/2416)	7.7% (92/1195)	14.3% (90/629)	20.0% (61/305)	8.7% (6/69)	12.8% (25/195)	17.9% (12/67)	16.7% (4/24)	36.0% (9/25)	11.0% (15/136)
MACE[2]	4.1% (98/2416)	6.9% (82/1195)	9.7% (61/629)	16.4% (50/305)	8.7% (6/69)	7.7% (15/195)	16.4% (11/67)	16.7% (4/24)	28.0% (7/25)	8.1% (11/136)
All Death	1.0% (25/2416)	1.3% (15/1195)	2.8% (18/636)	4.5% (14/312)	7.0% (5/71)	4.9% (10/204)	9.9% (7/71)	0.0% (0/24)	7.4% (2/27)	1.5% (2/136)
Cardiac Death	0.4% (10/2416)	0.4% (5/1195)	1.6% (10/636)	1.9% (6/312)	2.8% (2/71)	0.5% (1/204)	4.2% (3/71)	0.0% (0/24)	0.0% (0/27)	1.5% (2/136)
Non-Cardiac Death	0.6% (15/2416)	0.8% (10/1195)	1.3% (8/636)	2.6% (8/312)	4.2% (3/71)	4.4% (9/204)	5.6% (4/71)	0.0% (0/24)	7.4% (2/27)	0.0% (0/136)
MI	1.9% (45/2416)	3.1% (37/1195)	3.8% (24/629)	6.6% (20/305)	4.3% (3/69)	3.6% (7/195)	7.5% (5/67)	8.3% (2/24)	0.0% (0/25)	1.5% (2/136)
QMI	0.1% (3/2416)	0.4% (5/1195)	0.5% (3/629)	0.7% (2/305)	0.0% (0/69)	0.0% (0/195)	0.0% (0/67)	4.2% (1/24)	0.0% (0/25)	0.7% (1/136)
NQMI	1.7% (42/2416)	2.8% (33/1195)	3.3% (21/629)	5.9% (18/305)	4.3% (3/69)	3.6% (7/195)	7.5% (5/67)	4.2% (1/24)	0.0% (0/25)	0.7% (1/136)
Cardiac Death or MI	2.2% (54/2416)	3.3% (39/1195)	5.1% (32/629)	8.2% (25/305)	7.2% (5/69)	4.1% (8/195)	9.0% (6/67)	8.3% (2/24)	0.0% (0/25)	2.9% (4/136)
Ischemia-Driven Revascularization	3.8% (93/2416)	5.7% (68/1195)	11.1% (70/629)	14.8% (45/305)	2.9% (2/69)	10.3% (20/195)	13.4% (9/67)	8.3% (2/24)	36.0% (9/25)	13.2% (18/136)
Ischemia-Driven TLR	2.3% (56/2416)	4.6% (55/1195)	5.7% (36/629)	9.2% (28/305)	2.9% (2/69)	5.1% (10/195)	10.4% (7/67)	8.3% (2/24)	28.0% (7/25)	5.1% (7/136)
Ischemia-Driven TVR, Non TL	2.2% (54/2416)	2.4% (29/1195)	6.7% (42/629)	8.9% (27/305)	0.0% (0/69)	5.6% (11/195)	4.5% (3/67)	0.0% (0/24)	12.0% (3/25)	5.9% (8/136)
Stent Thrombosis[3]										
Per Protocol	0.17% (4/2389)	0.85% (10/1181)	1.0% (6/617)	1.7% (5/300)	3.0% (2/67)	2.1% (4/193)	4.5% (3/66)	0.0% (0/24)	0.0% (0/25)	2.2% (3/136)
ARC (Definite+Probable)	0.29% (7/2391)	1.10% (13/1181)	1.3% (8/619)	1.7% (5/299)	0.0% (0/66)	1.0% (2/193)	3.0% (2/66)	0.0% (0/24)	0.0% (0/25)	1.5% (2/136)

Notes:
-All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
-This table includes revascularizations on any target vessel(s)/lesion(s) for subjects with two target vessels/lesions treated.
-One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
-SPIRIT III 4.0 mm arm clinical data with 73 subjects are available for 2-year follow-up.
-SPIRIT II, III and IV based on intent-to-treat population (all subjects randomized, regardless of the treatment they actually received).
-SPIRIT FIRST based on per-treatment evaluable population (a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm [randomized versus actually received]).
-Revascularization includes TLR and non-TLR TVR; except for in SPIRIT SV where revascularization includes TVR and non-TVR, and non-treated vessel revascularization.
[1] TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion. SPIRIT SV used clinically indicated TLR and TVR definition rather than ischemia-driven TLR and TVR definition.
[2] MACE includes cardiac death, MI and ischemia-driven TLR.
[3] See Section 8.2 – Stent Thrombosis Definitions.
[4] SPIRIT IV, SPIRIT III, SPIRIT II, SPIRIT FIRST and SPIRIT SV include 28-day window.

8.2 Stent Thrombosis Definitions

Protocol defined stent thrombosis (ST) was categorized as acute (< 1 day), subacute (1 – 30 days) and late (> 30 days) and was defined as any of the following[7]:

- 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)[8] in the distribution of the target lesion within 30 days

All stent thrombosis events were also classified using the ST definitions proposed by the Academic Research Consortium (ARC)[9]. This was performed by an independent event committee blinded to the treatment group of the individual subject. The committee categorized each incident of ST by timing and level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

Timing:

- Early ST: 0 to 30 days post stent implantation
- Late ST: 31 days to 1 year post stent implantation
- Very late ST: > 1 year post stent implantation

Level of probability:

- Definite ST – considered to have occurred by either angiographic or pathologic confirmation
- Probable ST – considered to have occurred after intracoronary stenting in the following cases:
    1. Any unexplained death within the first 30 days.
    2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.
- Possible ST – considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up[10]

8.3 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures including coronary stent use in native coronary arteries include, but are not limited to:

- Abrupt closure
- Access site pain, hematoma, or hemorrhage
- Acute myocardial infarction
- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm

[7] For SPIRIT FIRST Stent Thrombosis is defined as total occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers, and ECG changes consistent with MI.
[8] Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.
[9] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circ* 2007;115:2344-51.
[10] All data within these Instructions for Use is presented as definite+probable only.

- Arterial perforation and injury to the coronary artery
- Arterial rupture
- Arteriovenous fistula
- Arrhythmias, atrial and ventricular
- Bleeding complications, which may require transfusion
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery
- Distal emboli (air, tissue or thrombotic)
- Emergent or non-emergent coronary artery bypass graft surgery
- Fever
- Hypotension and/or hypertension
- Infection and pain at insertion site
- Injury to the coronary artery
- Ischemia (myocardial)
- Myocardial infarction (MI)
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Renal failure
- Restenosis of the stented segment of the artery
- Shock/pulmonary edema
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of coronary artery
- Unstable or stable angina pectoris
- Vascular complications including at the entry site which may require vessel repair
- Vessel dissection

Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prophylaxis of organ rejection in adult kidney transplant recipients at low-moderate immunologic risk, at the dose of 1.5 mg/day. Outside the United States, Zortress® is sold under the brand name Certican® in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor® for the treatment of patients with advanced renal cell carcinoma (cancer) after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The following list includes the known risks of everolimus at the oral doses indicated above:

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough

- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dyspnea
- Dysgeusia
- Dyspepsia
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperlipidemia
- Hyperkalemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CY3PA4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain: extremity, incision site and procedural, and back
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis
- Thrombocytopenia
- Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/ Hemolytic uremic syndrome (HUS)
- Tremor
- Urinary tract infection
- Upper respiratory tract infection
- Vomiting

Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. Fetal harm can occur when administered to a pregnant woman. There may be other potential adverse events that are unforeseen at this time.

9.0 SPIRIT FAMILY OF CLINICAL TRIALS

9.1 SPIRIT III Pivotal Clinical Trial

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS® Express® stent (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consists of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy. Enrollment is complete in the RCT, the 4.0 mm diameter stent arm, and the Japan arm.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subject subset derived from the RCT[11] and Japan non-randomized arm (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan). Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level.

9.1.1 SPIRIT III Randomized Clinical Trial (RCT)

Primary Objective: The objective of the SPIRIT III RCT was to demonstrate the non-inferiority in in-segment late loss at 240 days and target vessel failure at 270 days of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 3.75 mm.

Design: The SPIRIT III RCT was a prospective, 2:1 (XIENCE V:TAXUS) randomized, active-controlled, single-blinded, parallel, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent 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. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent (see Section 5.3 – Multiple Stent Use). In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

If non-inferiority of the primary endpoint of in-segment late loss was demonstrated, it was pre-specified that testing for superiority could be conducted.

All subjects had clinical follow-up at 30, 180, and 270 days and annually from 1 to 5 years. A pre-specified subgroup of 564 subjects had angiographic follow-up at 240 days. Of these 564, 240 subjects had IVUS at baseline and 240 days. Subjects that received a bailout stent also had IVUS at baseline and angiographic and IVUS follow-up at 240 days.

[11] Includes one subject from the 4.0 mm non-randomized arm.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age was 63.2 years for the XIENCE V arm and 62.8 for the TAXUS arm. The XIENCE V arm had 70.1% (469/669) males and the TAXUS arm had 65.7% (218/332) males. The XIENCE V arm had 32.3% (215/666) of subjects with prior cardiac interventions and the TAXUS arm had 29.5% (98/332). The XIENCE V arm had 29.6% (198/669) of subjects with a history of diabetes and the TAXUS arm had 27.9% (92/330). The XIENCE V arm had 15.4% (103/669) of subjects with a lesion treated in two vessels and TAXUS had 15.4% (51/332). The XIENCE V arm had 8.1% (54/669) of subjects with planned stent overlap. The XIENCE V arm had 8.6% (57/666) of subjects with a history of prior CABG while the TAXUS arm had 3.6% (12/332) (p = 0.0033). The XIENCE V arm had 18.7% (123/657) of subjects with a history of unstable angina while the TAXUS arm had 25.1% (82/327) (p = 0.0243). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.1.1-1 Primary Endpoint Results, Table 9.1.1-2 Clinical Results, Table 9.1.1-3 Angiographic and IVUS Results, Figure 9.1.1-1 Time-to-Event Curve for TVF and Table 9.1.1-4 ARC-Defined Definite+Probable Stent Thrombosis. These analyses are based on the intent-to-treat population.

The co-primary endpoint of in-segment late loss at 240 days was met with measurements of 0.14 ± 0.41 mm (301) for the XIENCE V arm and 0.28 ± 0.48 mm (134) for the TAXUS arm (p < 0.0001 for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-segment late loss at 240 days (p = 0.0037).

The co-primary endpoint of ischemia-driven TVF through 284 days was met with rates of 7.6% (50/660) for the XIENCE V arm and 9.7% (31/320) for the TAXUS arm (p < 0.0001 for non-inferiority).

Table 9.1.1-1: SPIRIT III RCT Primary Endpoint Results

Measurements	XIENCE V (N = 669) (M = 376)	TAXUS (N = 333) (M = 188)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
8 Month[1] Late Loss, In-Segment (mm)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	-0.14 [-0.23, -0.05][2]	< 0.0001[3]	0.0037[4]
9 Month[5] Target Vessel Failure[6]	7.6% (50/660)	9.7% (31/320)	-2.11% [-5.93%, 1.71%][2]	< 0.0001[7]	Not Pre-specified

Notes:
- N is the total number of subjects; M is the total number of analysis lesions for the angiographic group.
- One subject in the SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- Analysis results include 9 month events identified at the 3 years follow-up.

[1] 8 month time frame includes follow-up window (240 + 28 days).
[2] By normal approximation.
[3] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.
[4] Two-sided p-value by superiority test using two-sample T-test, to be compared at a 0.05 significance level.
[5] 9 month time frame includes follow-up window (270 + 14 days).
[6] TVF is defined as hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[7] One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

Table 9.1.1-2: SPIRIT III RCT Clinical Results

	Outcomes at 9 Months			Outcomes at 3 Years (Latest Available Follow-Up)		
	XIENCE V (N = 669)	TAXUS (N = 333)	Difference [95% CI][1]	XIENCE V (N = 669)	TAXUS (N = 333)	Difference [95% CI][1]
Composite Efficacy and Safety						
TVF[2]	7.6% (50/660)	9.7% (31/320)	-2.11% [-5.93%, 1.71%]	14.3% (90/629)	20.0% (61/305)	-5.69% [-10.95%, -0.43%]
MACE[3]	5.0% (33/660)	8.8% (28/320)	-3.75% [-7.26%, -0.24%]	9.7% (61/629)	16.4% (50/305)	-6.70% [-11.45%, -1.94%]
Efficacy						
Ischemia-Driven TLR	2.7% (18/660)	5.0% (16/320)	-2.27% [-4.96%, 0.42%]	5.7% (36/629)	9.2% (28/305)	-3.46% [-7.17%, 0.26%]
TLR, CABG	0.2% (1/660)	0.0% (0/320)	0.15% [Assump. not met]	0.6% (4/629)	1.0% (3/305)	-0.35% [Assump. not met]
TLR, PCI	2.6% (17/660)	5.0% (16/320)	-2.42% [-5.10%, 0.25%]	5.2% (33/629)	8.2% (25/305)	-2.95% [-6.49%, 0.59%]
Ischemia-Driven TVR, Non TL	3.0% (20/660)	4.1% (13/320)	-1.03 % [-3.56 %, 1.50 %]	6.7% (42/629)	8.9% (27/305)	-2.18% [-5.91%, 1.56%]
Non-TLR TVR, CABG	0.5% (3/660)	0.6% (2/320)	-0.17% [Assump. not met]	1.4% (9/629)	2.3% (7/305)	-0.86% [-2.78%, 1.06%]
Non-TLR TVR, PCI	2.6% (17/660)	3.4% (11/320)	-0.86% [-3.20 %, 1.47 %]	5.2% (33/629)	6.9% (21/305)	-1.64% [-4.97%, 1.69%]
Safety						
All Death	1.1% (7/661)	0.9% (3/321)	0.12% [Assump. not met]	2.8% (18/636)	4.5% (14/312)	-1.66% [-4.29%,0.98%]
Cardiac Death	0.6% (4/661)	0.6% (2/321)	-0.02% [Assump. not met]	1.6% (10/636)	1.9% (6/312)	-0.35% [-2.16%,1.45%]
Non-Cardiac Death	0.5% (3/661)	0.3% (1/321)	0.14% [Assump. not met]	1.3% (8/636)	2.6% (8/312)	-1.31% [-3.26%,0.65%]
MI	2.3% (15/660)	3.1% (10/320)	-0.85% [-3.07%, 1.37%]	3.8% (24/629)	6.6% (20/305)	-2.74% [-5.90%, 0.41%]
QMI	0.2% (1/660)	0.0% (0/320)	0.15% [Assump. not met]	0.5% (3/629)	0.7% (2/305)	-0.18% [Assump. not met]
NQMI	2.1% (14/660)	3.1% (10/320)	-1.00% [-3.20%, 1.20%]	3.3% (21/629)	5.9% (18/305)	-2.56% [-5.56%,0.43%]
Cardiac Death or MI	2.9% (19/660)	3.8% (12/320)	-0.87% [-3.31%, 1.57%]	5.1% (32/629)	8.2% (25/305)	-3.11% [-6.63%, 0.42%]
Stent Thrombosis – Protocol Defined	0.6% (4/657)	0.0% (0/319)	0.61% [Assump. not met]	1.0% (6/617)	1.7% (5/300)	-0.69% [-2.34%, 0.95%]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (> 30 days)	0.2% (1/656)	0.0% (0/319)	0.15% [Assump. not met]	0.5% (3/616)	1.7% (5/300)	-1.18% [Assump. not met]]

Notes:

- One subject in the SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- 9 month and 3 year time frames include follow-up window (270 +14 days and 1095 + 28 days, respectively).
- 9 months analysis results include 9 month events identified at the 3 years follow-up.
- "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.1-3: SPIRIT III 8 Month Angiographic and IVUS Results

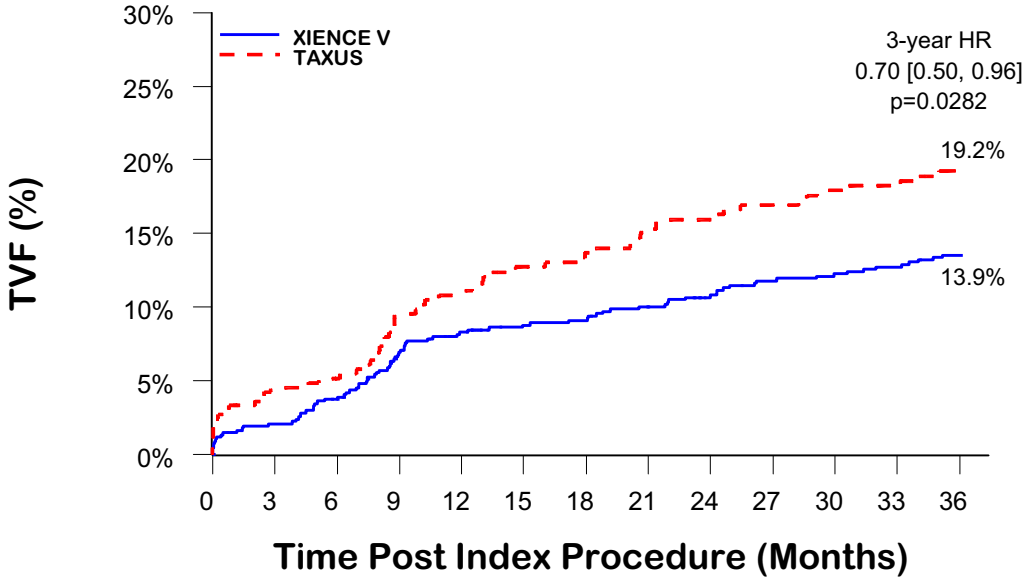
	XIENCE V (N = 376) (M_{ANGIO} = 427) (M_{IVUS} = 181)	TAXUS (N = 188) (M_{ANGIO} = 220) (M_{IVUS} = 93)	Difference [95% CI][1]
Angiographic Results			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD			
Post-Procedure	2.35 ± 0.44 (426)	2.36 ± 0.45 (220)	-0.01 [-0.08, 0.06]
8 Months	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
In-Stent %DS			
Post-Procedure	0.32 ± 8.86 (424)	-0.78 ± 10.65 (220)	1.10 [-0.55, 2.74]
8 Months	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment %DS			
Post-Procedure	13.89 ± 8.04 (425)	13.92 ± 7.20 (220)	-0.03 [-1.26, 1.19]
8 Months	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Late Loss			
In-Stent	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
In-Segment	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04]
Binary Restenosis			
In-Stent	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]
IVUS Results			
Neointimal Volume (mm^3)	10.13 ± 11.46 (101)	20.87 ± 13.51 (41)	-10.74 [-20.92, -0.56]
% Volume Obstruction	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%]
8 Months	25.6% (23/90)	16.3% (7/43)	9.28% [-4.97%, 23.52%]
Persistent	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% [Assump. not met]

Notes:

- N is the total number of subjects; M_{ANGIO} is the total number of lesions in the protocol required angiographic cohort and M_{IVUS} is the total number of lesions in the protocol required IVUS cohort.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- 8 month time frame includes follow-up window (240 + 28 days).
- "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

Figure 9.1.1-1: SPIRIT III: Kaplan Meier Time-to-Event Curve for Target Vessel Failure through 3 Years



TVF	Event Free	Event Rate	P-value[1]
XIENCE V	86.1%	13.9%	0.0282
TAXUS	80.8%	19.2%	

Note:
– Time Frame includes follow-up window (1095 + 28 days).
[1]P-value based on log rank and not adjusted for multiple comparisons

Table 9.1.1-4: SPIRIT III RCT ARC Defined Definite+Probable Stent Thrombosis through 3 Years

	XIENCE V (N = 669)	TAXUS (N = 333)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 3 years)	1.3% (8/619)	1.7% (5/299)	-0.38% [-2.08%, 1.32%]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (31 days – 1 year)	0.5% (3/649)	0.6% (2/316)	-0.17% [Assump. not met]
Very Late (1 – 3 years)	0.3% (2/617)	1.0% (3/298)	-0.68% [Assump. not met]

Notes:
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- Time Frame includes follow-up window (1095 + 28 days)
- "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.1.2 Dual Vessel Treatment in SPIRIT III

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. Subjects requiring both single and dual vessel treatment were included in the SPIRIT III trial; however there were no pre-specified hypotheses for these patient subgroups.

Table 9.1.2-1 shows the clinical outcomes through 9 months and 3 years in single vessel and dual vessel treated subjects from a post-hoc analysis of SPIRIT III. The number of vessels treated was one of the stratification factors used in the randomization to assure a balance between the XIENCE V and TAXUS treatment arms.

Table 9.1.2-1: Clinical Results in Single and Dual Vessel Treatment through 3 Years (SPIRIT III RCT)

	9 Months				3 Years			
	Single Vessel XIENCE V (N = 566)	Single Vessel TAXUS (N = 281)	Dual Vessel XIENCE V (N = 103)	Dual Vessel TAXUS (N = 51)	Single Vessel XIENCE V (N = 566)	Single Vessel TAXUS (N = 281)	Dual Vessel XIENCE V (N = 103)	Dual Vessel TAXUS (N = 51)
Ischemia-Driven TLR	2.5% (14/559)	4.1% (11/270)	4.0% (4/101)	10.0% (5/50)	5.5% (29/530)	8.2% (21/257)	7.1% (7/99)	14.6% (7/48)
Ischemia-Driven TVR, Non TL	2.7% (15/559)	2.2% (6/270)	5.0% (5/101)	14.0% (7/50)	5.3% (28/530)	6.6% (17/257)	14.1% (14/99)	20.8% (10/48)
All Death	1.3% (7/560)	0.4% (1/270)	0.0% (0/101)	3.9% (2/51)	3.2% (17/537)	3.8% (10/263)	1.0% (1/99)	8.2% (4/49)
Cardiac Death	0.7% (4/560)	0.4% (1/270)	0.0% (0/101)	2.0% (1/51)	1.7% (9/537)	1.1% (3/263)	1.0% (1/99)	6.1% (3/49)
Non-Cardiac Death	0.5% (3/560)	0.0% (0/270)	0.0% (0/101)	2.0% (1/51)	1.5% (8/537)	2.7% (7/263)	0.0% (0/99)	2.0% (1/49)
MI	2.0% (11/559)	2.2% (6/270)	4.0% (4/101)	8.0% (4/50)	3.0% (16/530)	4.3% (11/257)	8.1% (8/99)	18.8% (9/48)
Cardiac Death or MI	2.7% (15/559)	2.6% (7/270)	4.0% (4/101)	10.0% (5/50)	4.5% (24/530)	5.4% (14/257)	8.1% (8//99)	22.9% (11/48)
Stent Thrombosis								
Protocol Defined	0.4% (2/556)	0.0% (0/270)	2.0% (2/101)	0.0% (0/49)	0.6% (3/519)	1.2% (3/254)	3.1% (3/98)	4.3% (2/46)
ARC Definite+Probable	0.5% (3/557)	0.0% (0/270)	2.0% (2/101)	0.0% (0/49)	0.8% (4/520)	1.2% (3/253)	4.0% (4/99)	4.3% (2/46)

9.1.3 SPIRIT III US 4.0 mm Arm

Primary Objective: The objective of the SPIRIT III 4.0 mm arm was to demonstrate the non-inferiority in in-segment late loss at 240 days.

Design: The SPIRIT III 4.0 mm study was a prospective, single-arm, multi-center clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V stent in *de novo* native coronary artery lesions ≤ 28 mm in length with a RVD > 3.75 mm to ≤ 4.25 mm. Seventy-three (73)

subjects were enrolled in the SPIRIT III 4.0 mm study arm. For early demonstration of efficacy (in-segment late loss at 240 days), an interim analysis was performed after 69 of the enrolled subjects had completed their scheduled follow-up and after unblinding of the SPIRIT III RCT.

All subjects had clinical follow-up at 30, 180, 240, and 270 days, and annually from 1 to 5 years. In addition, all subjects had angiographic follow-up at 240 days. IVUS was performed for subjects who received a bailout stent at baseline and 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age in the SPIRIT III 4.0 arm was 61.9 years with 72.5% (50/69) male, 21.7% (15/69) had prior cardiac interventions, and 30.4% (21/69) had a history of diabetes.

Results: The results are presented in Table 9.1.3-1 (Primary Endpoint Result), Table 9.1.3-2 (Clinical Results), Table 9.1.3-3 (Angiographic Results), and Table 9.1.3-4 (ARC-Defined Definite+Probable Stent Thrombosis). These analyses were performed on the intent-to-treat population.

The primary endpoint of in-segment late loss at 240 days was met with measurements of 0.17 ± 0.38 mm (49 analysis lesions) for the XIENCE V 4.0 mm arm and 0.28 ± 0.48 mm (134 analysis lesions) for the TAXUS arm from the SPIRIT III RCT ($p < 0.0001$ for non-inferiority).

Table 9.1.3-1: SPIRIT III 4.0 mm Primary Endpoint Result

Measurements	XIENCE V (M = 69)	TAXUS (M = 188)	Difference [95% CI]	Non-Inferiority P-Value
8 Month Late Loss, In-Segment (mm)	0.17 ± 0.38 (49)	0.28 ± 0.48 (134)	-0.11 [-0.24, 0.03][1]	< 0.0001[2]

Notes:
- M is the total number of analysis lesions.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- Time Frame includes follow-up window (240 + 28 days)

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

Table 9.1.3-2: SPIRIT III 4.0 mm Clinical Results

	Outcomes at 9 Months XIENCE V (N = 73)	Outcomes at 2 Years (Latest Available Follow-up) XIENCE V (N = 73)
Composite Efficacy and Safety		
TVF[1]	6.8% (5/73)	8.7% (6/69)
MACE[2]	6.8% (5/73)	8.7% (6/69)
Efficacy		
Ischemia-Driven TLR	2.7% (2/73)	2.9% (2/69)
TLR, CABG	0.0% (0/73)	0.0% (0/69)
TLR, PCI	2.7% (2/73)	2.9% (2/69)
Ischemia-Driven Non-TLR TVR	0.0% (0/73)	0.0% (0/69)
Non-TLR TVR, CABG	0.0% (0/73)	0.0% (0/69)
Non-TLR TVR, PCI	0.0% (0/73)	0.0% (0/69)
Safety		
All Death	1.4% (1/73)	7.0% (5/71)
Cardiac Death	1.4% (1/73)	2.8% (2/71)
Non-Cardiac Death	0.0% (0/73)	4.2% (3/71)
MI	4.1% (3/73)	4.3% (3/69)
QMI	0.0% (0/73)	0.0% (0/69)
NQMI	4.1% (3/73)	4.3% (3/69)
Cardiac Death or MI	5.5% (4/73)	7.2% (5/69)
Stent Thrombosis – Protocol Defined	1.4% (1/72)	3.0% (2/67)
Acute (< 1 day)	1.4% (1/73)	1.4% (1/73)
Subacute (1 – 30 days)	0.0% (0/73)	0.0% (0/73)
Late (> 30 days)	0.0% (0/72)	1.5% (1/67)

Notes:

- 9 months and 2 years time frames include follow-up window (270 +14 days and 730 + 28 days, respectively). 9 month analysis includes 9 month events identified at the 2 years follow-up.

[1] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[2] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.1.3-3: SPIRIT III 4.0 mm 8 Month Angiographic Results

	XIENCE V (N = 69) (M = 69)
Angiographic Results	
In-Stent MLD	
Post-Procedure	3.46 ± 0.38 (69)
8 Months	3.36 ± 0.46 (49)
In-Segment MLD	
Post-Procedure	3.07 ± 0.43 (69)
8 Months	2.91 ± 0.51 (49)
In-Stent %DS	
Post-Procedure	2.12 ± 10.27 (69)
8 Months	4.78 ± 13.20 (49)
In-Segment %DS	
Post-Procedure	13.42 ± 8.08 (69)
8 Months	17.92 ± 10.83 (49)
Late Loss	
In-Stent	0.12 ± 0.34 (49)
In-Segment	0.17 ± 0.38 (49)
Binary Restenosis	
In-Stent	0.0% (0/49)
In-Segment	2.0% (1/49)

Notes:
- N is the total number of subjects; M is the total number of lesions at baseline.
- 8 month time frame includes follow-up window (240 + 28 days).

Table 9.1.3-4: SPIRIT III 4.0 mm ARC-Defined Definite+Probable Stent Thrombosis through 2 Years

	XIENCE V (N = 73)
ARC Definite+Probable Stent Thrombosis (0 days – 2 years)	0.0% (0/66)
Acute (< 1 day)	0.0% (0/73)
Subacute (1 – 30 days)	0.0% (0/73)
Late (31 days – 1 year)	0.0% (0/72)
Very Late (1 – 2 years)	0.0% (0/66)

Note:
- Time Frame includes follow-up window (730 + 28 days)

9.2 SPIRIT IV Clinical Trial

The SPIRIT IV clinical study was designed to confirm the safety and efficacy of the XIENCE V stent when compared to the TAXUS® Express® stent[12] (TAXUS stent). This randomized controlled trial (RCT) was conducted in the United States (US).

[12] Of the 1,229 subjects enrolled in the TAXUS arm, 1 subject received one TAXUS® Liberté® stent.

9.2.1 SPIRIT IV Randomized Clinical Trial

Primary Objective: The objective of the SPIRIT IV clinical trial was to determine the safety and effectiveness of the XIENCE V stent for the treatment of subjects with up to three *de novo* coronary artery lesions (maximum of two lesions per epicardial vessel).

Design: The SPIRIT IV clinical trial was a prospective, 2:1 randomized (XIENCE V: TAXUS), active-controlled, single-blinded, multi-center evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to three *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 4.25 mm. Subjects were stratified by diabetes mellitus (diabetic vs. non-diabetic) and lesion characteristics (complex vs. non-complex). Complex lesion characteristics included triple vessel treatment, or dual lesions per vessel treatment, or lesions involving RCA-aorto-ostial locations, or bifurcation lesions. The SPIRIT IV clinical trial was designed to enroll 3,690 subjects at up to 80 sites in the US.

The primary endpoint was target lesion failure (TLF) at 1 year. The major secondary endpoints were ischemia-driven TLR at 1 year and the composite of cardiac death or target vessel MI at 1 year. Formal non-inferiority and superiority testing were planned for the primary and the two major secondary endpoints. To control the familywise Type I error rate, all non-inferiority and superiority hypotheses were tested following a fixed sequence.

The XIENCE V stents used in the SPIRIT IV trial included stents 2.5, 3.0, and 3.5 mm in diameter, and 8, 18 and 28 mm in length. In the XIENCE V arm, 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 (see Section 5.3 – Multiple Stent Use). In the TAXUS arm, the treatment strategy for lesions > 22 mm and ≤ 28 mm was recommended to be in accordance to the TAXUS Directions for Use (DFU) at the time of enrollment; these lesions were treated with single 32 mm TAXUS stent or planned overlapping TAXUS stents.

Subjects were evaluated at 30, 180, and 270 days following the index procedure. Follow-up has been performed through 1 year, and further clinical observations will be performed at 2, 3, 4 and 5 years.

According to the guidelines from the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI), following the index procedure, all subjects were to be maintained on 75 mg clopidogrel bisulfate daily for 12 months if subjects were not at high risk for bleeding and ≥ 80 mg of aspirin daily throughout the length of the trial (5 years).

Demographics: The mean age was 63.3 years for both the XIENCE V arm and the TAXUS arm. The XIENCE V arm had 67.7% (1665/2458) males and the TAXUS arm had 67.8% (833/1229) males. The XIENCE V arm had 31.5% (772/2450) of subjects with prior cardiac interventions and the TAXUS arm had 30.7% (376/1224). The XIENCE V arm had 32.0% (786/2455) of subjects with a history of diabetes and the TAXUS arm had 32.5% (399/1228). The XIENCE V arm had 24.8% (609/2458) of subjects with two or more lesions treated and TAXUS had 25.3% (311/1229). The XIENCE V arm had 9.7% (239/2458) of subjects with planned stent overlap. The TAXUS arm had 8.1% (99/1229)[13] of subjects with planned stent overlap and 4.5% (55/1229) of subjects treated with single 32 mm TAXUS stent only. The XIENCE V arm had 27.7% (669/2416) of subjects with a history of unstable angina while the

[13] Includes 6 patients who received planned overlapping TAXUS stents, as well as a single 32 mm TAXUS stent in two different lesions.

TAXUS arm had 28.9% (347/1202). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.2.1-1 (Primary and Major Secondary Endpoint Results), Table 9.2.1-2 (Clinical Results), Figure 9.2.1-1 (Time-to-Event Curve for TLF), Figure 9.2.1-2 (Time-to-Event Curve for ID-TLR), and Figure 9.2.1-3 (Time-to-Event Curve for Cardiac Death or Target Vessel MI). These analyses are based on the intent-to-treat population.

Primary Endpoint Analysis (Table 9.2.1-1): The primary endpoint was met with TLF rates at 1 year of 4.0% (97/2416) for the XIENCE V arm and 6.8% (81/1195) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a pre-specified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent in terms of the primary endpoint of TLF at 1 year ($p_{Sup} = 0.0004$).

Major Secondary Endpoint Analysis (Table 9.2.1-1): The major secondary endpoint of ID-TLR was shown to be statistically non-inferior for the XIENCE V stent compared to the TAXUS stent. The ID-TLR rate through 1 year was 2.3% (56/2416) for the XIENCE V arm and 4.6% (55/1195) for the TAXUS arm ($p < 0.0001$ for non-inferiority). The XIENCE V arm also showed non-inferiority to the TAXUS arm in terms of the composite endpoint of cardiac death or target vessel MI, with rates of 2.2% (53/2416) for the XIENCE V arm and 3.2% (38/1195) for the TAXUS arm ($p < 0.0001$ for non-inferiority).

In a pre-specified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent in terms of ID-TLR at 1 year ($p_{Sup} = 0.0003$). The rate of the composite of cardiac death or target vessel MI was numerically lower in patients treated with the XIENCE V EECSS compared to the TAXUS stent ($p_{Sup} = 0.09$).

Table 9.2.1-1: SPIRIT IV Primary and Major Secondary Endpoint Results

Primary Endpoint	XIENCE V (N = 2458)	TAXUS (N = 1229)	Difference [Upper 1-Sided 97.5% CL]	Non-Inferiority P-Value	Superiority P-Value
1 Year TLF	4.0% (97/2416)	6.8% (81/1195)	-2.76% [-1.14%][1]	< 0.0001[2]	0.0004[3]
Major Secondary Endpoints	**XIENCE V (N = 2458)**	**TAXUS (N = 1229)**	**Difference [Upper 1-Sided 95% CL]**	**Non-Inferiority P-Value**	**Superiority P-Value**
1 Year ID-TLR	2.3% (56/2416)	4.6% (55/1195)	-2.28% [-1.17%][1]	< 0.0001[4]	0.0003[3]
1 Year Cardiac Death or Target Vessel MI	2.2% (53/2416)	3.2% (38/1195)	-0.99% [-0.02%][1]	< 0.0001[4]	0.09[3]

Notes:
- N is the total number of subjects.
- TLF includes cardiac death, target vessel MI (per protocol definition) and ischemia-driven TLR.
- Time Frame includes follow-up window (365 + 28 days).

[1] By normal approximation.
[2] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 3.1%, to be compared at a 0.025 significance level.
[3] Two-sided p-value by superiority test using Fisher's exact test, to be compared at a 0.05 significance level.
[4] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 2.1%, to be compared at a 0.05 significance level.

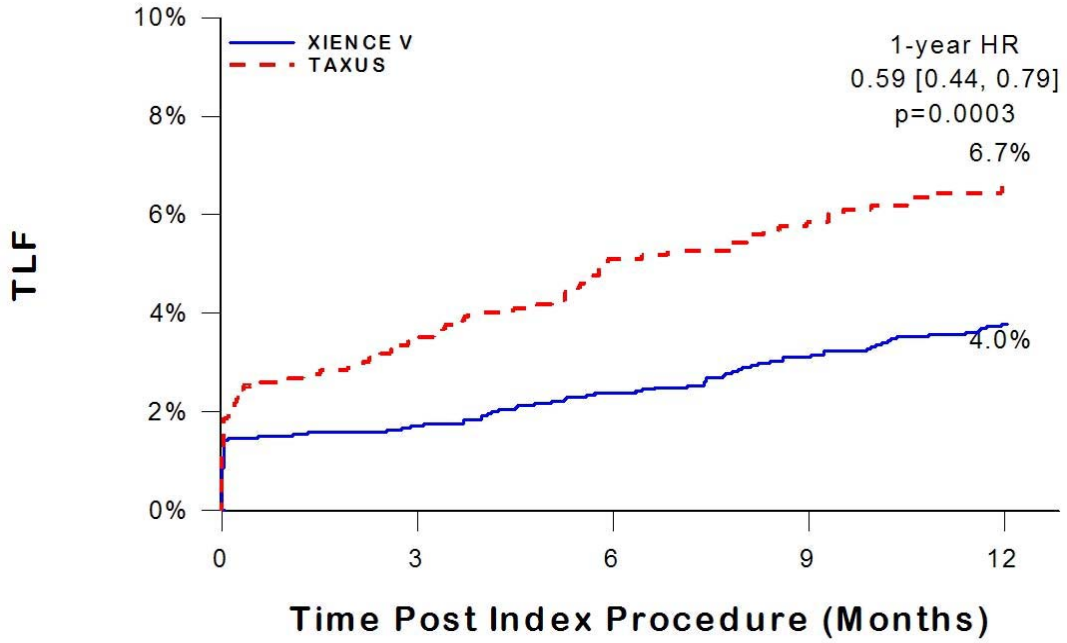
Table 9.2.1-2: SPIRIT IV Clinical Results through 1 Year

	XIENCE V (N = 2458)	TAXUS (N = 1229)	Difference [95% CI] [1]	P Value
Composite Efficacy and Safety				
TLF	4.0% (97/2416)	6.8% (81/1195)	-2.76% [-4.39%, -1.14%]	0.0004[2]
TVF	5.5% (134/2416)	7.7% (92/1195)	-2.15% [-3.92%, -0.39%]	
Efficacy				
Ischemia-Driven TLR	2.3% (56/2416)	4.6% (55/1195)	-2.28% [-3.62%, -0.95%]	0.0003[2]
TLR, CABG	0.4% (9/2416)	0.4% (5/1195)	-0.05% [-0.49%, 0.39%]	
TLR, PCI	2.0% (48/2416)	4.3% (51/1195)	-2.28% [-3.56%, -1.01%]	
Ischemia-Driven TVR	3.8% (93/2416)	5.7% (68/1195)	-1.84% [-3.36%, -0.32%]	
Safety				
All Death	1.0% (25/2416)	1.3% (15/1195)	-0.22% [-0.97%, 0.53%]	
Cardiac Death	0.4% (10/2416)	0.4% (5/1195)	-0.00% [-0.45%, 0.44%]	
Non-Cardiac Death	0.6% (15/2416)	0.8% (10/1195)	-0.22% [-0.82%, 0.39%]	
Target Vessel MI	1.8% (44/2416)	2.9% (35/1195)	-1.11% [-2.20%, -0.01%]	
Cardiac Death or Target Vessel MI	2.2% (53/2416)	3.2% (38/1195)	-0.99% [-2.14%, 0.17%]	0.09[2]
All MI	1.9% (45/2416)	3.1% (37/1195)	-1.23% [-2.35%, -0.11%]	
QMI	0.1% (3/2416)	0.4% (5/1195)	-0.29% [Assump. not met]	
NQMI	1.7% (42/2416)	2.8% (33/1195)	-1.02% [-2.09%, 0.04%]	
Cardiac Death or MI	2.2% (54/2416)	3.3% (39/1195)	-1.03% [-2.20%, 0.14%]	
Protocol Defined Stent Thrombosis				
Cumulative through 1 year	0.17% (4/2389)	0.85% (10/1181)	-0.68% [Assump. not met]	
Acute/Subacute (0 – 30 days)	0.12% (3/2451)	0.57% (7/1221)	-0.45% [Assump. not met]	
Late (31 days – 1 year)	0.04% (1/2389)	0.34% (4/1181)	-0.30% [Assump. not met]	
ARC Definite+Probable Stent Thrombosis				
Cumulative through 1 year	0.29% (7/2391)	1.10% (13/1181)	-0.81% [-1.44%, -0.17%]	
Acute/Subacute (0 – 30 days)	0.16% (4/2451)	0.74% (9/1221)	-0.57% [Assump. not met]	
Late (31 days – 1 year)	0.13% (3/2391)	0.42% (5/1181)	-0.30% [Assump. not met]	

Notes:
- Time Frame includes follow-up window (365 + 28 days).
- TLF is defined as a hierarchical composite of cardiac death, target vessel MI (per protocol definition), and ischemic-driven TLR.
- TVF is defined as a hierarchical composite of cardiac death, all MI (per protocol definition), ischemic-driven TLR and ischemic-driven non-TLR TVR.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.
[2] Two-sided p-value by pre-specified superiority test using Fisher's exact test, to be compared at a 0.05 significance level.

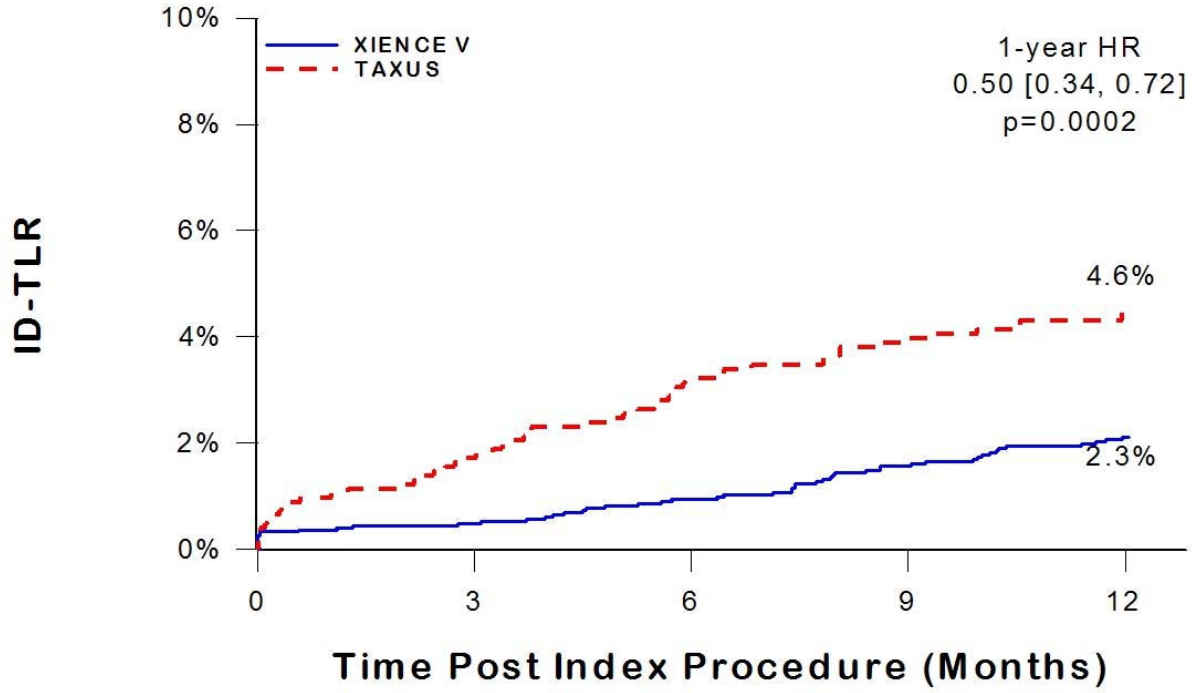
Figure 9.2.1-1: SPIRIT IV: Kaplan Meier Time-to-Event Curve for TLF through 1 Year



TLF	Event Free	Event Rate	P-value[1]
XIENCE V	96.0%	4.0%	0.0003
TAXUS	93.3%	6.7%	

Note:
– Time Frame includes follow-up window (365 + 28 days).
[1]P-value based on log rank and not adjusted for multiple comparisons

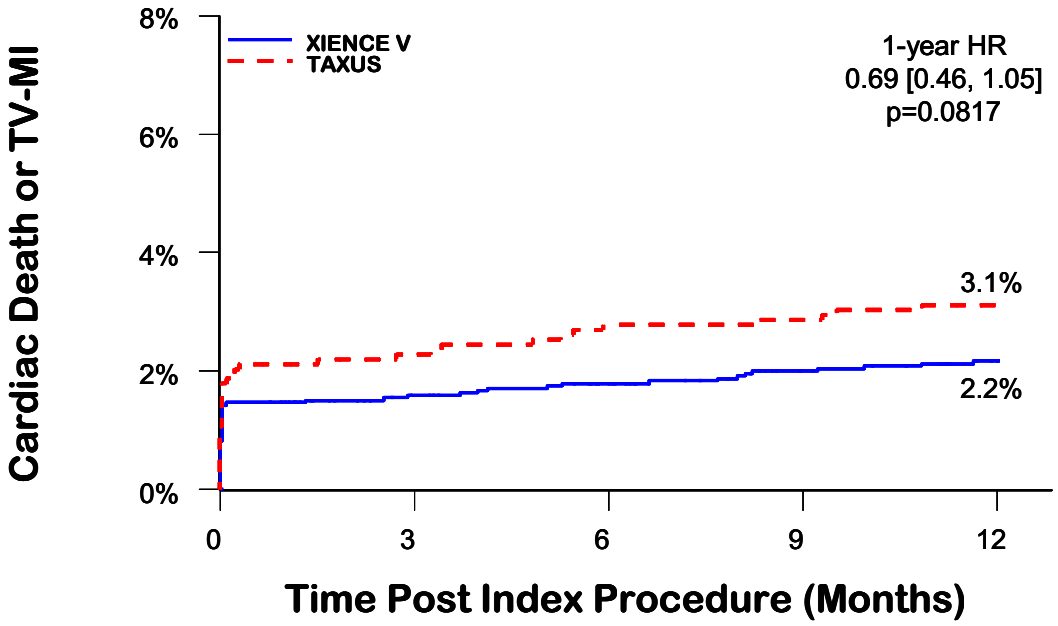
Figure 9.2.1-2: SPIRIT IV: Kaplan Meier Time-to-Event Curve for ID-TLR through 1 Year



ID-TLR	Event Free	Event Rate	P-value[1]
XIENCE V	97.7%	2.3%	0.0002
TAXUS	95.4%	4.6%	

Note:
– Time Frame includes follow-up window (365 + 28 days).
[1]P-value based on log rank and not adjusted for multiple comparisons

Figure 9.2.1-3: SPIRIT IV: Kaplan Meier Time-to-Event Curve for Cardiac Death or Target Vessel MI through 1 Year



Cardiac Death or TV-MI	Event Free	Event Rate	P-value[1]
XIENCE V	97.8%	2.2%	0.08
TAXUS	96.9%	3.1%	

Note:
– Time Frame includes follow-up window (365 + 28 days).
[1]P-value based on log rank and not adjusted for multiple comparisons

9.2.2 Multiple Vessel Treatment in SPIRIT IV

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. The SPIRIT IV trial allowed for up to 3 vessels to be treated. In the XIENCE V arm, 389 subjects received dual vessel treatment while 19 subjects received triple vessel treatment. In the TAXUS arm, 218 subjects received dual vessel treatment while 5 subjects received triple vessel treatment. There were no pre-specified hypotheses for patients in the single vessel treatment and multiple vessel treatment subgroups.

Table 9.2.2-1 shows the clinical outcomes through 1 year in single and multiple vessel treated subjects from a post-hoc analysis of SPIRIT IV.

Table 9.2.2-1: Clinical Results in Single and Multiple Vessel Treatment through 1 Year (SPIRIT IV)

	Single Vessel XIENCE V (N = 2050)	Single Vessel TAXUS (N = 1006)	Multiple Vessel XIENCE V (N = 408)	Multiple Vessel TAXUS (N = 223)
TLF	3.8% (76/2014)	6.0% (59/983)	5.2% (21/402)	10.4% (22/212)
Ischemia-Driven TLR	2.1% (42/2014)	4.0% (39/983)	3.5% (14/402)	7.5% (16/212)
Ischemia-Driven TVR, Non TL	1.9% (38/2014)	2.0% (20/983)	4.0% (16/402)	4.2% (9/212)
All Death	0.9% (18/2014)	1.3% (13/983)	1.7% (7/402)	0.9% (2/212)
Cardiac Death	0.3% (6/2014)	0.4% (4/983)	1.0% (4/402)	0.5% (1/212)
Non-Cardiac Death	0.6% (12/2014)	0.9% (9/983)	0.7% (3/402)	0.5% (1/212)
Target Vessel MI	1.8% (37/2014)	2.3% (23/983)	1.7% (7/402)	5.7% (12/212)
Cardiac Death or Target Vessel MI	2.1% (43/2014)	2.6% (26/983)	2.5% (10/402)	5.7% (12/212)
Stent Thrombosis				
Protocol Defined	0.15% (3/1996)	0.51% (5/971)	0.25% (1/393)	2.38% (5/210)
ARC Definite+Probable	0.20% (4/1996)	0.72% (7/971)	0.76% (3/395)	2.86% (6/210)

Notes:
- Time frame includes follow-up window (365 + 28 days)
- Multiple vessel subgroup included subjects having two or more vessels treated.
- There were 24 triple vessel treated subjects in SPIRIT IV; Of those, 19 were XIENCE V subjects and 5 were TAXUS subjects.

9.3 SPIRIT II Supportive Clinical Trial

Primary Objective: The objective of the SPIRIT II clinical study was to demonstrate the non-inferiority in in-stent late loss at 180 days of the XIENCE V stent to the TAXUS stent in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. The SPIRIT II clinical study arm allowed the treatment of *de novo* lesions ≤ 28 mm in length in coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 4.25 mm. If non-inferiority of in-stent late loss was demonstrated, it was pre-specified that testing for superiority could be conducted. SPIRIT II was performed outside of the U.S.

Design: The SPIRIT II clinical study was a prospective, active-control, 3:1 (XIENCE V:TAXUS) randomized, single-blinded, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent 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. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent (see Section 5.3 – Multiple Stent Use). In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage.

Three hundred (300) subjects were enrolled in the study at 28 international sites in Europe, India, and New Zealand. Of the 300 subjects enrolled, 223 received XIENCE V stents, 59 received TAXUS® Express® stents, and 17 received TAXUS® Liberté®[14] stents.

[14] One patient received a non-study stent.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiographic follow-up at 180 days with planned additional angiographic and IVUS follow-up at 2 years in a pre-specified subgroup of 152 consecutively enrolled subjects at selected sites.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

A subgroup of 39 subjects was enrolled in a pharmacokinetic (PK) substudy. Venous blood was drawn at regular intervals for PK analysis of total blood everolimus level at 7 pre-determined sites.

Demographics: The mean age was 62.0 years for the XIENCE V arm and 61.9 years for the TAXUS arm. The XIENCE V arm had 70.9% (158/223) males and the TAXUS arm had 79.2% (61/77) males. The XIENCE V arm had 23.3% (52/223) of subjects with prior cardiac interventions and the TAXUS arm had 22.1% (17/77). The XIENCE V arm had 22.9% (51/223) of subjects with a history of diabetes and the TAXUS arm had 23.7% (18/76). The XIENCE V arm had 16.6% (37/223) of subjects with a lesion treated in two vessels and TAXUS had 18.2% (14/77). The XIENCE V arm had 10.8% (24/223) of subjects with planned stent overlap. The XIENCE V arm had 18.4% (40/217) of subjects with a history of an MI within two months while the TAXUS arm had 7.8% (6/77) (p = 0.0284). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

Results: The results are presented in Table 9.3-1 (Primary Endpoint Result), Table 9.3-2 (Clinical Results), Table 9.3-3 (Angiographic and IVUS Results), and Table 9.3-4 (ARC-Defined Definite+Probable Stent Thrombosis). These analyses were based on the intent-to-treat population.

The primary endpoint of in-stent late loss at 180 days was met with measurements of 0.11 ± 0.27 mm (201) for the XIENCE V arm and 0.36 ± 0.39 mm (73) for the TAXUS arm (p < 0.0001 for non-inferiority). In a pre-specified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-stent late loss at 180 days (p < 0.0001).

Table 9.3-1: SPIRIT II Primary Endpoint Result

Measurements	XIENCE V (N = 223) (M = 201)	TAXUS (N = 77) (M = 73)	Difference [95% CI]	Non-Inferiority P-Value	Superiority P-Value
180 Day Late Loss, In-Stent (mm)	0.11 ± 0.27 (201)	0.36 ± 0.39 (73)	-0.24 [-0.34, -0.15][1]	< 0.0001[2]	< 0.0001[3]

Notes:
– N is the number of subjects and M is the number of analysis lesions with Late-Loss measurement available..
[1] By normal approximation.
[2] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16 mm, to be compared at a 0.0448 significance level.
[3] P-value from two-sided t-test.

Table 9.3-2: SPIRIT II Clinical Results

	Outcomes at 6 Months			Outcomes at 4 Years (latest available follow-up)		
	XIENCE V (N = 223)	TAXUS (N = 77)	Difference [95% CI][1]	XIENCE V (N = 223)	TAXUS (N = 77)	Difference [95% CI][1]
Composite Efficacy and Safety						
TVF[2]	3.6% (8/222)	6.5% (5/77)	-2.89% [-8.92%, 3.14%]	12.8% (25/195)	17.9% (12/67)	-5.09% [-15.40%, 5.22%]
MACE[3]	2.7% (6/222)	6.5% (5/77)	-3.79% [-9.69%, 2.11%]	7.7% (15/195)	16.4% (11/67)	-8.73% [-18.35%, 0.90%]
Efficacy						
Ischemia-Driven TLR	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	5.1% (10/195)	10.4% (7/67)	-5.32% [-13.27%, 2.63%]
TLR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.5% (1/195)	0.0% (0/67)	0.51% [Assump. not met]
TLR, PCI	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	5.1% (10/195)	10.4% (7/67)	-5.32% [-13.27%, 2.63%]
Ischemia-Driven Non-TLR TVR	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	5.6% (11/195)	4.5% (3/67)	1.16% [Assump. not met]
Non-TLR TVR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.5% (1/195)	0.0% (0/67)	0.51% [Assump. not met]
Non-TLR TVR, PCI	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	5.1% (10/195)	4.5% (3/67)	0.65% [Assump. not met]
Safety						
All Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	4.9% (10/204)	9.9% (7/71)	-4.96% [-12.50%, 2.58%]
Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	0.5% (1/204)	4.2% (3/71)	-3.74% [Assump. not met]
Non-Cardiac Death	0.0% (0/222)	0.0% (0/77)	-0.00% [Assump. not fulfilled]	4.4% (9/204)	5.6% (4/71)	-1.22% [Assump. not met]
MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	3.6% (7/195)	7.5% (5/67)	-3.87% [-10.69%,2.94%]
QMI	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/195)	0.0% (0/67)	0.00% [Assump. not met]
NQMI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	3.6% (7/195)	7.5% (5/67)	-3.87% [-10.69%,2.94%]
Cardiac Death or MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	4.1% (8/195)	9.0% (6/67)	-4.85% [-12.24%, 2.53%]
Stent Thrombosis – Protocol Defined	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	2.1% (4/193)	4.5% (3/66)	-2.47% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Late (> 30 days)	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	2.1% (4/193)	4.5% (3/66)	-2.47% [Assump. not met]

Notes:

– 6 months time frame includes follow-up window (180 +14 days).

– "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.3-3: SPIRIT II 180 Day and 2 Year Angiographic and IVUS Results

	XIENCE V (N = 223) (M = 260)	TAXUS (N = 77) (M = 91)	Difference [95% CI][1]
Angiographic Results			
In-Stent MLD			
Post-Procedure	2.49 ± 0.40 (260)	2.62 ± 0.45 (91)	-0.13 [-0.24, -0.03]
6 Months	2.38 ± 0.50 (237)	2.27 ± 0.54 (86)	0.10 [-0.03, 0.23]
2 Years	2.18 ± 0.46 (100)	2.40 ± 0.48 (35)	-0.22 [-0.40, -0.03]
In-Segment MLD			
Post-Procedure	2.15 ± 0.44 (260)	2.22 ± 0.53 (91)	-0.07 [-0.19, 0.05]
6 Months	2.10 ± 0.51 (237)	2.08 ± 0.54 (86)	0.02 [-0.11, 0.15]
2 Years	1.97 ± 0.46 (99)	2.12 ± 0.50 (35)	-0.14 [-0.34, 0.05]
In-Stent %DS			
Post-Procedure	13.01 ± 6.02 (260)	12.66 ± 5.53 (91)	0.35 [-1.01, 1.71]
6 Months	15.70 ± 9.88 (237)	20.89 ± 11.59 (86)	-5.18 [-7.96, -2.41]
2 Years	19.25 ± 13.79 (100)	18.76 ± 11.40 (35)	0.49 [-4.23, 5.22]
In-Segment %DS			
Post-Procedure	22.51 ± 8.98 (260)	23.36 ± 11.20 (91)	-0.86 [-3.43, 1.72]
6 Months	23.61 ± 11.65 (237)	27.05 ± 12.68 (86)	-3.44 [-6.53, -0.35]
2 Years	26.39 ± 14.02 (99)	26.88 ± 14.29 (35)	-0.49 [-6.09, 5.11]
Late Loss			
6-Month In-Stent	0.12 ± 0.29 (237)	0.37 ± 0.38 (86)	-0.25 [-0.34, -0.16]
6-Month In-Segment	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
2-Year In-Stent	0.33 ± 0.36 (100)	0.34 ± 0.34 (35)	-0.01 [-0.15, 0.12]
2-Year In-Segment	0.20 ± 0.37 (99)	0.17 ± 0.38 (35)	0.03 [-0.12, 0.18]
Binary Restenosis			
6-Month In-Stent	1.3% (3/237)	3.5% (3/86)	-2.22% [Assump. not met]
6-Month In-Segment	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]
2-Year In-Stent	2.0% (2/100)	2.9% (1/35)	-0.86% [Assump. not met]
2-Year In-Segment	5.1% (5/99)	8.6% (3/35)	-3.52% [Assump. not met]
IVUS Results			
6-Month Neointimal Volume (mm^3)	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	-10.60 [-15.87, -5.32]
2-Year Neointimal Volume (mm^3)	9.12 ± 11.75 (78)	11.56 ± 16.12 (32)	-2.44 [-8.78, 3.89]
6-Month % Volume Obstruction	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
2-Year % Volume Obstruction	5.37 ± 6.44 (78)	5.80 ± 6.31 (32)	-0.43 [-3.10, 2.24]
Incomplete Apposition			
Post-Procedure	11.1% (12/108)	5.6% (2/36)	5.56% [Assump. not met]
6 Months	9.8% (10/102)	7.7% (3/39)	2.11% [Assump. not met]
Persistent	7.6% (9/119)	4.9% (2/41)	2.68% [Assump. not met]
Late Acquired	0.0% (0/102)	0.0% (0/38)	0.00% [Assump. not met]
2 Years	18.8% (15/80)	13.8% (4/29)	4.96% [Assump. not met]
Persistent	7.8% (9/115)	5.3% (2/38)	2.56% [Assump. not met]
Late Acquired	6.1% (5/82)	3.6% (1/28)	2.53% [Assump. not met]

Notes:
- N is the total number of subjects; M is the total number of lesions.
- "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity, and is meant for descriptive purposes only.

Table 9.3-4: SPIRIT II ARC Defined Definite+Probable Stent Thrombosis through 4 Years

	XIENCE V (N = 223)	TAXUS (N = 77)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 4 years)	1.0% (2/193)	3.0% (2/66)	-1.99% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	1.3% (1/77)	-1.30% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/220)	1.3% (1/77)	-1.30% [Assump. not met]
Very Late (1 – 4 years)	1.0% (2/193)	1.5% (1/65)	-0.50% [Assump. not met]

Note:
– "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.
[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

9.4 SPIRIT FIRST Randomized Clinical Trial

Objective: The objective of the SPIRIT FIRST randomized clinical trial was to assess the feasibility and performance of the XIENCE V stent (called VISION-E within the SPIRIT FIRST study) in the treatment of subjects with a single *de novo* native coronary artery lesion with reference vessel diameter (RVD) of 3.0 mm and lesion length ≤ 12 mm. This study compared the XIENCE V stent to a matched uncoated metallic stent control (MULTI-LINK VISION).

Design: SPIRIT FIRST was a single-blinded, multi-center, randomized, controlled trial to assess the safety and performance of everolimus eluting from a durable polymer on a cobalt chromium stent (XIENCE V stent). Sixty (60) subjects were enrolled in the study.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiography and IVUS at baseline and at 180 days and 1 year follow-up.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 3 months, and aspirin daily to be taken throughout the length of the trial (1 year).

Demographics: The mean age was 64.2 years for the XIENCE V arm and 61.4 years for the VISION arm. The XIENCE V arm had 70.4% (19/27) males and the VISION arm had 75.9% (22/29) males. The XIENCE V arm had 18.5% (5/27) subjects with prior cardiac interventions and the VISION arm had 6.9% (2/29). The XIENCE V arm had 11.1% (3/27) subjects with a history of diabetes and the VISION arm had 10.3% (3/29). XIENCE V arm had 70.4% (19/27) of subjects with hypertension requiring medication while the VISION arm had 41.4% (12/29) (p = 0.035). The remaining subject baseline clinical features were also well-matched between the XIENCE V arm and the VISION arm.

Results: The results are presented in Table 9.4-1 (Primary Endpoint Result), Table 9.4-2 (Clinical Results), Table 9.4-3 (Angiographic and IVUS Results), and Table 9.4-4 (ARC-Defined Definite+Probable Stent Thrombosis). These analyses were based on the per-protocol evaluable population.

The superiority of the primary endpoint of in-stent late loss at 180 days was met with measurements of 0.10 ± 0.23 mm (23) for the XIENCE V arm and 0.85 ± 0.36 mm (27) for the MULTI-LINK VISION arm (p < 0.0001).

Table 9.4-1: SPIRIT FIRST Primary Endpoint Result

Measurements	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]	Superiority P-value [2]
180 Days Late Loss, In-Stent (mm)	0.10± 0.23 (23)	0.85± 0.36 (27)	-0.76 [-0.93, -0.59]	< 0.0001

Note: N is the number of subjects.
[1] By normal approximation
[2] One-tailed p-value by t-test, to be compared to a 5% significance level

Table 9.4-2: SPIRIT FIRST Clinical Results

	OUTCOMES AT 6 MONTHS[1]			OUTCOMES AT 5 YEARS[1] (latest available follow-up)		
	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][2]
Composite Efficacy and Safety						
TVF[3]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]]	16.7% (4/24)	36.0% (9/25)	-19.33% [Assump. not met]
MACE[4]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	16.7% (4/24)	28.0% (7/25)	--11.33% [Assump. not met]
Efficacy						
Ischemia-Driven TLR	3.8% (1/26)	21.4% (6/28)	-17.58% [Assump. not met]	8.3% (2/24)	28.0% (7/25)	-19.67% [Assump. not met]
TLR, CABG	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]	0.0% (0/24)	4.0% (1/25)	-4.00% [Assump. not met]
TLR, PCI	3.8% (1/26)	17.9% (5/28)	-14.01% [Assump. not met]	8.3% (2/24)	24.0% (6/25)	-15.67% [Assump. not met]
Ischemia-Driven Non-TLR TVR	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]	0.0% (0/24)	12.0% (3/25)	-12.00% [Assump. not met]
Non-TLR TVR, CABG	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/24)	4.0% (1/25)	-4.00% [Assump. not met]
Non-TLR TVR, PCI	0.0% (0/26)	3.6% (1/28)	3.57% [Assump. not met]	0.0% (0/24)	8.0% (2/25)	-8.00% [Assump. not met]
Safety						
All Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/24)	7.4% (2/27)	-7.41% [Assump. not met]
Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/24)	0.0% (0/27)	0.00% [Assump. not met]
Non-Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/24)	7.4% (2/27)	-7.41% [Assump. not met]
MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	8.3% (2/24)	0.0% (0/25)	8.33% [Assump. not met]
QMI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	4.2% (1/24)	0.0% (0/25)	4.17% [Assump. not met]
NQMI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	4.2% (1/24)	0.0% (0/25)	4.17% [Assump. not met]
Cardiac Death or MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	8.3% (2/24)	0.0% (0/25)	8.33% [Assump. not met]
Stent Thrombosis – Protocol Defined	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/24)	0.0% (0/25)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Late (> 30 days)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/24)	0.0% (0/25)	0.00% [Assump. not met]

Note:

– "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

[1] 6 month and 5 year time frames include follow-up window (180 +14 days and 1825 + 28 days, respectively).

[2] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity, and is meant for descriptive purposes only.

[3] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

[4] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.4-3: SPIRIT FIRST 180 Day Angiographic and IVUS Results

	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]
Angiographic Results			
In-Stent MLD			
Post-Procedure	2.34± 0.26 (27)	2.43± 0.30 (29)	-0.09 [-0.24, 0.06]
6 Months	2.28± 0.33 (23)	1.58± 0.41 (27)	0.70 [0.49,0.91]
In-Segment MLD			
Post-Procedure	2.07± 0.37 (27)	2.15± 0.37 (29)	-0.08 [-0.28, 0.12]
6 Months	2.04 ± 0.40 (23)	1.54± 0.41 (27)	0.50 [0.27, 0.73]
In-Stent %DS			
Post-Procedure	12.34 ± 4.02 (27)	14.85 ± 4.76 (29)	-2.51 [-4.87, -0.16]
6 Months	15.57 ± 7.64 (23)	38.61 ± 14.25 (27)	-23.05 [-29.45, -16.64]
In-Segment %DS			
Post-Procedure	20.82 ± 7.65 (27)	23.14 ± 8.03% (29)	-2.32 [-6.52, 1.88]
6 Months	21.89 ± 11.15 (23)	40.78 ± 13.67 (27)	-18.89 [-25.95,-11.83]
Late Loss			
In-Stent	0.10 ± 0.23 (23)	0.85 ± 0.36 (27)	-0.76 [-0.93, -0.59]
In-Segment	0.09 ± 0.20 (23)	0.61 ± 0.37 (27)	-0.53 [-0.69, -0.36]
Binary Restenosis			
In-Stent	0.0% (0/23)	25.9% (7/27)	-25.93% [Assump. not met]
In-Segment	4.3% (1/23)	33.3% (9/27)	-28.99% [Assump. not met]
IVUS Results			
Neointimal Volume (mm^3)	10.29± 13.32 (21)	38.29± 19.08 (24)	-28.00 [-37.82, -18.19]
% Volume Obstruction	7.95± 10.44 (21)	28.11± 13.98 (24)	-20.16 [-27.53, -12.79]
Incomplete Apposition			
Post-Procedure	0.0% (0/27)	10.7% (3/28)	-10.71% [Assump. not met]
6 Months	0.0% (0/21)	0.0% (0/21)	0.00% [Assump. not met]
Persistent	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Late Acquired	0.0% (0/21)	0.0% (0/22)	0.00% [Assump. not met]

Note:

– "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity, and is meant for descriptive purposes only.

Table 9.4-4: SPIRIT FIRST ARC Defined Definite+Probable Stent Thrombosis through 5 Years

	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 5 years)	0.0% (0/24)	0.0% (0/25)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Very Late (1 – 5 years)	0.0% (0/24)	0.0% (0/25)	0.00% [Assump. not met]

Note:

– "Assump. not met" means that assumption of normal approximation was not met due to small sample size or frequency of events.

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity, and is meant for descriptive purposes only.

9.5 SPIRIT Small Vessel Registry

Objective: The objective of the SPIRIT Small Vessel Registry (SPIRIT SV) trial was to evaluate the safety and effectiveness of the 2.25 mm XIENCE V EECSS in improving coronary luminal diameter in subjects with ischemic heart disease due to a maximum of two *de novo* native coronary artery lesions in small vessels, each in a different epicardial vessel.

Design: The SPIRIT SV trial enrolled a total of 150 subjects at 33 sites. Additionally, there was an angiographic cohort of 69 subjects who received the 2.25 mm XIENCE V EECSS. Subjects enrolled in the SPIRIT SV trial were allowed to have: 1) one target lesion (treated with one 2.25 mm XIENCE V EECSS), 2) two target lesions (treated with two 2.25 mm XIENCE V EECSS) in separate epicardial vessels or 3) one target lesion (treated with one 2.25 mm XIENCE V EECSS) and one non-target lesion (treated with commercial sizes of XIENCE V EECSS) in separate epicardial vessels. Planned overlap was allowed for both the target and non-target lesions only with commercial sizes of XIENCE V EECSS. Bailout was allowed with a commercial XIENCE V or 2.25 mm XIENCE V EECS. The protocol-required RVD for the target lesion was ≥ 2.25 mm to < 2.50 mm and the lesion length was ≤ 28 mm. The 2.25 mm XIENCE V EECSS was available in stent lengths of 8, 18 and 28 mm. The non-target lesion could be treated by the commercial XIENCE V EECSS with a RVD of ≥ 2.5 mm to ≤ 4.25 mm. The commercial XIENCE V EECSS was available in stent diameters of 2.5, 2.75, 3.0, 3.5, 4.0 mm and stent lengths of 8, 12, 15, 18, 23, 28 mm. The primary endpoint was target lesion failure (TLF, defined as the composite of cardiac death, target vessel myocardial infarction and clinically-indicated target lesion revascularization) at 1 year.

Demographics: For the subjects treated with the 2.25 mm XIENCE V EECS, the mean age was 63 ± 11 years, and the majority of the population was male (61.8%, 89/144). In subjects treated with the 2.25 mm XIENCE V EECS, 22.9% (32/140) were tobacco users, 81.9% (118/144) were hypertensive requiring medication, 86.5% (122/141) had hypercholesterolemia requiring medication, and 39.2% (56/143) were diabetic. Additionally, 68.8% (99/144) of the subjects had stable angina and 27.1% (39/144) had unstable angina.

Results: The results are presented in Table 9.5-1 (Primary Endpoint Results), Table 9.5-2 (Clinical Results), Table 9.5-3 (Stent Thrombosis Results), Table 9.5-4 (Angiographic Results) and Figure 9.5-1 (Time-to-Event Curve for TLF). These analyses are based on the full analysis set (FAS) population (defined as subjects that received the 2.25 mm XIENCE V EECSS). The primary analysis of the primary endpoint was analyzed in the FAS population. The 1-year TLF rate was 8.1% with an upper limit of the one-sided 95% confidence interval of 13.03%, which met the pre-specified performance goal of 20.4% ($p < 0.0001$).

Table 9.5-1: SPIRIT Small Vessel Primary Endpoint Result

Primary Endpoint	2.25 mm XIENCE V (N = 144)	Upper 1-Sided 95% CL	P-Value[1]
1 Year TLF	8.1% (11/136)	13.03%	< 0.0001

Notes:
- N is the total number of subjects.
- TLF includes cardiac death, target vessel MI (per protocol definition) and clinical-indicated TLR.
- Time Frame includes follow-up window (365 ± 28 days).

[1] One-sided p-value by testing against the performance goal of 20.4% using exact test at 0.05 significance level.

Table 9.5-2: SPIRIT Small Vessel Clinical Endpoint Results through 1 Year

2.25 mm XIENCE V Arm	Per Protocol Definition
Acute Success	ITT* (N = 149)
Clinical Device Success	95.21% (139/146)
Clinical Procedure Success	97.93% (142/145)
Clinical Endpoints	FAS (N = 144)
Component Endpoints	
All Death	1.5% (2/136)
Cardiac Death	1.5% (2/136)
Non-Cardiac Death	0.0% (0/136)
Target Vessel MI	1.5% (2/136)
Non Target Vessel MI	0.0% (0/136)
Clinically-Indicated TLR (CI-TLR)	5.1% (7/136)
Clinically-Indicated TVR (CI-TVR)	8.8% (12/136)
All TLR	6.6% (9/136)
All TVR	10.3% (14/136)
All Revascularization	14.7% (20/136)
Composite Endpoints	
Cardiac Death or MI	2.9% (4/136)
Cardiac Death or All MI or CI-TLR	8.1% (11/136)
All Death or All MI or All Revascularization	16.9% (23/136)

Notes:
- N is the total number of subjects; L is the number of lesions.
- Per protocol MI definition was used for Target Vessel MI, Non Target Vessel MI and all composite endpoints.
- Time Frame includes follow-up window (365 ± 28 days).
- Non Target Vessel MI includes MI not attributed to the treated vessel.
- All Revascularization includes TVR and non-TVR, and non-treated vessel revascularization.
- FAS (full analysis set) is defined as subjects that received the 2.25 mm XIENCE V EECS in the SPIRIT SV trial.

- Clinical Device Success: The successful delivery and deployment of the first study stent intended to be implanted at the intended target lesion (or in an overlapping stent setting, a successful delivery and deployment of the intended first and second investigational stents) and successful withdrawal of the stent delivery system with attainment of final residual stenosis of less than 50% of the target lesion by QCA (or by visual estimation if QCA unavailable). Bailout lesions were included as device success only if the above criteria for clinical device success were met for the bailout stent.
- Clinical Procedure Success: The achievement of a final in-stent diameter stenosis (DS) of < 50% (by QCA) using the assigned device and with any adjunctive devices, without the occurrence of cardiac death, target vessel MI (per protocol definition), or repeat coronary revascularization of the target lesion during the hospital stay (up to 7 days if a subject still is in the hospital). If QCA %DS was not available, procedure success data were considered missing.

* The ITT population provides the most accurate estimate of successful 2.25 mm XIENCE V stent implantation because it includes all subjects regardless of whether the attempted implantation of 2.25 mm XIENCE V stent was successful.

Table 9.5-3: SPIRIT Small Vessel Stent Thrombosis Results through 1 Year

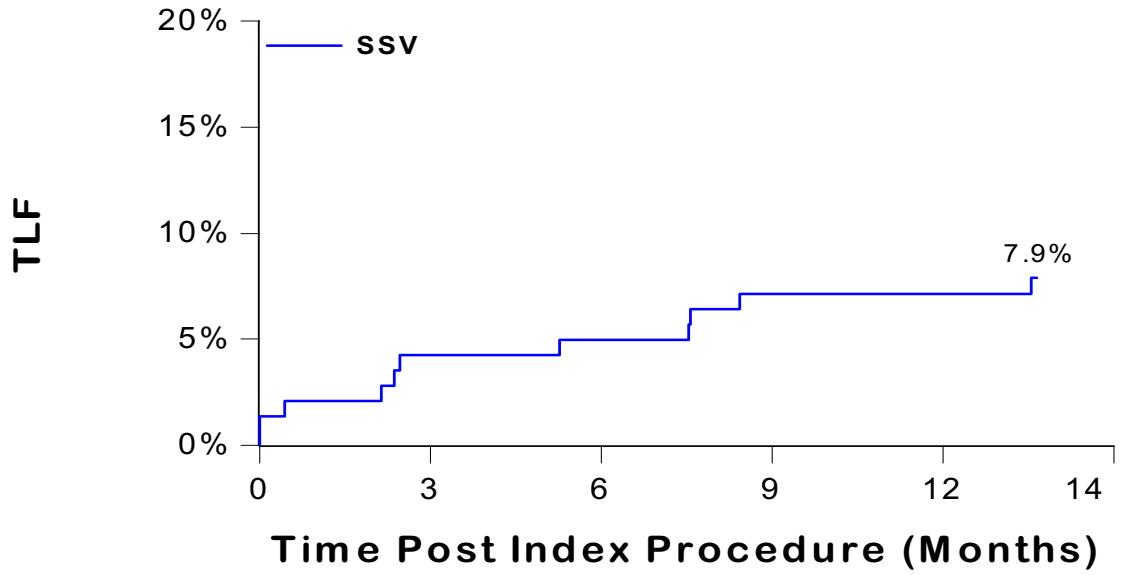
2.25 mm XIENCE V Arm	FAS (N = 144)	FAS (N = 144)
Stent Thrombosis	**Per Protocol Definition**	**Per ARC Definition (Definite+Probable)**
Acute (≤ 1 day)	0.0% (0/143)	0.0% (0/143)
Subacute (>1 – 30 days)	0.7% (1/140)	0.7% (1/140)
Acute / Subacute (0 – 30 days)	0.7% (1/140)	0.7% (1/140)
Late (31 – 393 days)	1.5% (2/135)	0.7% (1/135)
Overall (0 – 393 days)	2.2% (3/136)	1.5% (2/136)

Table 9.5-4: SPIRIT Small Vessel 240-Day Angiographic Results (Angiographic Cohort[1])

XIENCE V 2.25 mm Arm	FAS (N = 69) (L = 69)
240-day Late Loss	
In-Stent	0.20 ± 0.40 (52)
In-Segment	0.16 ± 0.41 (52)
Proximal	0.21 ± 0.35 (34)
Distal	0.00 ± 0.28 (45)
240-day %DS	
In-Stent	12.86 ± 19.58 (52)
In-Segment	20.85 ± 22.53 (52)
Proximal	14.31 ± 13.16 (37)
Distal	10.40 ± 8.45 (46)
240-day ABR	
In-Stent	3.8% (2/52)
In-Segment	9.6% (5/52)
Proximal	2.7% (1/37)
Distal	0.0% (0/46)

Notes:
N is the total number of subjects. L is the total number of lesions.
240-day angiographic data is available for 52 subjects.
[1] Per Protocol defined qualifying angiogram with follow-up window extended to 268 days.

Figure 9.5-1: SPIRIT Small Vessel: Kaplan Meier Time-to-Event Curve for TLF through 1 Year



TLF	Event Free	Event Rate
XIENCE V 2.25 mm ARM	92.1%	7.9%

Note:
– Time Frame includes follow-up window (365 + 28 days).

9.6 Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Analysis

A subject-level pooled analysis of three randomized, single-blinded, controlled trials was conducted to provide an assessment of safety outcomes with increased precision and to better estimate the incidence of low frequency events in specific subgroups. Definitive proof of the presence or absence of any differences between such subgroups requires prospectively powered assessment in dedicated clinical trials.

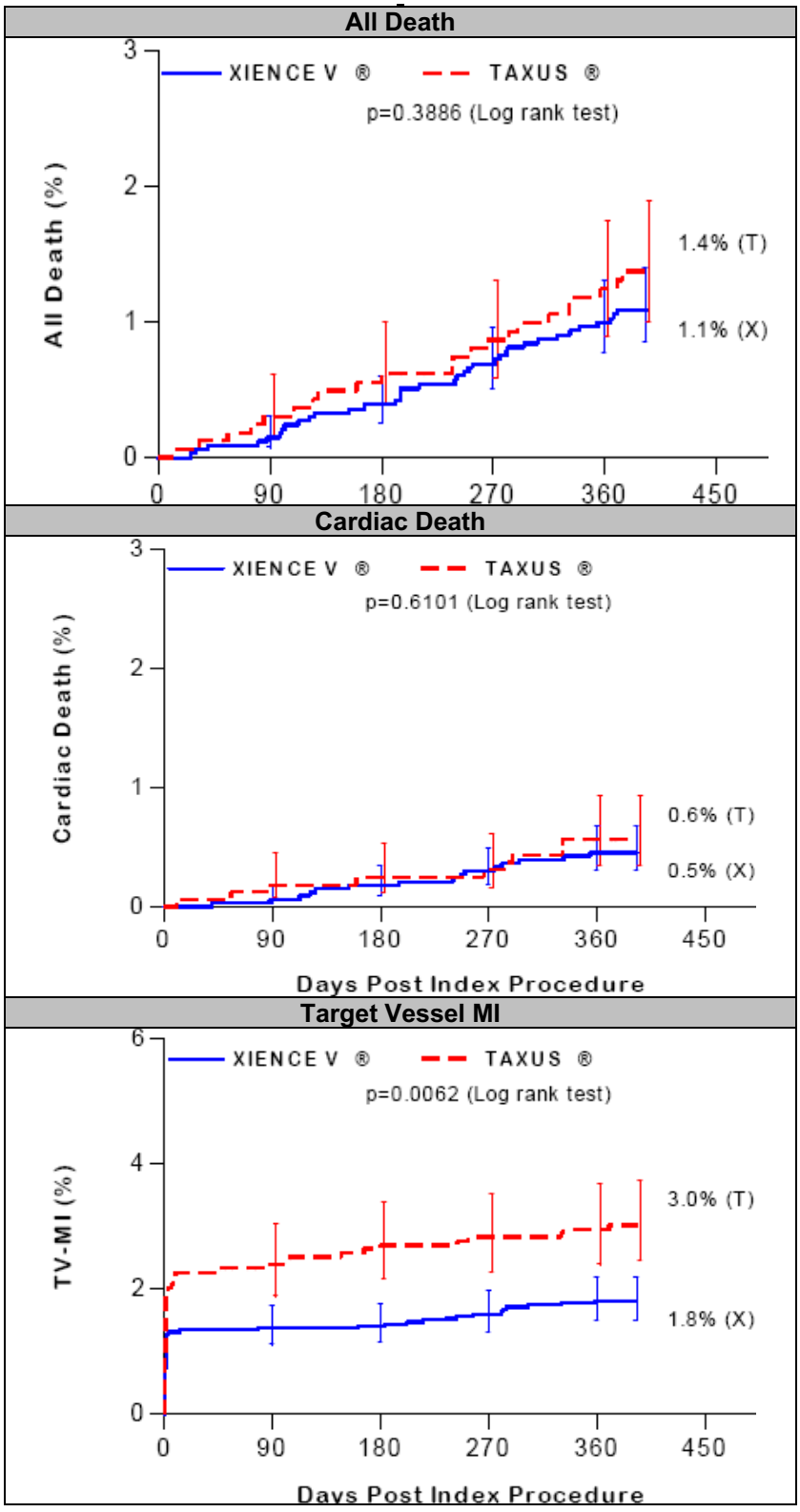
Data from the SPIRIT II, SPIRIT III randomized control trial (RCT) arm and SPIRIT IV clinical trials were pooled to compare the XIENCE V stent to the TAXUS stent in 4989 subjects (with 6233 lesions) through 1 year (393 days) of follow-up. Although SPIRIT IV permitted the enrollment of somewhat more complex patients, the three studies have subjects with generally similar baseline and angiographic characteristics and share key elements of study design, allowing pooling of the data for the purposes of these safety analyses.

Table 9.6-1: Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Clinical Results through 1 Year

Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	XIENCE V (N = 3350) [95% CI][1]	TAXUS (N = 1639)[2] [95% CI][1]
All Death	1.1% (36/3295) [0.77%, 1.51%]	1.4% (22/1592) [0.87%, 2.08%]
Cardiac Death	0.5% (15/3295) [0.26%, 0.75%]	0.6% (9/1592) [0.26%, 1.07%]
Non-Cardiac Death	0.6% (21/3295) [0.39%, 0.97%]	0.8% (13/1592) [0.44%, 1.39%]
Target Vessel MI	1.8% (60/3295) [1.39%, 2.34%]	3.1% (49/1592) [2.29%, 4.05%]
Cardiac Death or Target Vessel MI	2.2% (73/3295) [1.74%, 2.78%]	3.4% (54/1592) [2.56%, 4.40%]
All MI	2.0% (65/3295) [1.53%, 2.51%]	3.3% (53/1592) [2.50%, 4.33%]
QMI	0.2% (5/3295) [0.05%, 0.35%]	0.4% (6/1592) [0.14%, 0.82%]
NQMI	1.8% (60/3295) [1.39%, 2.34%]	3.0% (48/1592) [2.23%, 3.98%]
Cardiac Death or All MI	2.4% (78/3295) [1.88%, 2.95%]	3.6% (57/1592) [2.72%, 4.61%]
Protocol Defined Stent Thrombosis		
Cumulative through 1 Year	0.3% (10/3258) [0.15%, 0.56%]	0.8% (13/1574) [0.44%, 1.41%]
Acute/Subacute (0 – 30 Days)	0.2% (6/3341) [0.07%, 0.39%]	0.4% (7/1628) [0.17%, 0.88%]
Late (31 Days – 1 Year)	0.1% (4/3257) [0.03%, 0.31%]	0.4% (7/1574) [0.18%, 0.91%]
ARC Definite+Probable Stent Thrombosis		
Cumulative through 1 Year	0.4% (13/3261) [0.21%, 0.68%]	1.0% (16/1574) [0.58%, 1.65%]
Acute/Subacute (0 – 30 Days)	0.2% (7/3341) [0.08%, 0.43%]	0.6% (10/1628) [0.29%, 1.13%]
Late (31 days – 1 Year)	0.2% (6/3260) [0.07%, 0.40%]	0.5% (8/1574) [0.22%, 1.00%]

Notes:
– Time Frame includes follow-up window (365 + 28 days)
[1] By Clopper-Pearson Exact Confidence Interval
[2] In the pooled TAXUS stent arm, there were 18 subjects who received at least one TAXUS® Liberté® stent.

Figure 9.6-1: Kaplan Meier Time-to-Event Curves through 1 Year (Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV)



Note: P-value based on log rank and not adjusted for multiple comparisons

9.6.1 Analysis of Diabetic Subjects in SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Trials

Diabetic subjects comprise an important subject subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic subjects were included in the SPIRIT family of trials, there were no pre-specified hypotheses for the use of the XIENCE V stent in diabetic individuals.

Table 9.6.1-1 and 9.6.1-2 show the clinical outcomes through 1 year in subjects from a post-hoc analysis of the SPIRIT IV and the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population. History of diabetes was one of the stratification factors used in randomization to assure a balance between the XIENCE V and TAXUS treatment arms for each individual trial. In XIENCE V patients, there were numerically higher event rates in diabetics compared with non-diabetics. Given the potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

Table 9.6.1-1: Clinical Results in Diabetics and Non-Diabetics through 1 Year (SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT and SPIRIT IV Population)

SPIRIT IV	Non-Diabetics XIENCE V (N = 1669)	Non-Diabetics TAXUS (N = 829)	All Diabetics XIENCE V (N = 786)	All Diabetics TAXUS (N = 399)
TLF	3.1% (52/1652)	6.7% (55/815)	5.9% (45/761)	6.9% (26/379)
Ischemia-Driven TLR	1.8% (29/1652)	4.5% (37/815)	3.5% (27/761)	4.7% (18/379)
Ischemia-Driven TVR, Non TL	1.5% (24/1652)	2.2% (18/815)	3.9% (30/761)	2.9% (11/379)
Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	**Non-Diabetics XIENCE V (N = 2312)**	**Non-Diabetics TAXUS (N = 1125)**	**All Diabetics XIENCE V (N = 1035)**	**All Diabetics TAXUS (N = 509)**
All Death	0.8% (19/2284)	1.7% (19/1106)	1.7% (17/1008)	0.6% (3/482)
Cardiac Death	0.2% (5/2284)	0.7% (8/1106)	1.0% (10/1008)	0.2% (1/482)
Non-Cardiac Death	0.6% (14/2284)	1.0% (11/1106)	0.7% (7/1008)	0.4% (2/482)
Target Vessel MI	1.3% (30/2284)	3.0% (33/1106)	3.0% (30/1008)	3.3% (16/482)
Cardiac Death or Target Vessel MI	1.5% (35/2284)	3.3% (37/1106)	3.8% (38/1008)	3.5% (17/482)
Stent Thrombosis				
Protocol Defined	0.1% (3/2265)	0.7% (8/1091)	0.7% (7/990)	1.0% (5/479)
ARC Definite+Probable	0.1% (3/2265)	0.9% (10/1091)	1.0% (10/993)	1.3% (6/479)

Notes:
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time frame includes follow-up window (365 + 28 days).

Table 9.6.1-2: Clinical Results in Diabetics through 1 Year (SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Population – XIENCE V Subjects)

SPIRIT IV	Non-Diabetics (N = 1669)	All Diabetics (N = 786)	Insulin-Dependent Diabetics (N = 209)	Non-Insulin-Dependent Diabetics (N = 577)
TLF	3.1% (52/1652)	5.9% (45/761)	7.0% (14/199)	5.5% (31/562)
Ischemia-Driven TLR	1.8% (29/1652)	3.5% (27/761)	5.0% (10/199)	3.0% (17/562)
Ischemia-Driven TVR, Non TL	1.5% (24/1652)	3.9% (30/761)	6.5% (13/199)	3.0% (17/562)
Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	**Non-Diabetics (N = 2312)**	**All Diabetics (N = 1035)**	**Insulin-Dependent Diabetics (N = 272)**	**Non-Insulin-Dependent Diabetics (N = 763)**
All Death	0.8% (19/2284)	1.7% (17/1008)	2.3% (6/262)	1.5% (11/746)
Cardiac Death	0.2% (5/2284)	1.0% (10/1008)	1.1% (3/262)	0.9% (7/746)
Non-Cardiac Death	0.6% (14/2284)	0.7% (7/1008)	1.1% (3/262)	0.5% (4/746)
Target Vessel MI	1.3% (30/2284)	3.0% (30/1008)	4.6% (12/262)	2.4% (18/746)
Cardiac Death or Target Vessel MI	1.5% (35/2284)	3.8% (38/1008)	5.0% (13/262)	3.4% (25/746)
Stent Thrombosis				
Protocol Defined	0.1% (3/2265)	0.7% (7/990)	0.8% (2/256)	0.7% (5/734)
ARC Definite+Probable	0.1% (3/2265)	1.0% (10/993)	1.2% (3/257)	1.0% (7/736)

Notes:
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time frame includes follow-up window (365 + 28 days)

9.7 Gender-Based Analysis of the SPIRIT Clinical Trials

9.7.1 Background

Cardiovascular disease is the leading cause of death for both women and men in the U.S. and coronary artery disease is a major cause of morbidity and mortality in women. It is estimated that the prevalence of coronary artery disease in the United States is 9.1% (9,200,000) in males and 7.0% (8,400,000) in females for adults at least 20 years old according to the American Heart Association 2010 Update.[15] However, it is estimated that only 36% of annual PCIs are performed in women.[16] In PCI clinical trials, women represent only 25-35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in these trials may be partly attributable to gender differences in symptoms and pathophysiology,[17] which may lead to under-diagnosis and under-referral of female patients with CAD. Women tend to have worse clinical outcomes compared to men, most likely due to a higher baseline risk profile and more complex angiographic characteristics.[18,19,20]

[15] Lloyd-Jones D, Adams R, Carnethon M, De Simone G, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; 121:e46-215.
[16] Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; 119(3):e21-181.
[17] Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: Gender Differences in Traditional and Novel Risk Factors, Symptom Evaluation, and Gender-Optimized Diagnostic Strategies. J Am Coll Cardiol 2006 47: S4-20.
[18] Mahoney EM, Jurkovitz CT, Chu H, Becker ER, Culler S, Kosinski AS, et al. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *Jama* 2002; 288(15):1851-8.

9.7.2 Gender-Based Analysis of SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Clinical Trials

To evaluate gender-specific clinical outcomes with the XIENCE V stent, Abbott Vascular conducted a pooled analysis of SPIRIT II, SPIRIT III RCT, and SPIRIT IV. The pooled SPIRIT trial data were assessed for differences between males and females in baseline characteristics and study outcomes, as well as for any interaction between treatment and gender. Results suggest that the general conclusions of safety and effectiveness of the XIENCE V stent can be generalized for males and females.

In the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV intent-to-treat population, 1584 subjects were female (32%) and 3404 subjects were male (68%). The gender proportions enrolled in this trial are similar to other drug-eluting stent trials.[21,22]

Of the 1584 female subjects in the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population, 1058 were XIENCE V subjects and 526 were TAXUS subjects.

Table 9.7.2-1 shows the demographics, risk factors, and baseline angiographic characteristics of female and male subgroups of the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population.

[19] Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009; 157(1):141-8.
[20] Vaina S, Voudris V, Morice M-C, de Bruyne B, Colombo A, Macaya C, Richardt, G, Fajadet, J et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularization in patients with multivessel coronary artery disease: Insights from ARTS I and ARTS II. *EuroInterv*. 2009; 4(4):492-501.
[21] Lansky AJ, Costa RA, Mooney M, et al. Gender-Based Outcomes After Paclitaxel-Eluting Stent Implantation in Patients With Coronary Artery Disease. J Am Coll Cardiol 2005 45: 1180-5.
[22] Solinas E, Nikolsky E, Lansky AJ, et al. Gender-Specific Outcomes After Sirolimus-Eluting Stent Implantation. J Am Coll Cardiol 2007;50:2111–6

Table 9.7.2-1: Demographics, Risk Factors, and Baseline Angiographic Characteristics for the All Female and All Male Subgroups (Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Population)

Subject Characteristics	All Females (N = 1584; 32%) (M = 1901)	All Males (N = 3404; 68%) (M = 4332)	P Value[1]
Baseline Demographics, Mean ± SD (n)			
Age (year)	65.7 ± 10.5 (1584)	62.0 ± 10.2 (3404)	< 0.0001
Baseline Risk Factors, % (No./total)			
All Diabetes	35.9% (569/1583)	28.7% (975/3398)	< 0.0001
Diabetes Treated with Insulin	12.1% (192/1583)	6.5% (222/3398)	< 0.0001
Current Tobacco Use	21.7% (337/1550)	23.2% (772/3321)	0.2555
Hypertension Requiring Medication	80.7% (1278/1584)	73.9% (2511/3398)	< 0.0001
Hypercholesterolemia Requiring Medication	73.2% (1143/1562)	75.9% (2537/3341)	0.0399
Stable Angina	57.2% (889/1554)	57.7% (1933/3348)	0.7327
Unstable Angina	29.1% (452/1554)	25.5% (854/3348)	0.0092
Prior MI	15.8% (245/1551)	23.6% (783/3316)	< 0.0001
Target Vessel, % (No./total)			
LAD	43.1% (820/1901)	39.6% (1712/4327)	0.0085
Circumflex or Ramus	21.9% (416/1901)	26.8% (1159/4327)	< 0.0001
RCA	35.0% (665/1901)	33.6% (1454/4327)	0.2959
LMCA	0.0% (0/1901)	0.0% (2/4327)	1.0000
Pre-Procedure QCA Analysis, Mean ± SD (m)			
Lesion Length (mm)	14.22 ± 6.25 (1888)	14.79 ± 6.51 (4293)	0.0012
Pre-Procedure RVD (mm)	2.66 ± 0.44 (1894)	2.79 ± 0.48 (4303)	<0.0001
Pre-Procedure MLD (mm)	0.79 ± 0.38 (1899)	0.78 ± 0.40 (4310)	0.2207
Pre-Procedure Percent Diameter Stenosis (%DS)	69.92 ± 12.84 (1899)	71.58 ± 13.05 (4310)	<0.0001

Notes:

– N is the total number of subjects; M is the total number of lesions analyzed
[1]P values are displayed for descriptive purposes only

Table 9.7.2-1 shows that females in the SPIRIT family of trials were older and had higher rates of diabetes, hypertension, and unstable angina compared with males. The generally higher clinical risk profile in females is consistent with gender differences in baseline demographics reported from other PCI studies. [23,24,25,26,27,28,29]

Table 9.7.2-2 presents key clinical outcomes through 1 year in female and male subjects from the SPIRIT IV trial and the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population. In post-hoc analyses of the pooled SPIRIT II, SPIRIT III RCT and SPIRIT IV population, rates of death, target vessel MI and stent thrombosis through 1 year were comparable between females and males. However, rates of bleeding complications were numerically higher in females compared to males. At 1 year, post-hoc analyses of the SPIRIT IV trial suggest that females treated with XIENCE V stents (despite generally increased clinical risk factors at baseline) had numerically similar adverse event rates compared to males treated with XIENCE V stents. Comparisons of study outcomes in patients receiving the XIENCE V stent versus the TAXUS stent were

[23] Correa-De-Araujo R. Serious gaps: how lack of sex/gender- based research impairs health. *J Womens Health (Larchmt)* 2006; 15(10):1116-22.
[24] Abbott JD, Vlachos HA, Selzer F, Sharaf BL, Holper E, Glaser R et al. Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents (from the National Heart, Lung, and Blood Institute Dynamic Registry). *Am J Cardiol* 2007; 99(5):626-31.
[25] Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009; 157(1):141-8.
[26] Vaina S, Voudris V, Morice M-C, de Bruyne B, Colombo A, Macaya C, Richardt, G, Fajadet, J et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularization in patients with multivessel coronary artery disease: Insights from ARTS I and ARTS II. *EuroInterv*. 2009; 4(4):492-501.
[27] Blomkalns AI, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005; 45(6):832-7.
[28] Lansky AJ, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, et al. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigations to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation* 2005; 111(13):1611-8.
[29] Lansky AJ, Costa RA, Mooney M, Midei MG, Lui HK, Strickland W, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. *J Am Coll Cardiol* 2005; 45 (8):1180-5.

consistent within each gender subgroup. Based on the interaction p-value calculated from Wald Chi-square statistics of logistic regression analysis, no significant treatment-by-gender interaction effect was observed at a 0.15 significance level. These analyses suggest that the conclusions regarding safety and effectiveness of the XIENCE V stent are generalizable to both males and females. However, it should be noted that there were no pre-specified hypotheses for the use of the XIENCE V stent in females.

Table 9.7.2-2: Clinical Results in XIENCE V Females, XIENCE V Males and All Subjects through 1 Year (SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Population)

Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	Females XIENCE V (N = 1058)	Males XIENCE V (N = 2292)	All Subjects XIENCE V (N = 3350)	All Subjects TAXUS (N = 1639)
All Death	1.2% (12/1038)	1.1% (24/2257)	1.1% (36/3295)	1.4% (22/1592)
Cardiac Death	0.5% (5/1038)	0.4% (10/2257)	0.5% (15/3295)	0.6% (9/1592)
Non-Cardiac Death	0.7% (7/1038)	0.6% (14/2257)	0.6% (21/3295)	0.8% (13/1592)
Target Vessel MI	1.9% (20/1038)	1.8% (40/2257)	1.8% (60/3295)	3.1% (49/1592)
Cardiac Death or Target Vessel MI	2.4% (25/1038)	2.1% (48/2257)	2.2% (73/3295)	3.4% (54/1592)
Bleeding Complication	4.5% (46/1029)	2.5% (56/2232)	3.1% (102/3261)	3.3% (52/1573)
Stent Thrombosis				
Protocol Defined	0.4% (4/1028)	0.3% (6/2230)	0.3% (10/3258)	0.8% (13/1574)
ARC Definite+Probable	0.4% (4/1028)	0.4% (9/2233)	0.4% (13/3261)	1.0% (16/1574)
SPIRIT IV	**Females XIENCE V (N = 793)**	**Males XIENCE V (N = 1665)**	**All Subjects XIENCE V (N = 2458)**	**All Subjects TAXUS (N = 1229)**
TLF	4.0% (31/777)	4.0% (66/1639)	4.0% (97/2416)	6.8% (81/1195)
Ischemia-Driven TLR	2.2% (17/777)	2.4% (39/1639)	2.3% (56/2416)	4.6% (55/1195)
Ischemia-Driven TVR, Non TL	2.7% (21/777)	2.0% (33/1639)	2.2% (54/2416)	2.4% (29/1195)

Notes:
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time frame includes follow-up window (365 + 28 days).
- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI (per protocol definition), and ischemia-driven TLR.

9.7.3 Gender-Based Analysis of SPIRIT Small Vessel Clinical Trial

Abbott Vascular also performed a post-hoc multivariable gender analysis of the SPIRIT Small Vessel clinical trial. However, it should be noted that the SPIRIT SV trial was not powered to detect any differences between genders, and a subgroup analysis was not pre-specified in the Statistical Analysis Plan. Therefore, due to the limited sample size and the small number of events, the results from the analysis below should be considered exploratory without definitive conclusions.

The baseline SPIRIT SV trial subject characteristics stratified by gender are shown in Table 9.7.3-1. Compared to the men, women were more likely to be diabetics treated with insulin [27.3% (15/55) for females versus 8.0% (7/88) for males], and less likely to be smokers [13.0% (7/54) smokers for females versus 29.1% (25/86) smokers for males]. In terms of baseline angiographic characteristics, the differences in lesion length and pre-procedure RVD, MLD, or %DS were not found to differ significantly between females and males in this post-hoc analysis.

Table 9.7.3-1 Demographics, Risk Factors, and Baseline Angiographic Characteristics for All Female and All Male Subgroups in the SPIRIT SV Clinical Trial

Subject Characteristics	Females (N=55) (M=55)	Males (N=89) (M=90)	P Value
Baseline Demographics, Mean ± SD (n)			
Age (year)	64.74 ± 11.28 (55)	61.88 ± 10.05 (89)	0.1260
Baseline Risk Factors, % (No./total)			
All Diabetes	49.1% (27/55)	33.0% (29/88)	0.0778
Diabetes Treated with Insulin	27.3% (15/55)	8.0% (7/88)	0.0034
Current Tobacco Use	13.0% (7/54)	29.1% (25/86)	0.0378
Hypertension Requiring Medication	83.6% (46/55)	80.9% (72/89)	0.8243
Hypercholesterolemia Requiring Medication	85.2% (46/54)	87.4% (76/87)	0.8012
Stable Angina	72.7% (40/55)	66.3% (59/89)	0.4632
Unstable Angina	25.5% (14/55)	28.1% (25/89)	0.8474
Prior MI	20.4% (11/54)	31.8% (28/88)	0.1759
Target Vessel, % (No./total)			
LAD	45.5% (25/55)	37.8% (34/90)	0.3876
Circumflex or Ramus	30.9% (17/55)	31.1% (28/90)	1.0000
RCA	23.6% (13/55)	31.1% (28/90)	0.3502
LMCA	0.0% (0/55)	0.0% (0/90)	N/A
Pre-Procedure QCA Analysis, Mean ± SD (m)			
Lesion Length (mm)	13.62 ± 5.81 (55)	13.23 ± 5.00 (89)	0.6808
Pre-Procedure RVD (mm)	2.11 ± 0.24 (55)	2.14 ± 0.22 (90)	0.4615
Pre-Procedure MLD (mm)	0.55 ± 0.19 (55)	0.55 ± 0.20 (90)	0.9914
Pre-Procedure Percent Diameter Stenosis (%DS)	72.74 ± 8.31 (55)	72.90 ± 9.83 (90)	0.9150

Table 9.7.3-2 presents key clinical outcomes through 1 year in female and male subjects in the SPIRIT SV clinical trial. At 1 year, post-hoc analyses of the SPIRIT SV trial are limited with regards to conclusions that can be drawn regarding any differences in adverse event rates between female and male subjects due to the small sample size.

Table 9.7.3-2: Clinical Results for All Female and All Male Subgroups in the SPIRIT SV Clinical Trial through 1 Year

SPIRIT SV	Females (N=55)	Males (N=89)
All Death	0.0% (0/51)	2.4% (2/85)
Cardiac Death	0.0% (0/51)	2.4% (2/85)
Non-Cardiac Death	0.0% (0/51)	0.0% (0/85)
Target Vessel MI	0.0% (0/51)	2.4% (2/85)
Cardiac Death or Target Vessel MI	0.0% (0/51)	4.7% (4/85)
Bleeding Complication	5.9% (3/51)	2.4% (2/84)
Stent Thrombosis		
Protocol defined	0.0% (0/51)	3.5% (3/85)
ARC Definite+Probable	0.0% (0/51)	2.4% (2/85)
TLF	11.8% (6/51)	5.9% (5/85)
Ischemia-Driven TLR	11.8% (6/51)	1.2% (1/85)
Ischemia-Driven TVR, non TL	7.8% (4/51)	4.7% (4/85)

10.0 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the PROMUS stent. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy. Stenting is generally avoided in those patients at a heightened risk of bleeding (e.g., patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

Antiplatelet drugs should be used in combination with the PROMUS stent. Physicians should use information from the SPIRIT clinical trials, coupled with current drug-eluting stent (DES) literature and the specific needs of individual patients to determine the specific antiplatelet/anticoagulation regimen to be used for their patients in general practice. See also Section 5.2 – Precautions, Pre- and Post-Procedure Antiplatelet Regimen, Section 5.6 – Precautions, Use in Special Populations, and Section 5.7 – Precautions, Lesion/Vessel Characteristics.

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

11.0 PATIENT COUNSELING AND PATIENT INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with an everolimus-eluting stent.
- Discuss the risks of early discontinuation of the antiplatelet therapy.
- Discuss the risks of late stent thrombosis with DES use in higher risk patient subgroups.
- Discuss the risk/benefit issues for this particular patient.
- Discuss alteration to current life-style immediately following the procedure and over the long term.

The following patient materials are available for this product:

- A Patient Information Guide which includes information on coronary artery disease, the implant procedure and the PROMUS Everolimus-Eluting Coronary Stent System (provided to physician, on-line at www.bostonscientific.com/promus, or by calling customer service 1-888-272-1001)
- A Stent Implant Card that includes both patient information and stent implant information (provided in package)

12.0 HOW SUPPLIED

Sterile: This device is sterilized with ethylene oxide gas, non-pyrogenic. It is intended for single use only. Do not resterilize. Do not use if the package is opened or damaged.

Contents: One (1) PROMUS Everolimus-Eluting Coronary Stent System, one (1) Flushing Tool, (for the PROMUS Rapid Exchange (RX) Stent System), and one (1) Stent Implant Card

Storage: Store in a dry, dark, cool place. Protect from light. Do not remove from carton until ready for use. Store at 25°C (77°F); excursions permitted to 15°– 30°C (59°– 86°F).

13.0 OPERATOR'S INSTRUCTIONS

13.1 Inspection Prior to Use

- Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
- Do not use after the "Use by" date.
- Tear open the foil pouch and remove the inner pouch. **Note: the outside of the inner pouch is NOT sterile.** Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
- Prior to using the PROMUS Everolimus-Eluting Coronary Stent System, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not use if any defects are noted. However, **do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination or stent dislodgement from the delivery balloon.

Note: At any time during use of the PROMUS Rapid Exchange (RX) Everolimus-Eluting Coronary Stent System, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

13.2 Materials Required

- Appropriate guiding catheter(s). See Table 1-1, PROMUS Stent System Product Description
- 2 – 3 syringes (10 – 20 ml)
- 1,000 u/500 ml heparinized normal saline (HepNS)
- 0.014 inch (0.36 mm) x 175 cm (minimum length) guide wire
- Rotating hemostatic valve with appropriate minimum inner diameter (0.096 inch [2.44 mm])
- 60% contrast diluted 1:1 with heparinized normal saline
- Inflation device
- Pre-deployment dilatation catheter
- Three-way stopcock
- Torque device
- Guide wire introducer
- Appropriate arterial sheath
- Appropriate anticoagulation and antiplatelet drugs

13.3 Preparation

13.3.1 Packaging Removal

Note: The foil pouch is not a sterile barrier. The inner header bag (pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Rapid Exchange (RX) system, do not bend or kink the hypotube during removal.

2. Remove the product mandrel and protective stent sheath by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent sheath removal, do not use this product and replace with another. Follow product returns procedure for the unused device.

13.3.2 Guide Wire Lumen Flush

1. Over the Wire (OTW) only: Flush the guide wire lumen with HepNS until fluid exits the distal end of the delivery system.

2. Rapid Exchange (RX) only: Flush the guide wire lumen with HepNS using the flushing tool supplied with the product. Insert the flushing tool into the tip of the catheter and flush until fluid exits the guide wire exit notch.

Note: Avoid manipulation of the stent while flushing the guide wire lumen, as this may disrupt the placement of the stent on the balloon.

13.3.3 Delivery System Preparation

1. Prepare an inflation device/syringe with diluted contrast medium.
2. Attach an inflation device/syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to delivery system; pull negative for 30 seconds; release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.
7. If a syringe was used, attach a prepared inflation device to stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral

Note: While introducing the delivery system into the vessel, do not induce negative pressure on the delivery system. This may cause dislodgement of the stent from the balloon.

Note: If air is seen in the shaft, repeat Section 13.3.3 – Delivery System Preparation, steps 3 through 5, to prevent uneven stent expansion.

13.4 Delivery Procedure

1. Prepare the vascular access site according to standard practice.

2. **Pre-dilate the lesion with a PTCA catheter of appropriate length and diameter for the vessel/lesion to be treated.** Limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the PROMUS Stent.

Note: The labeled stent diameter refers to expanded stent inner diameter.

3. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as wide as possible.

4. Backload the delivery system onto the proximal portion of the guide wire while maintaining guide wire position across the target lesion.

5. Carefully advance the delivery system into the guiding catheter and over the guide wire to the target lesion. When using a Rapid Exchange (RX) system be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the stent system into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guiding catheter, do not force passage. Resistance may indicate a problem and the use of excessive force may result in stent damage or dislodgement. Maintain guide wire placement across the lesion and remove the delivery system and guiding catheter as a single unit.

6. Advance the delivery system over the guide wire to the target lesion under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Section 5.14 – Precautions, Stent System Removal). The balloon markers indicate both the stent edges and the balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion.

Note: Should **any resistanc**e be felt **at any tim**e during either lesion access or removal of the delivery system post-stent implantation, **remove the entire system as a single unit.** See Section 5.14 – Precautions, Stent System Removal for specific delivery system removal instructions.

7. Tighten the rotating hemostatic valve. The stent is now ready to be deployed.

13.5 Deployment Procedure

CAUTION: Refer to Table 14-1: Typical PROMUS Stent Compliance for *in vitro* stent inner diameter, nominal pressure, and RBP.

1. Prior to deployment, reconfirm the correct position of the stent relative to the target lesion using the radiopaque balloon markers.

2. Deploy the stent slowly by pressurizing the delivery system in 2 atm increments, every 5 seconds, until stent is completely expanded. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter ratio of about 1.1 times the reference vessel diameter (see Table 14-1). Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall. **Do not exceed the labeled rated burst pressure (RBP) of 16 atm (1.62 MPa).**

3. Fully cover the entire lesion and balloon treated area (including dissections) with the PROMUS stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.

4. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to guiding catheter position.

5. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).

6. If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is sub-optimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent geometry. Deployed stents should not be left underdilated.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.25 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

7. If more than one PROMUS stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents the balloon

marker bands of the second PROMUS stent should be positioned inside the deployed stent prior to expansion.

8. Reconfirm stent position and angiographic results. Repeat inflations until optimal stent deployment is achieved.

13.6 Removal Procedure

1. Deflate the balloon by pulling negative pressure on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position.

2. Fully open the rotating hemostatic valve.

3. While maintaining the guide wire position and negative pressure on the inflation device, withdraw the delivery system.

Note: Should **any resistance** be felt **at any time** during either lesion access or removal of the delivery system post-stent implantation, the entire system should be **removed as a single unit**. See Section 5.14 – Precautions, Stent System Removal for specific delivery system removal instructions.

4. Tighten the rotating hemostatic valve.

5. Repeat angiography to assess the stented area. If post-dilatation is necessary, ensure that the final stent diameter matches the reference vessel diameter. **Assure that the stent is not underdilated.**

13.7 Post-Deployment Dilatation of Stent Segments

1. All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to the vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guide wire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

CAUTION: Do not dilate the stent beyond the following limits.

Nominal Stent Diameter	Dilatation Limit
2.25 mm to 3.0 mm	**3.5 mm**
3.5 mm to 4.0 mm	**4.5 mm**

14.0 *IN VITRO* COMPLIANCE INFORMATION

Table 14-1: Typical PROMUS Stent Compliance

Nominal pressure for each diameter indicated by bold font

Pressure		Stent ID (mm) by System Size					
(atm)	(MPa)	2.25 mm	2.5 mm	2.75 mm	3.0 mm	3.5 mm	4.0 mm
8	0.81	**2.27**	**2.46**	**2.74**	2.90	3.46	3.86
9	0.91	2.33	2.52	2.81	**2.97**	**3.55**	**3.95**
10	1.01	2.38	2.58	2.87	3.04	3.63	4.03
11	1.11	2.43	2.63	2.92	3.10	3.69	4.10
12	1.22	2.47	2.68	2.97	3.15	3.75	4.17
13	1.32	2.50	2.72	3.01	3.19	3.80	4.23
14	1.42	2.53	2.75	3.05	3.23	3.84	4.28
15	1.52	2.56	2.78	3.08	3.26	3.89	4.33
16 (RBP)*	1.62	2.59	2.81	3.11	3.30	3.93	4.37
17	1.72	2.62	2.84	3.14	3.33	3.97	4.42
18	1.82	2.64	2.87	3.18	3.36	4.00	4.46

Note: These nominal data are based on *in vitro* testing at 37°C and do not take into account lesion resistance.
Ensure full deployment of the stent (see Section 13.5 — Operator's Instructions, Deployment Procedure) and confirm the stent sizing angiographically.
*Do not exceed the rated burst pressure (RBP).

15.0 REUSE PRECAUTION STATEMENT

Do not use if sterile barrier is damaged. If damage is found call your Boston Scientific, Cardiac Therapies representative.

For single patient use only. Do not reuse, reprocess, or resterilize.

16.0 PATENTS AND TRADEMARKS

This product and/or its use may be covered by one or more of the following United States Patents: 5,514,154; 5,569,295; 5,636,641; 5,649,952; 5,665,772; 5,759,192; 5,780,807; 5,868,706; 6,131,266; 6,179,810; 6,309,412; 6,369,355; 6,384,046; 6,419,693; 6,440,990; 6,482,166; 6,629,991; 6,629,994; 6,656,220; 6,736,843; 6,746,423; 6,827,734; 6,887,219; 6,887,510; 6,890,318; 6,908,479; 6,929,657; 6,939,373; 6,957,152. Other U.S. patents pending. Foreign patents issued and pending.

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Graphical Symbols for Medical Device Labeling

Manufacturer	REF Catalogue Number	F French Size
Do not reuse	STERILE EO Sterilized using Ethylene Oxide	Consult Instructions for Use
Use By	LOT Batch Code	Date of Manufacture
Guiding Catheter	PYROGEN Non-Pyrogenic	# Contents (Numeral represents quantity of units inside)
Inner Diameter	MR MR Conditional	