
The XIENCE™ V Everolimus Eluting Coronary Stent System
Instructions for Use



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1.0 PRODUCT DESCRIPTION

The XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE V EECSS or XIENCE V stent system) 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.

Table 1-1: XIENCE V Stent System Product Description

	XIENCE V Rapid-Exchange (RX) EECSS	XIENCE V 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)	2.5, 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 2.5 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)	<table border="0"> <tr> <td></td> <td><u>2.5–3.0 mm</u></td> <td><u>3.5–4.0 mm</u></td> </tr> <tr> <td>Distal:</td> <td>0.032"</td> <td>0.035"</td> </tr> <tr> <td>Proximal:</td> <td>0.026"</td> <td>0.026"</td> </tr> </table>		<u>2.5–3.0 mm</u>	<u>3.5–4.0 mm</u>	Distal:	0.032"	0.035"	Proximal:	0.026"	0.026"	<table border="0"> <tr> <td></td> <td><u>2.5 mm</u></td> <td><u>2.75 x 8 – 3.5 x 18</u></td> <td><u>3.5 x 23 – 4.0 x 28</u></td> </tr> <tr> <td>Distal:</td> <td>0.032"</td> <td>0.034"</td> <td>0.036"</td> </tr> <tr> <td>Proximal:</td> <td>0.042"</td> <td>0.042"</td> <td>0.042"</td> </tr> </table>		<u>2.5 mm</u>	<u>2.75 x 8 – 3.5 x 18</u>	<u>3.5 x 23 – 4.0 x 28</u>	Distal:	0.032"	0.034"	0.036"	Proximal:	0.042"	0.042"	0.042"
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Figure 1-2: Non-erodible Polymer Chemical Structures

PBMA	PVDF-HFP
$\left[\text{CH}_2 - \underset{\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \\ \text{O} \\ \\ (\text{CH}_2)_3 \\ \\ \text{CH}_3 \end{array}}{\overset{\text{CH}_3}{\text{C}}} \right]_n$	$\left[\text{CH}_2 - \text{CF}_2 \right]_n \left[\text{CF}_2 - \underset{\text{CF}_3}{\overset{\text{F}}{\text{C}}} \right]_m$

1.2.3 Product Matrix and Everolimus Content

Table 1-3: XIENCE V 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)
1009539-08	1009545-08	2.5	8	37
1009540-08	1009546-08	2.75	8	37
1009541-08	1009547-08	3.0	8	37
1009542-08	1009548-08	3.5	8	53
1009543-08	1009549-08	4.0	8	53
1009539-12	1009545-12	2.5	12	56
1009540-12	1009546-12	2.75	12	56
1009541-12	1009547-12	3.0	12	56
1009542-12	1009548-12	3.5	12	75
1009543-12	1009549-12	4.0	12	75
1009539-15	1009545-15	2.5	15	75
1009540-15	1009546-15	2.75	15	75
1009541-15	1009547-15	3.0	15	75
1009542-15	1009548-15	3.5	15	98
1009543-15	1009549-15	4.0	15	98
1009539-18	1009545-18	2.5	18	88
1009540-18	1009546-18	2.75	18	88
1009541-18	1009547-18	3.0	18	88
1009542-18	1009548-18	3.5	18	113
1009543-18	1009549-18	4.0	18	113
1009539-23	1009545-23	2.5	23	113
1009540-23	1009546-23	2.75	23	113
1009541-23	1009547-23	3.0	23	113
1009542-23	1009548-23	3.5	23	151
1009543-23	1009549-23	4.0	23	151
1009539-28	1009545-28	2.5	28	132
1009540-28	1009546-28	2.75	28	132
1009541-28	1009547-28	3.0	28	132
1009542-28	1009548-28	3.5	28	181
1009543-28	1009549-28	4.0	28	181

2.0 INDICATIONS

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

3.0 CONTRAINDICATIONS

The XIENCE V stent is contraindicated for use in patients:

- Who cannot receive antiplatelet and/or anti-coagulant 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, and 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 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 is 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 current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from the XIENCE V SPIRIT family of 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 9.4 SPIRIT II and SPIRIT III Pooled Analysis, for more information). In the XIENCE V SPIRIT family of trials analyzed to date, the differences in the incidence of stent thrombosis observed with the XIENCE V stent compared to the TAXUS stent 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 DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.

- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the XIENCE V SPIRIT family of trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, 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 triglycerides levels.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In XIENCE V 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 XIENCE V SPIRIT II and SPIRIT III clinical trials, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 6 months post-procedure (75 mg per day). Aspirin was administered (a minimum of 75 mg per day) pre-procedure and continued for 1 to 5 years (depending on the study). Based on the case report forms from the SPIRIT II and III randomized clinical trials, approximately 92% of patients remained on dual antiplatelet therapy at 6 months and 62% at 1 year See Section 9.0 – Clinical Studies, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, 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 guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines^{1,2}).
- It is very important that the patient is compliant with the post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of 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 interventionalist 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

¹ Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121

² King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209

be monitored carefully for 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 vessels. Use of more than two stents to treat lesions longer than 28 mm has not been evaluated and may increase patient complication risks. Studies evaluating the effects of higher drug doses have not been conducted.

Effects of multiple stenting using XIENCE V stents combined with other drug-eluting stents are also unknown. When multiple drug-eluting stents are required, use only XIENCE V 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. Although *in vitro* tests combining L-605 CoCr alloy with 316 L stainless steel did not increase corrosion potential, these studies have not been conducted *in vivo*.

5.4 Brachytherapy

XIENCE V stent safety and effectiveness has 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 (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with XIENCE V 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 XIENCE V 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 XIENCE V 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

No safety- or effectiveness-related gender differences were observed in the individual XIENCE V clinical trials.

5.6.4 Ethnicity

Insufficient subject numbers prevent ethnicity-related analyses on XIENCE V safety and effectiveness.

5.6.5 Pediatric Use

Safety and effectiveness of the XIENCE V stent in pediatric subjects have not been established.

5.6.6 Geriatric Use

Clinical studies of the XIENCE V stent did not suggest that patients age 65 years and over differed with regard to safety and effectiveness compared to younger patients.

5.7 Lesion/Vessel Characteristics

Safety and effectiveness of the XIENCE V stent have not been established for subject populations with the following clinical settings:

- Unresolved vessel thrombus at the lesion site
- Coronary artery reference vessel diameters < 2.5 mm or > 4.25 mm
- Lesion lengths > 28 mm
- Lesions located in saphenous vein grafts
- Lesions located in unprotected left main coronary artery, ostial lesions, chronic total occlusions, 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
- Patients with longer than 24 months follow-up.

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 XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics).

Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a XIENCE V Stent.

5.9 Immune Suppression Potential

Everolimus, the XIENCE V stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the XIENCE V clinical trials. However, for patients who receive several XIENCE V 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 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 XIENCE V stent are expected to be significantly lower than concentrations usually obtained in transplant patients. Increased serum cholesterol and triglycerides were not observed in the XIENCE V SPIRIT family of clinical trials.

5.11 Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated that the XIENCE V 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 720 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning or less

The XIENCE V 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 XIENCE V stent.

Stent heating was derived by relating the measured non-clinical, *in vitro* temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil to the local specific absorption rates (SARs) in a digitized human heart model. The maximum whole body averaged SAR was determined by validated calculation. At overlapped lengths up to 68 mm, the XIENCE V stent produced a non-clinical maximum local temperature rise of 3°C at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for 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 XIENCE V 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 XIENCE V stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of XIENCE V 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.
- **Do not induce negative pressure on the delivery system prior to placing the stent across the lesion.** 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 XIENCE V stents has 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 XIENCE V 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 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.

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 Clinical Studies). 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 XIENCE V 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

Everolimus pharmacokinetics (PK) when eluted from the XIENCE V Stent post-implantation has been evaluated in three different substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the US randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The 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 6-1.

Table 6-1: 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; $t_{1/2}$, 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 gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE V stent because of limited systemic exposure to everolimus eluted from XIENCE V (see Section 6.2 Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE V stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods³ listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepin, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra[®]) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit juice

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of XIENCE V 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 (XIENCE V 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 XIENCE V stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies were conducted on the XIENCE V 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 XIENCE V stent is not genotoxic.

³ Certican® Investigator's Brochure. Novartis Pharmaceutical Corporation

In addition, a reproductive toxicity (teratology) study was conducted to demonstrate that implantation of XIENCE V stents in female Sprague-Dawley rats does not affect their fertility or reproductive capability and shows a lack of any reproductive toxicity on their offspring. The XIENCE V stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (XIENCE V 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 XIENCE V 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 XIENCE V stent related studies in pregnant women. Effects of the XIENCE V 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 XIENCE V stent and continued for one year post-implantation. The XIENCE V stent should be used in pregnant women only if potential benefits justify potential risks.

Safety of the XIENCE V 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 XIENCE V 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

Principal XIENCE V safety and effectiveness information is derived from the SPIRIT III clinical trial and is supported by the SPIRIT FIRST and SPIRIT II clinical trials. These studies evaluated XIENCE V EECSS performance 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 EXPRESS²™ Paclitaxel Eluting Coronary Stent System (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 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Enrollment is complete in the RCT 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 clinically-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 1 year 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 1 year 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 RCT⁴ 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 II clinical trial was a randomized, single-blind, 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) were enrolled at 28 sites outside the United States. The primary endpoint was in-stent late loss at 6 months. 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 2 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-blind, 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 6 months on the per-treatment evaluable population, and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 6 months based on IVUS analysis of the per-treatment evaluable population. Follow-up through 3 years 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.

⁴ Includes one subject from the 4.0 mm non-randomized arm

Table 7-1: XIENCE V SPIRIT Clinical Trial Designs

Study Type/Design	SPIRIT III clinical trial		SPIRIT II clinical trial		SPIRIT FIRST clinical trial
	RCT	Registries			
	<ul style="list-style-type: none"> Multi-center Randomized Single-blinded Active-Control 	<ul style="list-style-type: none"> Multi-center Single-arm Open-label 	<ul style="list-style-type: none"> Multi-center Randomized Single-blinded Active-Control 	<ul style="list-style-type: none"> Multi-center Randomized Single-blinded Control 	<ul style="list-style-type: none"> Multi-center Randomized Single-blinded Control
Number of Subjects Enrolled	Total: 1,002 XIENCE V: 668 TAXUS Control: 334	Total: 168 4.0 mm: 80 Japan: 88*	Total: 300 XIENCE V: 225 TAXUS Control: 75	Total: 60 XIENCE V: 30 VISION Control: 30	Total: 60 XIENCE V: 30 VISION Control: 30
Treatment	Up to two <i>de novo</i> lesions in different epicardial vessels	Up to two <i>de novo</i> lesions in different epicardial vessels	Up to two <i>de novo</i> lesions in different epicardial vessels	Single <i>de novo</i> lesion	Single <i>de novo</i> lesion
Lesion Size	RVD: $\geq 2.5 \leq 3.75$ mm Length: ≤ 28 mm	4.0 mm RVD: $> 3.75 \leq 4.25$ mm Length: ≤ 28 mm	RVD: $\geq 2.5 \leq 4.25$ mm Length: ≤ 28 mm	RVD: 3 mm Length: ≤ 12 mm	RVD: 3 mm Length: ≤ 12 mm
Stent Sizes (XIENCE V)	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm	Japan RVD: $\geq 2.5 \leq 4.25$ mm Length: ≤ 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: 3.0 mm Length: 18 mm
Post-procedure Antiplatelet Therapy	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 3 months minimum (or ticlopidine per site standard), Aspirin 1 year
Primary Endpoint	In-segment late loss at 240-days	In-segment late loss at 240-days	In-segment late loss at 180-days	In-stent late loss at 180-days	In-stent late loss at 180-days
Co-Primary Endpoint	TVF at 270-days	None	None	None	None
Clinical Follow-up	30, 180, 240, 270 days, 1 to 5 years	30, 180, 240, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years
Angiographic Follow-up	240 days (N=564)	240 days (All registry)	180-day (all), 2-years (N=152)	180-days, 1-year (all)	180-days, 1-year (all)
IVUS Follow-up	240 days (N=240)	240 days (Japan only)	180-day, 2-years (N=152)	180-days, 1-year (all)	180-days, 1-year (all)
PK Study	US: Minimum 15 subjects with single lesion, maximum 20 with dual lesions Japan: Minimum 10 subjects with single lesion, maximum 20 with dual lesions	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 year reported; 2, 3, 4 and 5 years planned	One and 2 years reported; 3, 4 and 5 years planned	One, 2, and 3 years reported; 4 and 5 years planned	One, 2, and 3 years reported; 4 and 5 years planned

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



8.0 ADVERSE EVENTS

8.1 Observed Adverse Events

Principal adverse event information is derived from SPIRIT III, SPIRIT II and SPIRIT FIRST 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 – Clinical Studies for more complete study design descriptions and results.

**Table 8.1-1: SPIRIT III, II and FIRST:
Principal Adverse Events From Post-Procedure to 1 Year**

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
In Hospital							
TVF ¹	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
MACE ²	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)	0.0% (0/28)
All Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Non-Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
QMI	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
NQMI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Cardiac Death or MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/28)
Ischemia-Driven Revascularization	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven TLR	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)	0.0% (0/28)
Ischemia-Driven Non- TLR TVR	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
Stent Thrombosis ³ (Per Protocol)	0.3% (2/669)	0.0% (0/330)	1.4% (1/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/28)
9 Months⁴							
TVF ¹	7.6% (50/657)	9.7% (31/320)	5.9% (4/68)	4.5% (10/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
MACE ²	5.0% (33/657)	8.8% (28/320)	5.9% (4/68)	2.7% (6/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
All Death	1.1% (7/658)	0.9% (3/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.6% (4/658)	0.6% (2/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.3% (15/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
QMI	0.2% (1/657)	0.0% (0/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.1% (14/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Ischemia-Driven Revascularization	5.3% (35/657)	6.6% (21/320)	1.5% (1/68)	3.6% (8/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	1.5% (1/68)	1.8% (4/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TVR, non TLR TVR	2.9% (19/657)	4.1% (13/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis ³							
Protocol	0.6% (4/654)	0.0% (0/319)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
1 Year⁵							
TVF ¹	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	4.5% (10/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
MACE ²	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	2.7% (6/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	3.6% (8/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven non- TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis ³							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.0% (0/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)

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 is excluded from all data analyses.
 - SPIRIT II and III 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.
 - 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 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.
 - o If non procedural/spontaneous MI, CKMB is greater than or equal to 2 times upper limit of normal
 - o If post PCI, CKMB is greater than or equal to 3 times upper limit of normal
 - o 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 CBAG, 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.
² MACE includes cardiac death, MI and ischemia-driven TLR.
³ See Section 8.2 – Stent Thrombosis Definitions.
⁴ SPIRIT III and SPIRIT FIRST includes 14 day window. SPIRIT III includes 9 month events identified at the 1 year follow-up.
⁵ SPIRIT III and SPIRIT FIRST includes 28 day window.

**Table 8.1-2: SPIRIT III, II and FIRST:
Principal Adverse Events from Latest Follow-up**

	SPIRIT III 1 Year ⁴			SPIRIT II 2 Year ⁴		SPIRIT FIRST 3 Year ⁴	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
TVF ¹	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	10.0% (21/211)	12.3% (9/73)	15.4% (4/26)	32.1% (9/28)
MACE ²	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	6.6% (14/211)	11.0% (8/73)	15.4% (4/26)	25.0% (7/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	3.7% (8/218)	6.5% (5/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.5% (1/218)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non-Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	3.2% (7/218)	5.2% (4/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/211)	0.0% (0/73)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	3.3% (7/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	7.1% (15/211)	9.6% (7/73)	7.7% (2/26)	32.1% (9/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	3.8% (8/211)	6.8% (5/73)	7.7% (2/26)	25.0% (7/28)
Ischemia-Driven non- TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	3.8% (8/211)	4.1% (3/73)	0.0% (0/26)	10.7% (3/28)
Stent Thrombosis ³							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	1.9% (4/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.9% (2/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)

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 is excluded from all data analyses.
- SPIRIT II and III 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.

¹ TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.

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

³ See Section 8.2 – Stent Thrombosis Definitions.

⁴ SPIRIT III, SPIRIT II and SPIRIT FIRST includes 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 following⁵:

- 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)⁶ 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)⁷. 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-up⁸

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

⁵ 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.

⁶ Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.

⁷ 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.

⁸ All data within this Instructions for Use is presented as definite + probable only.

-
- 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
 - 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

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- Abdominal pain
- Acne
- Anemia
- Coagulopathy
- Diarrhea
- Edema
- Hemolysis
- Hypercholesterolemia
- Hyperlipidemia

-
- Hypertension
 - Hypertriglyceridemia
 - Hypogonadism male
 - Infections: wound infection, urinary tract infection, pneumonia, pyelonephritis, sepsis and other viral, bacterial and fungal infections
 - Leukopenia
 - Liver function test abnormality
 - Lymphocele
 - Myalgia
 - Nausea
 - Pain
 - Rash
 - Renal tubular necrosis
 - Surgical wound complication
 - Thrombocytopenia
 - Venous thromboembolism
 - Vomiting

There may be other potential adverse events that are unforeseen at this time.

9.0 XIENCE V 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 EXPRESS²™ Paclitaxel Eluting Coronary Stent System (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 and the Japan arm.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subject subset derived from the RCT⁹ 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 at pre-determined sites.

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

⁹ Includes one subject from the 4.0 mm non-randomized arm

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. 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.

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.

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 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 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 endpoints), Table 9.1.1-2 (Clinical Results), Table 9.1.1-3 (Angiographic and IVUS Results), Figure 9.1.1-1 (TVF Free Survival) and Table 9.1.1-4 (ARC-Defined 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% (50/657) for the XIENCE V arm and 9.7% (31/320) for the TAXUS arm ($p < 0.001$ for non-inferiority).

Table 9.1.1-1: SPIRIT III RCT Primary Endpoints 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% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%] ²	<0.0001 ⁷	Not Pre- specified

Notes:

- N is the total number of subjects; M is the total number of analysis lesions.
 - One in SPIRIT III TAXUS arm subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
 - Analysis results include 9 month events identified at the 1 year 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 1 YEAR (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 & SAFETY						
TVF ²	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]	8.6% (56/653)	11.3% (36/320)	-2.67% [-6.75%, 1.40%]
MACE ³	5.0% (33/657)	8.8% (28/320) ⁷	-3.73% [-7.24%, -0.21%]	6.0% (39/653)	10.3% (33/320)	-4.34% [-8.14%, -0.54%]
EFFICACY						
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	-2.26% [-4.95%, 0.43%]	3.4% (22/653)	5.6% (18/320)	-2.26% [-5.13%, 0.62%]
TLR, CABG	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.0% (0/320)	0.31% [Assump. not met]
TLR, PCI	2.6% (17/657)	5.0% (16/320)	-2.41% [-5.09%, 0.27%]	3.1% (20/653)	5.6% (18/320)	-2.56% [-5.41%, 0.29%]
Ischemia-Driven non-TLR TVR	2.9% (19/657)	4.1% (13/320)	-1.17% [-3.68%, 1.34%]	3.1% (20/653)	4.4% (14/320)	-1.31% [-3.91%, 1.29%]
non-TLR TVR, CABG	0.5% (3/657)	0.6% (2/320)	-0.17% [Assump. not met]	0.6% (4/653)	0.6% (2/320)	-0.01% [Assump. not met]
non-TLR TVR, PCI	2.4% (16/657)	3.4% (11/320)	-1.00% [-3.32%, 1.32%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
SAFETY						
All Death	1.1% (7/658)	0.9% (3/321)	0.13% [Assump. not met]	1.2% (8/655)	1.2% (4/321)	-0.02% [Assump. not met]
Cardiac Death	0.6% (4/658)	0.6% (2/321)	-0.02% [Assump. not met]	0.8% (5/655)	0.9% (3/321)	-0.17% [Assump. not met]
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.14% [Assump. not met]	0.5% (3/655)	0.3% (1/321)	0.15% [Assump. not met]
MI	2.3% (15/657)	3.1% (10/320)	-0.84% [-3.06%, 1.38%]	2.8% (18/653)	4.1% (13/320)	-1.31% [-3.81%, 1.20%]
QMI	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.3% (1/320)	-0.01% [Assump. not met]
NQMI	2.1% (14/657)	3.1% (10/320)	-0.99% [-3.20%, 1.21%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	-0.86% [-3.30%, 1.59%]	3.4% (22/653)	4.7% (15/320)	-1.32% [-4.02%, 1.38%]
Stent Thrombosis – Protocol defined	0.6% (4/654)	0.0% (0/319)	0.61% [Assump. not met]	0.8% (5/647)	0.6% (2/317)	0.14% [Assump. not met]
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% (1/653)	0.0% (0/319)	0.15% [Assump. not met]	0.3% (2/646)	0.6% (2/317)	-0.32% [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 is excluded from all data analyses.
- 9 month and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively.
- 9 months analysis results include 9 month events identified at the 1 year follow-up.
- Assump. not met means that assumption of normal approximation 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

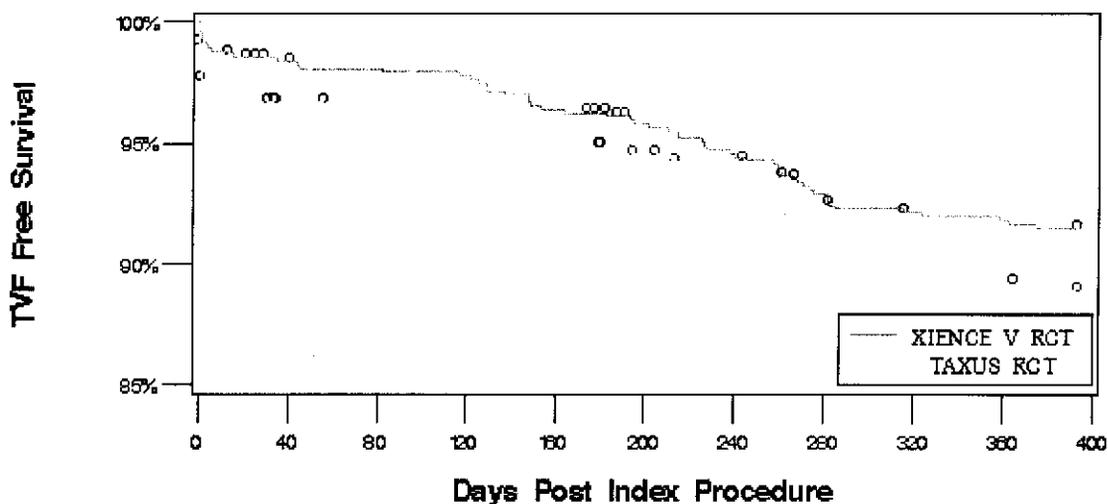
	XIENCE V (N=376) (M_{ANGIO}=427) (M_{IVUS}=181)	TAXUS (N=188) (M_{ANGIO}=220) (M_{IVUS}=93)	Difference [95% CI]¹
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD			
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 month	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 is excluded from all data analyses.
- 8 month time frame includes follow-up window (240 + 28 days).
- Assump. not met means that assumption of normal approximation 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: Survival Free of Target Vessel Failure through 1 Year



TVF	Event Free	Event Rate	P-value ¹
XIENCE V	91.5%	8.5%	0.18
TAXUS	88.9%	11.1%	

Note:

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

¹P-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 1 Year

	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI] ¹
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	1.1% (7/648)	0.6% (2/317)	0.45% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.4% (3/667)	0.0% (0/330)	0.45% [Assump. not met]
Late (> 30 days)	0.5% (3/647)	0.6% (2/317)	-0.17% [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 is excluded from all data analyses.

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

- Assump. not met means that assumption of normal approximation 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 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 compared to the TAXUS arm of the SPIRIT III RCT.

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. Sixty-nine (69) subjects were enrolled in the SPIRIT III 4.0 mm study arm.

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 9.1.2-1 (Primary endpoints), Table 9.1.2-2 (Clinical Results), Table 9.1.2-3 (Angiographic Results), and Table 9.1.2-4 (ARC-Defined 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) for the XIENCE V 4.0 mm arm and 0.28 ± 0.48 mm (134) for the TAXUS arm from the SPIRIT III RCT ($p < 0.0001$ for non-inferiority).

Table 9.1.2-1: SPIRIT III 4.0 mm Primary Endpoints Results

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 is 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 9.1.2-2: SPIRIT III 4.0 mm Clinical Results

	OUTCOMES AT 9 MONTHS XIENCE V (N=69)	OUTCOMES AT 1 YEAR (latest available follow-up) XIENCE V (N=69)
COMPOSITE EFFICACY & SAFETY		
TVF ¹	5.9% (4/68)	5.9% (4/68)
MACE ²	5.9% (4/68)	5.9% (4/68)
EFFICACY		
Ischemia-Driven TLR	1.5% (1/68)	1.5% (1/68)
TLR, CABG	0.0% (0/68)	0.0% (0/68)
TLR, PCI	1.5% (1/68)	1.5% (1/68)
Ischemia-Driven non-TLR TVR	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, CABG	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, PCI	0.0% (0/68)	0.0% (0/68)
SAFETY		
All Death	1.5% (1/68)	1.5% (1/68)
Cardiac Death	1.5% (1/68)	1.5% (1/68)
Non-Cardiac Death	0.0% (0/68)	0.0% (0/68)
MI	4.4% (3/68)	4.4% (3/68)
QMI	0.0% (0/68)	0.0% (0/68)
NQMI	4.4% (3/68)	4.4% (3/68)
Cardiac Death or MI	5.9% (4/68)	5.9% (4/68)
Stent Thrombosis – Protocol defined	1.5% (1/67)	1.5% (1/67)
Acute (< 1 day)	1.4% (1/69)	1.4% (1/69)
Subacute (1 – 30 days)	0.0% (0/69)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)	0.0% (0/67)

Notes:

- 9 months and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively. 9 month analysis includes 9 month events identified at the 1 year 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 9.1.2-3: 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 9.1.2-4: SPIRIT III 4.0 mm ARC defined Definite+Probable Stent Thrombosis Through 1 Year

	XIENCE V (N=69)
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	0.0% (0/67)
Acute (< 1 day)	0.0% (0/69)
Subacute (1 – 30 days)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)

Notes:

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

9.2 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-blind, 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. 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.

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 were 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 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 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 9.2-1 (Primary endpoint), Table 9.2-2 (Clinical Results), Table 9.2-3 (Angiographic and IVUS Results), and Table 9.2-4 (ARC-Defined 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 prespecified 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 9.2-1: 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 total number of analysis lesions.

¹By normal approximation.

²One-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.

³P-value from two-sided t-test.

Table 9.2-2: SPIRIT II Clinical Results

	OUTCOMES AT 6 MONTHS			OUTCOMES AT 2 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 & SAFETY						
TVF ²	3.6% (8/222)	6.5% (5/77)	-2.89% [-8.92%, 3.14%]	10.0% (21/211)	12.3% (9/73)	-2.38% [-10.93%, 6.18%]
MACE ³	2.7% (6/222)	6.5% (5/77)	-3.79% [-9.69%, 2.11%]	6.6% (14/211)	11.0% (8/73)	-4.32% [-12.24%, 3.59%]
EFFICACY						
Ischemia-Driven TLR	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
TLR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
TLR, PCI	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
Ischemia-Driven non-TLR TVR	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.8% (8/211)	4.1% (3/73)	-0.32% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.5% (1/211)	0.0% (0/73)	0.47% [Assump. not met]
non-TLR TVR, PCI	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.3% (7/211)	4.1% (3/73)	-0.79% [Assump. not met]
SAFETY						
All Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.7% (8/218)	6.5% (5/77)	-2.82% [-8.87%, 3.22]
Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	0.5% (1/218)	1.3% (1/77)	-0.84% [Assump. not met]
Non-Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.2% (7/218)	5.2% (4/77)	-1.98% [Assump. not met]
MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
QMI	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
NQMI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
Cardiac Death or MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	3.3% (7/211)	5.5% (4/73)	-2.16% [Assump. not met]
Stent Thrombosis – Protocol defined	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [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]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]

Notes:

- 6 months and 2 year time frames include follow-up window (180 +14 days and 730 + 28 days).

- Assump. not met means that assumption of normal approximation 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 9.2-3: SPIRIT II 180-Day 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]
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]
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]
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]
Late Loss			
In-Stent	0.12 ± 0.29 (237)	0.37 ± 0.38 (86)	-0.25 [-0.34, -0.16]
In-Segment	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
Binary Restenosis			
In-Stent	1.3% (3/237)	3.5% (3/86)	-2.22% [Assump. not met]
In-Segment	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]
IVUS RESULTS			
Neointimal Volume (mm ³)	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	-10.60 [-15.87, -5.32]
% Volume Obstruction	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
Incomplete Apposition			
Post Procedure	6.5% (7/108)	5.6% (2/36)	0.93% [Assump. not met]
6 month	2.9% (3/103)	0.0% (0/39)	2.91% [Assump. not met]
Persistent	2.5% (3/120)	0.0% (0/42)	2.50% [Assump. not met]
Late Acquired	0.0% (0/104)	0.0% (0/39)	0.00% [Assump. not met]

Notes:

- N is the total number of subjects; M is the total number of lesions.
- Assump. not met means that assumption of normal approximation 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 9.2-4: SPIRIT II ARC defined Definite+Probable Stent Thrombosis Through 2 Years

	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI] ¹
ARC Definite+Probable Stent Thrombosis (0 days – 2 years)	0.9% (2/211)	1.4% (1/73)	-0.42% [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 – 2 years)	0.9% (2/211)	0.0% (0/72)	0.95% [Assump. not met]

Note:

– Assump. not met means that assumption of normal approximation 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.

9.3 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-blind 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 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 to 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 9.3-1 (Primary endpoint), Table 9.3-2 (Clinical Results), Table 9.3-3 (Angiographic and IVUS Results), and Table 9.3-4 (ARC-Defined Stent Thrombosis). These analyses were based on the per protocol evaluable population.

The primary superiority 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 9.3-1: 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] ¹	< 0.0001

Note: N is the number of subjects.

¹By normal approximation

²One-tailed p-value by t-test, to be compared to a 5% significance level

Table 9.3-2: SPIRIT FIRST Clinical Results

	OUTCOMES AT 6 MONTHS ¹			OUTCOMES AT 3 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 & SAFETY						
TVF ³	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	15.4% (4/26)	32.1% (9/28)	-16.76% [Assump. not met]
MACE ⁴	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	15.4% (4/26)	25.0% (7/28)	-9.62% [Assump. not met]
EFFICACY						
Ischemia-Driven TLR	3.8% (1/26)	21.4% (6/28)	-17.58% [Assump. not met]	7.7% (2/26)	25.0% (7/28)	-17.31% [Assump. not met]
TLR, CABG	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
TLR, PCI	3.8% (1/26)	17.9% (5/28)	-14.01% [Assump. not met]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]
Ischemia-Driven non-TLR TVR	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	10.7% (3/28)	-10.71% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
non-TLR TVR, PCI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	7.1% (2/28)	-7.14% [Assump. not met]
SAFETY						
All Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Non-Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
QMI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
NQMI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
Cardiac Death or MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
Stent Thrombosis – Protocol defined	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Late (> 30 days)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:

¹ Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

² 6 month and 3 year time frames include follow-up window (180 + 14 days and 1095 + 28 days) respectively.

³ Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

⁴ TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

⁵ MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

Table 9.3-3: 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 month	0.0% (0/ 21)	0.0% (0/ 22)	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 assumption of normal approximation not met due to small sample size or frequency of events.

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

Table 9.3-4: SPIRIT FIRST ARC defined Definite+Probable Stent Thrombosis Through 3 Years

	XIENCE V (N=27)	VISION (N=29)	Difference [95% CI] ¹
ARC Definite+Probable Stent Thrombosis (0 days – 3 years)	0.0% (0/26)	0.0% (0/28)	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 – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:

- Assump. not met means that assumption of normal approximation 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 II AND SPIRIT III POOLED ANALYSIS

In order to better estimate the incidence of low frequency events or outcomes in various specific subject subgroups, a subject-level pooled analysis was conducted of both randomized trials comparing the XIENCE V stent versus the TAXUS stent. Data from the SPIRIT II and SPIRIT III clinical trials were pooled to compare the XIENCE V stent to the TAXUS control stent in 1302 subjects out to 1 year (393 days) of follow-up. These two studies have subjects with similar baseline and angiographic characteristics and the key elements of study design including inclusion and exclusion criteria and endpoint definitions are comparable. The subject level data were included until the latest available time point of 1 year for each trial. Table 9.4-1 shows the subject disposition over time for the SPIRIT II and III RCT. The percentage of the total number of subjects that were enrolled in the studies and completed their 1 year follow-up was 96.5%.

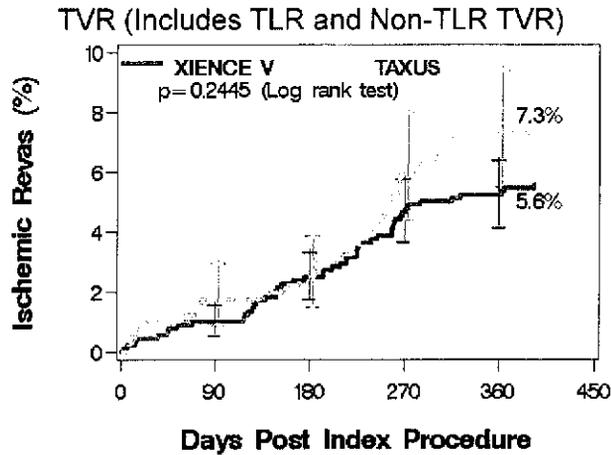
Table 9.4-1: Subject Disposition Table (N=1302; SPIRIT II and SPIRIT III RCT)

	30-Day Follow-up		9-Month Follow-up		1-Year Follow-up	
	XIENCE V (890)		XIENCE V (873)		XIENCE V (866)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	223	667	220	653	220	646
	TAXUS (407)		TAXUS (395)		TAXUS (392)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	77	330	76	319	76	316

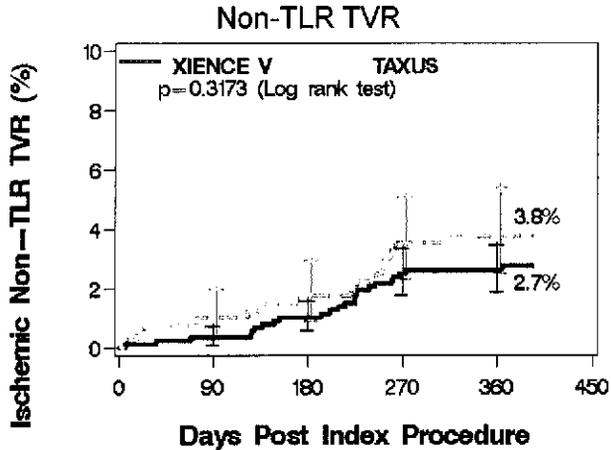
It is acknowledged that these retrospective pooled analyses are exploratory and hypothesis-generating. Definitive proof of the presence or absence of any differences between such subgroups requires prospectively powered assessment in dedicated clinical trials. The pooled analysis from SPIRIT II and SPIRIT III trials includes subjects from single-blind trials with similar inclusion and exclusion criteria in 1,302 subjects with 1,506 lesions.

As shown in Figure 9.4-1, at one year, the analyses of pooled trials suggest a reduction in the rates of TVR and TLR for the XIENCE V stent compared to the TAXUS stent through one year. All CI bars represent a 1.5 standard error.

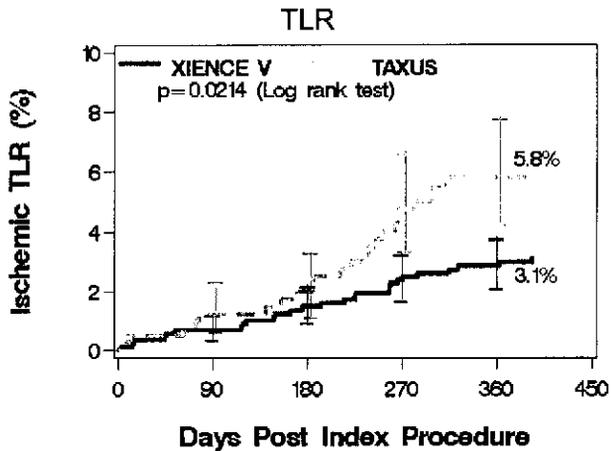
Figure 9.4-1: Kaplan Meier Hazard Curves for Time to First TVR or TLR Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



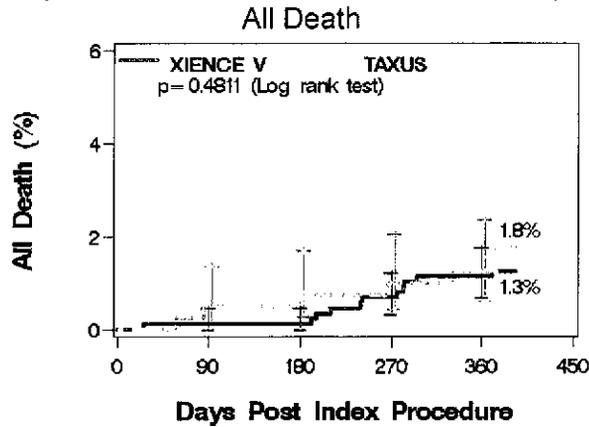
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



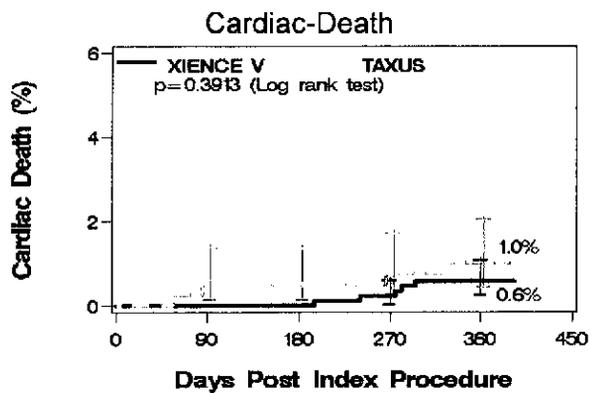
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of all death, cardiac death, and non-cardiac death through 1 year are shown in Figure 9.4-2.

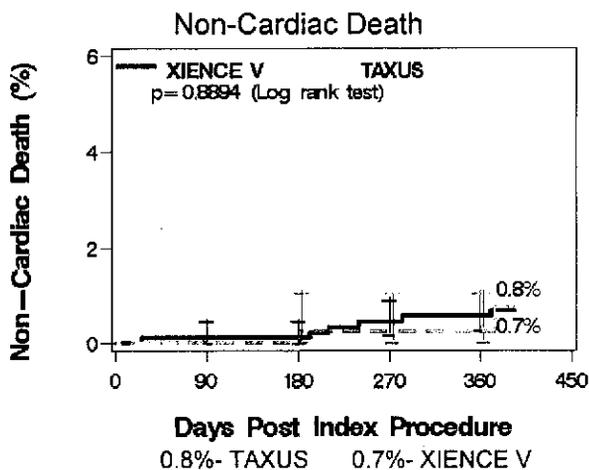
Figure 9.4-2: Kaplan Meier Hazard Curves for Time to Death through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



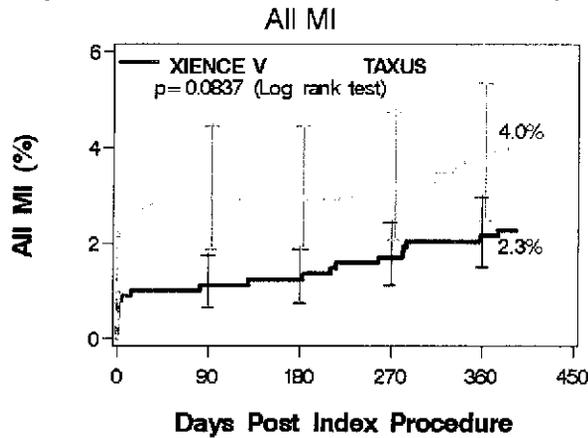
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



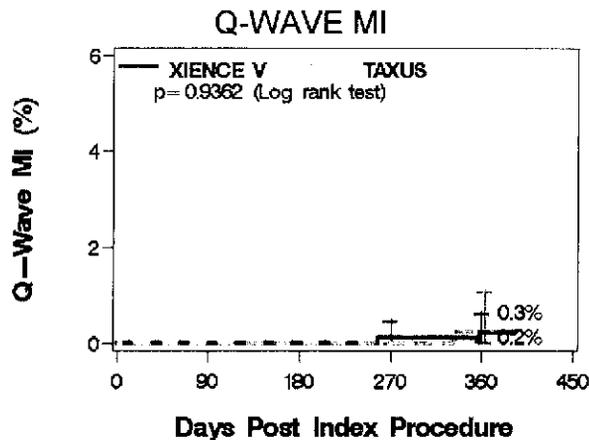
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of MIs through 1 year are shown in Figure 9.4-3.

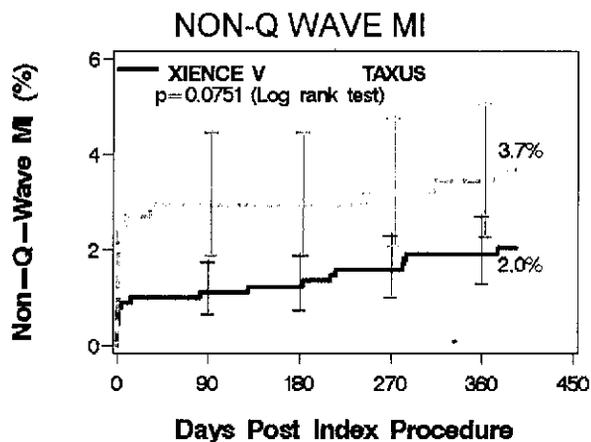
Figure 9.4-3: Kaplan Meier Hazard Curves for Time to First MI Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.1 Stent Thrombosis in SPIRIT II and SPIRIT III Pooled Analysis

The results for the pooled analysis rates of stent thrombosis at one year are shown below in Figure 9.4.1-1. Rates were low for both treatments in this pooled analysis and consistent with the published literature¹⁰. The rates of stent thrombosis were evaluated based on the SPIRIT II and III protocol defined definition and the ARC definition for definite + probable thrombosis (see definitions above in Section 8.2). These data are presented in table 9.4.1-1.

Table 9.4.1-1 Pooled Results for Stent Thrombosis through 1 year (SPIRIT II and SPIRIT III RCT)

	XIENCE V (N=892)	95% CI ¹	TAXUS (N=410)	95% CI ¹
0 - 30 days				
Protocol	0.3% (3/890)	[0.07%, 0.98%]	0.0% (0/407)	[0.00%, 0.90%]
ARC (definite + probable)	0.4% (4/890)	[0.12%, 1.15%]	0.2% (1/407)	[0.01%, 1.36%]
31 days - 1 year				
Protocol	0.3% (3/866)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.3% (3/867)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
0 - 1 year				
Protocol	0.7% (6/867)	[0.25%, 1.50%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.8% (7/868)	[0.32%, 1.65%]	0.8% (3/394)	[0.16%, 2.21%]

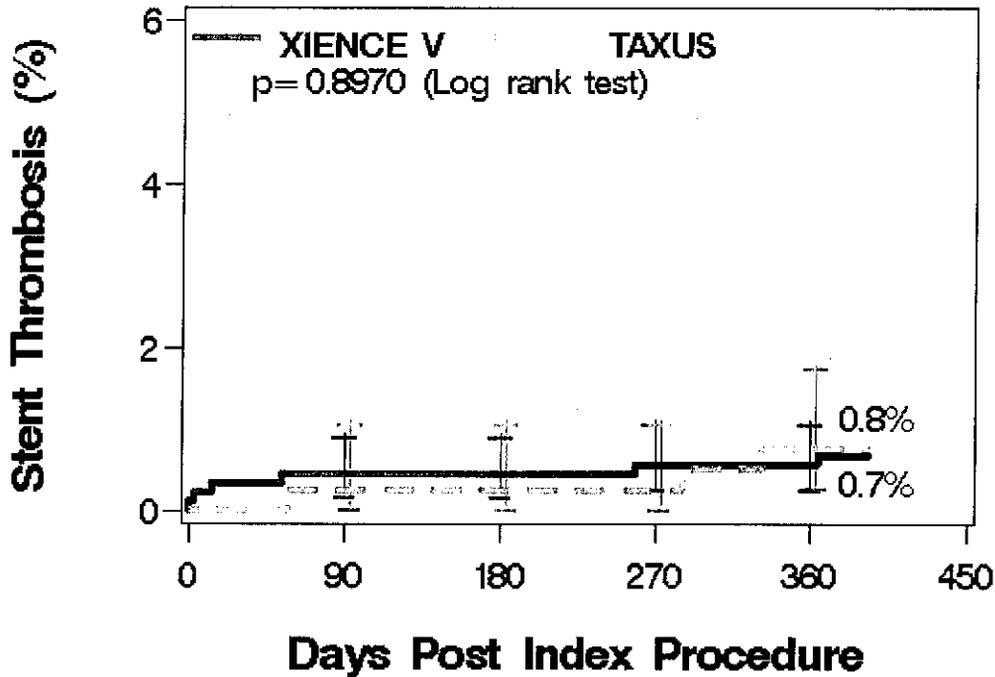
Note: timeframe for 1 year includes the follow-up window (365 + 28 days).

¹ By Clopper-Pearson Exact Confidence Interval

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

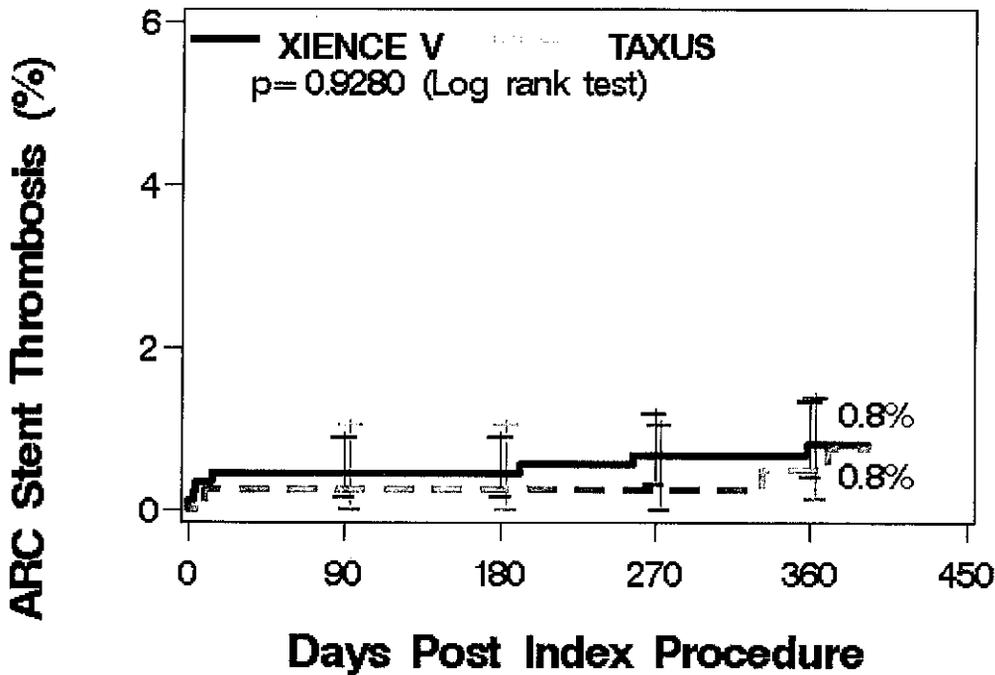
Figure 9.4.1-1: Kaplan Meier Hazard Curves for Time to First Stent Thrombosis Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

Protocol Defined Stent Thrombosis



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

ARC Defined Stent Thrombosis (Definite + Probable)



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

9.4.2 Diabetics in SPIRIT II and SPIRIT III Pooled Analysis

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 or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in diabetic individuals.

Table 9.4.2-1 shows the clinical outcomes through 1 year in subjects pooled from SPIRIT II and III. The randomization was stratified by history of diabetes to assure a balance between the XIENCE V and TAXUS treatment arms. In XIENCE V patients, there were numerically higher event rates in diabetics compared with non-diabetics. The event rates for TAXUS in diabetics were lower than the event rates for TAXUS non-diabetics. Given the relatively small sample size of the diabetic population and potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

Table 9.4.2-1: Clinical Results in Diabetics and Non-Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Non-Diabetics XIENCE V (N=643)	Non-Diabetics TAXUS (N=296)	All Diabetics XIENCE V (N=249)	All Diabetics TAXUS (N=110)
TLR	2.5% (16/629)	7.6% (22/290)	4.5% (11/244)	1.0% (1/104)
TVR(CABG/PCI), non TL	2.5% (16/629)	4.1% (12/290)	3.3% (8/244)	2.9% (3/104)
All Death	1.0% (6/631)	2.4% (7/291)	2.0% (5/246)	0.0% (0/104)
Cardiac Death	0.3% (2/631)	1.4% (4/291)	1.2% (3/246)	0.0% (0/104)
Non-Cardiac Death	0.6% (4/631)	1.0% (3/291)	0.8% (2/246)	0.0% (0/104)
MI	1.4% (9/629)	4.5% (13/290)	4.5% (11/244)	2.9% (3/104)
Cardiac Death or MI	1.7% (11/629)	5.2% (15/290)	5.3% (13/244)	2.9% (3/104)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.0% (3/287)	1.3% (3/240)	0.0% (0/104)
ARC definite + probable	0.3% (2/627)	0.7% (2/287)	2.1% (5/241)	1.0% (1/104)

Table 9.4.2-2: Clinical Results in Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population – XIENCE V Subjects)

	Non-Diabetics (N=643)	All Diabetics (N=249)	Insulin-Dependent Diabetics (N=63)	Non-Insulin-Dependent Diabetics (N=186)
TLR	2.5% (16/629)	4.5% (11/244)	6.5% (4/62)	3.8% (7/182)
TVR(CABG/PCI), non TL	2.5% (16/629)	3.3% (8/244)	1.6% (1/62)	3.8% (7/182)
All Death	1.0% (6/631)	2.0% (5/246)	3.2% (2/63)	1.6% (3/183)
Cardiac Death	0.3% (2/631)	1.2% (3/246)	1.6% (1/63)	1.1% (2/183)
Non-Cardiac Death	0.6% (4/631)	0.8% (2/246)	1.6% (1/63)	0.5% (1/183)
MI	1.4% (9/629)	4.5% (11/244)	9.7% (6/62)	2.7% (5/182)
Cardiac Death or MI	1.7% (11/629)	5.3% (13/244)	9.7% (6/62)	3.8% (7/182)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.3% (3/240)	1.6% (1/61)	1.1% (2/179)
ARC definite + probable	0.3% (2/627)	2.1% (5/241)	1.6% (1/61)	2.2% (4/180)

9.4.3 Dual Vessel treatment in SPIRIT II and SPIRIT III Pooled Analysis

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. Although subjects requiring both single and dual vessel treatment were included in the SPIRIT family of trials,

there were no pre-specified hypothesis or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in dual vessel individuals.

Table 9.4.3-1 shows the clinical outcomes through 1 year in subjects pooled from SPIRIT II and III. The randomization was stratified by the number of vessels treated to assure a balance between the XIENCE V and TAXUS treatment arms. Numerically lower event rates were observed for XIENCE V and TAXUS in single compared to dual vessel treatment. However, given the small sample size for dual vessel treatment, no conclusions can be drawn from this post-hoc analysis.

Table 9.4.3-1: Clinical Results in Single and Dual Vessel Treatment through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

	Single Vessel XIENCE V (N=752)	Single Vessel TAXUS (N=344)	Dual Vessel XIENCE V (N=140)	Dual Vessel TAXUS (N=65)
TLR	2.9% (21/735)	4.5% (15/333)	4.3% (6/138)	12.5% (8/64)
TVR(CABG/PCI), non TL	2.3% (17/735)	2.1% (7/333)	5.1% (7/138)	12.5% (8/64)
All Death	1.5% (11/739)	1.2% (4/333)	0.0% (0/138)	4.6% (3/65)
Cardiac Death	0.7% (5/739)	0.6% (2/333)	0.0% (0/138)	3.1% (2/65)
Non-Cardiac Death	0.8% (6/739)	0.6% (2/333)	0.0% (0/138)	1.5% (1/65)
MI	1.9% (14/735)	3.0% (10/333)	4.3% (6/138)	9.4% (6/64)
Cardiac Death or MI	2.4% (18/735)	3.3% (11/333)	4.3% (6/138)	10.9% (7/64)
Stent Thrombosis				
Protocol defined	0.3% (2/729)	0.6% (2/332)	2.9% (4/138)	1.6% (1/62)
ARC definite + probable (TLR not censored)	0.5% (4/730)	0.6% (2/332)	2.2% (3/138)	1.6% (1/62)

10.0 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the XIENCE V 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 XIENCE V 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 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 XIENCE V Everolimus Eluting Coronary Stent System (provided to physician, on-line at www.XIENCEV.com/PatientGuide, or by calling customer service 1-800-227-9902).
- 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) XIENCE V Everolimus Eluting Coronary Stent System, one (1) Flushing tool, (for the XIENCE V EECSS Rapid Exchange (RX) Stent System), one (1) Stent Implant Card, one (1) Patient Information Guide.

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 XIENCE V 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 XIENCE V Rapid Exchange (RX) EECSS, 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, XIENCE V 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: If air is seen in the shaft, repeat *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 XIENCE V 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, Delivery 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 resistance** be felt at any time 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, Delivery 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 XIENCE V 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 XIENCE V 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 under-dilated.

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

<u>Nominal Stent Diameter</u>	<u>Dilatation Limit</u>
2.5 mm to 3.0 mm	3.5 mm
3.5 mm to 4.0 mm	4.5 mm

7. If more than one XIENCE V 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 XIENCE V 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, Delivery 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 under-dilated.**

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.

<u>Nominal Stent Diameter</u>	<u>Dilatation Limit</u>
2.5 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 XIENCE V Stent Compliance
Nominal pressure for each diameter indicated by bold font.

Pressure		Stent ID (mm) by System Size				
(atm)	(MPa)	2.5 mm	2.75 mm	3.0 mm	3.5 mm	4.0 mm
8	0.81	2.46	2.74	2.90	3.46	3.86
9	0.91	2.52	2.81	2.97	3.55	3.95
10	1.01	2.58	2.87	3.04	3.63	4.03
11	1.11	2.63	2.92	3.10	3.69	4.10
12	1.22	2.68	2.97	3.15	3.75	4.17
13	1.32	2.72	3.01	3.19	3.80	4.23
14	1.42	2.75	3.05	3.23	3.84	4.28
15	1.52	2.78	3.08	3.26	3.89	4.33
16 (RBP)*	1.62	2.81	3.11	3.30	3.93	4.37
17	1.72	2.84	3.14	3.33	3.97	4.42
18	1.82	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 Abbott Vascular, Cardiac Therapies representative.

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

16.0 PATENTS

This product and/or its use are covered by one or more of the following United States patents: 5,040,548 ; 5,061,273 ; 5,154,725 ; 5,234,002 ; 5,242,396 ; 5,350,395 ; 5,451,233 ; 5,496,346 ; 5,514,154 ; 5,569,295 ; 5,603,721 ; 5,636,641 ; 5,649,952 ; 5,728,158 ; 5,735,893 ; 5,759,192 ; 5,780,807 ; 5,868,706 ; 6,056,776 ; 6,131,266 ; 6,179,810 ; 6,273,911 ; 6,309,412 ; 6,312,459 ; 6,369,355 ; 6,419,693 ; 6,432,133 ; 6,482,166 ; 6,485,511 ; 6,629,991 ; 6,629,994 ; 6,651,478 ; 6,656,220 ; 6,736,843 ; 6,746,423 ; 6,753,071 ; 6,818,247 ; 6,827,734 ; 6,887,219 ; 6,887,510 ; 6,890,318 ; 6,908,479 ; 6,921,411 ; 6,929,657 ; 6,939,373 ; 6,957,152. Other US 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, do not re-sterilize	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		

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Patient Information Guide, XIENCE V™

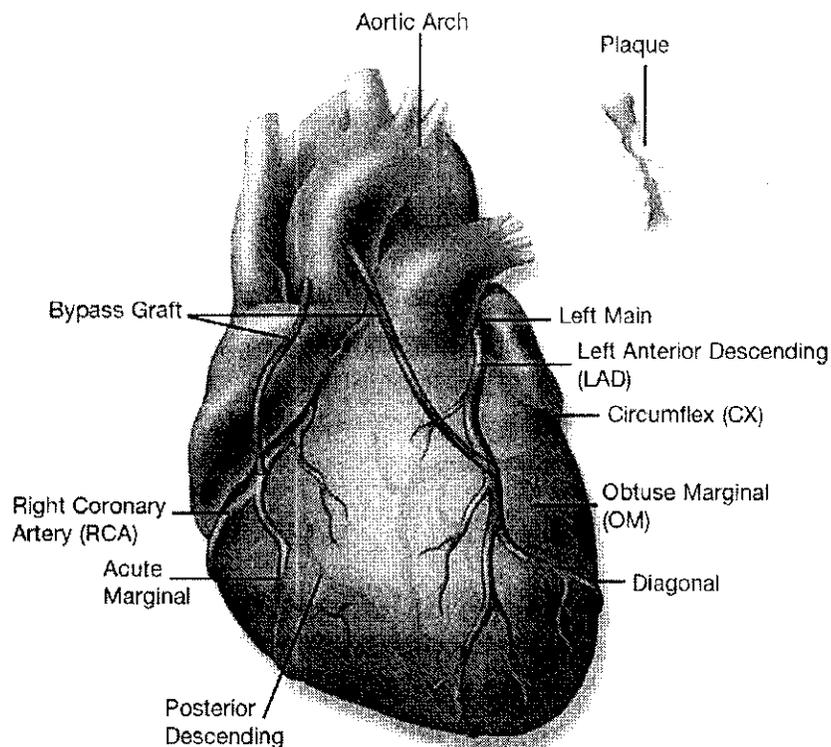
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Coronary Vasculature



Coronary Artery Disease (CAD)

Your Heart

Your heart is a muscle that pumps blood throughout your body. The blood carries oxygen and nutrients that your body needs to work correctly. For the heart to be able to function properly, it also needs a constant supply of oxygen-filled blood. The vessels that supply this blood to the heart are called coronary arteries. If these arteries become blocked or narrowed, treatment may be required to restore blood flow and the vital supply of oxygen to the heart.

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What is Coronary Artery Disease (CAD)?

CAD is the most common form of heart disease. It is a condition that occurs when the arteries that supply oxygen-rich blood and nutrients to the heart muscle become narrowed or blocked by a gradual build-up of “plaque.” Plaque is made up of fatty deposits (cholesterol), white blood cells, calcium, and other substances that collect over time in the wall of a coronary artery. As the plaque narrows the opening (lumen) of a coronary artery, it makes it difficult for adequate quantities of blood to flow to the heart muscle. This process is called “atherosclerosis.” Gradual reduction of blood flow to the heart muscle can cause chest pain (angina). A heart attack (myocardial infarction) can occur if the artery suddenly becomes completely blocked, usually by a blood clot that forms over ruptured (broken) plaque. Heart attacks cause irreversible damage to the heart muscle. The first symptom of CAD can also be sudden death.

Improved medical treatment, combined with earlier diagnosis, and increased public awareness of the symptoms and risk factors that contribute to this disease are helping to decrease the death rate from CAD.

What are the Symptoms of CAD?

Two common symptoms of CAD are chest pain, also known as angina, and shortness of breath, which are caused by the reduction of blood flow to the heart muscle. If plaque build-up does not reduce blood flow excessively, there may be no noticeable symptoms at rest, but symptoms such as heaviness in the chest may occur with increased activity or stress.

Other symptoms that may be experienced are:

- Pain in the jaw or neck
- Pain radiating to the arms or back
- Heartburn
- Nausea
- Vomiting
- Heavy sweating

When blood flow is significantly reduced and the heart muscle does not receive enough blood to meet its needs, severe symptoms such as chest pain (angina pectoris), heart attack (myocardial infarction), or heart rhythm disturbances

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(arrhythmias) may occur.

There are some patients who report no symptoms of CAD. It is possible to have a heart attack without experiencing any symptoms.

Recent research has shown that some women experience different CAD symptoms from men and are less likely than men to report chest pain, heaviness in the chest, or chest discomfort during a heart attack. Women may notice other early symptoms, such as unusual tiredness or sleep disturbances up to one month prior to a heart attack. These differences in symptoms may cause some women to delay seeking help or treatment.

What are the Risk Factors of CAD?

Two main risk factors for CAD are:

- Increasing age (over age 65)
- Being male or a menopausal female¹

Other risk factors that may increase your chances of developing CAD are:

- Family history of heart disease (close relatives with heart disease at a young age)
- Diabetes
- High blood cholesterol levels
- Smoking
- High blood pressure
- Stress
- Obesity (being overweight)
- High fat diet
- Lack of exercise

¹Menopausal women begin to develop and die of heart disease at a rate equal to men. Menopause is the transition in a woman's life when production of the hormone estrogen in the body falls permanently to very low levels, the ovaries stop producing eggs, and menstrual periods stop.

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How Can My Doctor Tell if I Have CAD?

If your doctor suspects that you have CAD or if you have symptoms of the disease, he/she will ask you about your risk factors and your symptoms. A complete physical exam and blood tests to identify injury to your heart muscle will also be completed. In addition, some of the tests used to make the diagnosis are:

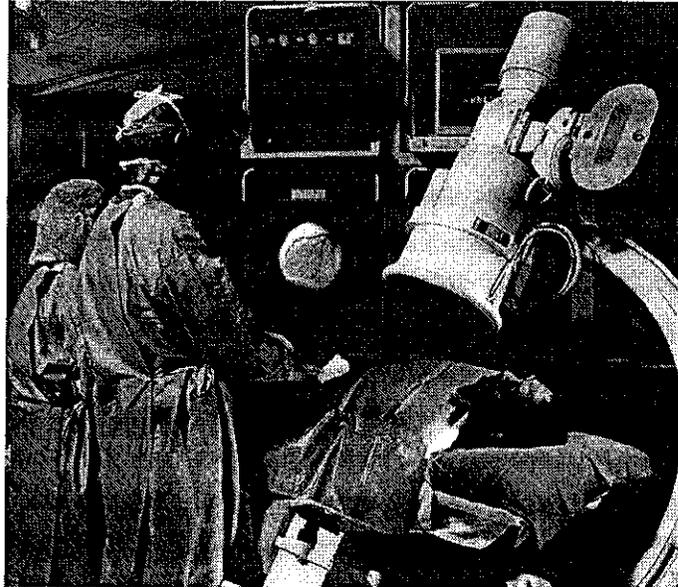
Electrocardiogram (ECG/EKG) is a commonly used test that records your heart's electrical activity and can show certain problems such as abnormal heartbeats or damage to the heart muscle. An ECG can be done at rest or while you are walking or running on a treadmill or pedaling a stationary bicycle (Stress ECG).

Stress Tests are used to evaluate your heart rate, heart rhythm, and ECG while you are exercising. The results of a stress test can help your doctor determine the areas of heart muscle which are affected by lack of blood flow due to CAD.

Echocardiography is an exam of the heart using sound waves.

Coronary Angiogram or Heart Catheterization is a procedure carried out in the cardiac catheterization laboratory (cath lab) by a cardiologist. Angiography is a procedure in which coronary arteries are visualized using X-rays. A catheter (long, thin, hollow tube) is inserted into an artery in the groin or arm. The tip of this tube is positioned at the beginning of the arteries supplying blood to the heart, and a special fluid called contrast dye is injected through the tube to visualize the blood vessels on X-rays so that pictures, called angiograms, can be taken. These angiograms allow the doctor to see any blockage and/or narrowings in your coronary arteries and determine their severity.

Using the information gathered from one or more of these tests, your doctor is better able to decide the best treatment plan for you.



Cardiac Catheterization Laboratory

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Your Treatment Options

Once a diagnosis has been made, your doctor will recommend the most appropriate form of treatment, depending on the condition and severity of your CAD. CAD can be managed by a combination of changes in lifestyle (eating a healthy, low-saturated fat diet, regular exercise, and quitting smoking) and medical treatment. Your treatment may include medications to relieve your chest pain and/or to expand the coronary arteries, increasing blood flow to your heart. However, because medicine alone may not clear blocked arteries, you may need more treatment, including surgery, angioplasty, and/or stenting to treat your symptoms.

Your doctor will explain the risks and benefits of your treatment options and answer any questions you or your family may have. You are encouraged to discuss your treatment options with your doctor.

Surgery

Coronary artery bypass grafting is a common surgical procedure that removes a section of artery or vein from another part of your body. This vessel is then connected (grafted) to the coronary artery at the blockage site. This creates a new path for blood to flow around (bypass) the blocked artery and to your heart. Often, several blocked arteries are bypassed during the same operation. Most coronary bypass patients remain in the hospital for about a week, followed by a recovery period at home.

Angioplasty

Angioplasty is a procedure used to open blocked arteries. You may also hear it referred to as PTCA (Percutaneous Transluminal Coronary Angioplasty). This procedure is performed under local anesthetic in a cardiac catheterization laboratory. A catheter with a small balloon mounted on the end is passed into the coronary artery. The catheter is then positioned at the narrowed portion of the artery and the balloon is inflated. As the balloon inflates, it pushes out against the wall of the coronary artery and compresses the plaque. The balloon is then deflated and the catheter is removed from the artery. This opens the narrowing in the coronary artery and improves the blood flow to the heart muscle. In balloon angioplasty, no permanent device remains in the artery after the balloon catheter is removed. Balloon angioplasty can be performed with a balloon alone or can involve placement of a permanent device called a stent, within the coronary artery.

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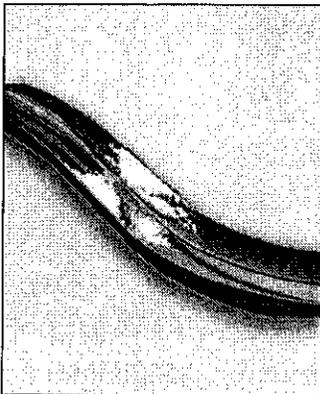
Although balloon angioplasty enlarges the lumen of coronary arteries, many patients develop re-narrowing of the vessel in the months following the procedure. This process is called restenosis, and it is caused by the growth of scar tissue within the coronary artery.

Step 1: The doctor guides a catheter with a small balloon through the blood vessel to the narrowed section of the artery. By watching the progress of this catheter on the fluoroscope (an X-ray device that creates real-time images of the internal structures of the body that can be viewed on a TV monitor), the doctor is able to maneuver it into the blocked coronary artery.

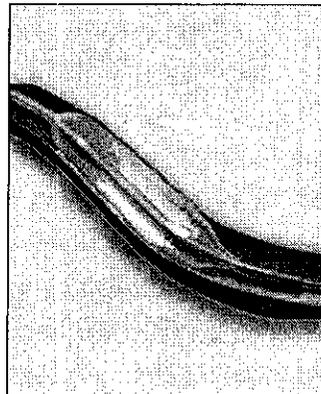
Step 2: The balloon is inflated, pushing out against the wall of the artery and compressing the plaque. The balloon is deflated and the catheter is removed.

Step 3: The inside of the blood vessel is now larger and the blood flow is improved.

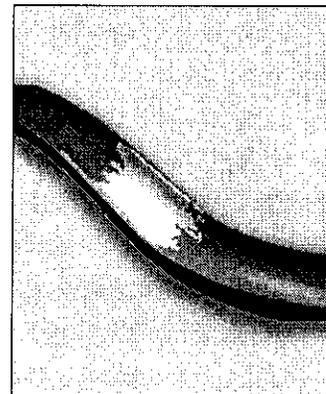
Step 1



Step 2



Step 3



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Coronary Artery Stents

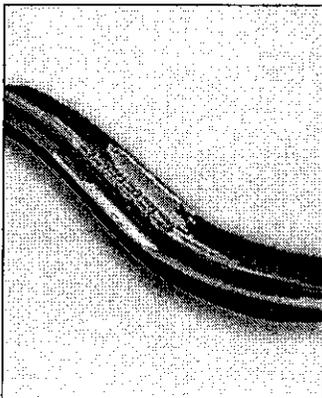
Coronary artery stents are devices (small metallic mesh tubes) that are placed over a balloon catheter and delivered to the narrowed portion of the coronary artery. The balloon is used to expand the stent. The stent presses against the narrowed vessel wall holding the vessel open. This makes a wider channel to improve blood flow to the heart muscle. This may be followed by repeat balloon inflations within the stent to achieve the result desired by your doctor. Once the balloon has been deflated and withdrawn, the stent stays in place permanently, holding the coronary artery open. The inner lining of the artery grows over the surface of the stent, making the stent a permanent part of your artery.

Step 1: The doctor maneuvers the catheter into the blocked artery and inflates the balloon.

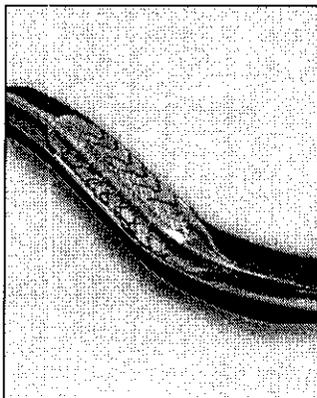
Step 2: The stent expands against the vessel wall as the balloon is inflated.

Step 3: Once the balloon has been deflated and the catheter is withdrawn, the stent stays in place permanently, holding the blood vessel open and improving blood flow.

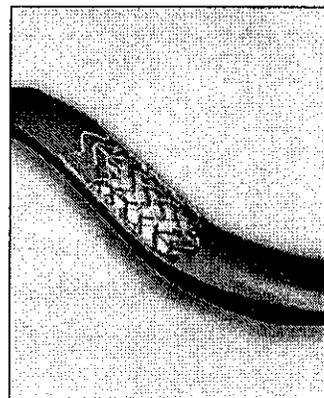
Step 1



Step 2



Step 3



Coronary artery stents are less invasive than bypass surgery. Stenting involves a shorter hospital stay — usually one to three days — and faster recovery than surgery. However, restenosis can also occur in some patients who receive stents (in-stent restenosis) due to the build-up of scar tissue within the stent leading to narrowing of the stent lumen.

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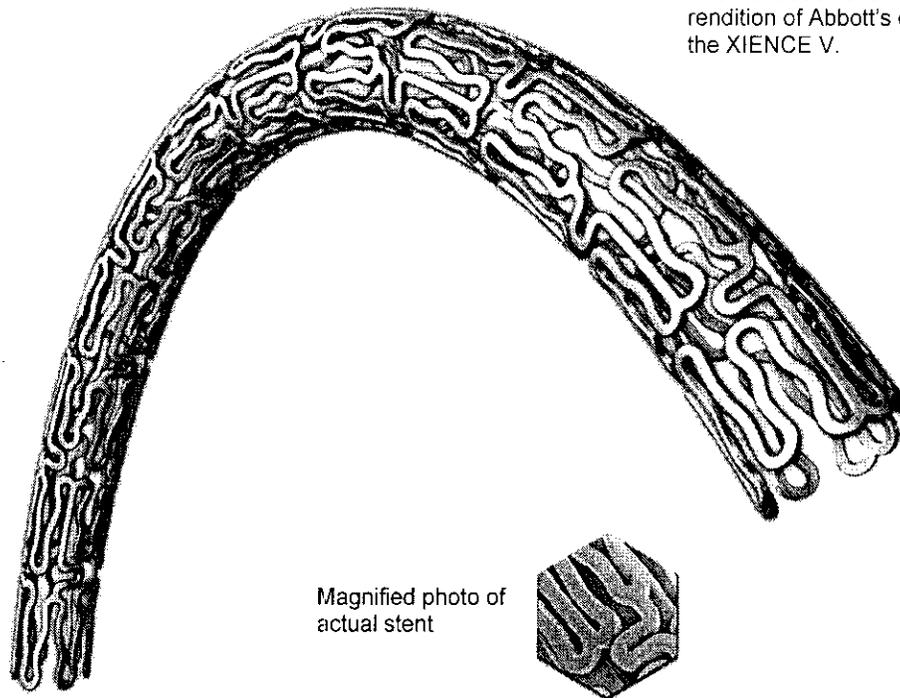
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Drug Eluting Stents (DES)

To help prevent restenosis, “drug-eluting” stents have been developed. These stents provide the same structural support as uncoated stents, but they also have a drug coated on them. The drug is released over time, helping to prevent restenosis by limiting the overgrowth of normal tissue within the stent.

XIENCE V™ Everolimus Eluting Coronary Stent System

The illustration shown is an artist's rendition of Abbott's drug eluting stent, the XIENCE V.



Magnified photo of actual stent

Caution: Federal law restricts this device to sale by or on the order of a physician

The XIENCE V stent is designed to prevent re-narrowing within the stent (in-stent restenosis). It consists of a medical grade cobalt chromium stent with a thin coating of a drug called everolimus on its surface. This stent is based on the design of the clinically proven MULTI-LINK VISION® stent and provides mechanical support to the artery while everolimus is slowly released into the artery wall around the stent from a thin polymer (a type of plastic) coating. The polymer coating helps control the release of everolimus into the arterial wall. The

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polymer used on the XIENCE V stent has a long history of being used in medical products in contact with blood. The release of everolimus is intended to limit the overgrowth of tissue within the coronary stent.

Contraindications

- If you have a known hypersensitivity (allergy) or contraindication to everolimus or structurally-related compounds cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers
- If you cannot take aspirin or blood-thinning medications (also called antiplatelet or anticoagulant therapy)
- If your physician decides that the coronary artery blockage will not allow complete inflation of the angioplasty balloon or proper placement of the stent

Potential Adverse Events Associated with the XIENCE V Stent

The risk of using the XIENCE V stent is similar to those that are associated with standard stent procedures. If the stent clots, you may need another angioplasty procedure. It may also lead to a heart attack, the need for urgent bypass surgery, or death. Even with successful stent implants, there is a chance of re-narrowing of your coronary artery. This may require further treatments, such as repeat angioplasty and/or bypass surgery, to reopen the artery and to increase blood flow to the heart. The risks from using balloon catheters after stent implants are similar to the risks that may occur during the initial stent implant. These may be serious enough to require surgery or cause death.

Other risks from these devices are the same as treatment procedures for a narrowed coronary artery. Some problems associated with standard balloon angioplasty and stenting include, but are not limited to:

Common Risks

- Bruise or bleeding at the catheter insertion site in the groin or arm
- Pain at the catheter insertion site
- Irregular heartbeats
- Chest pains during and after the procedure
- Spasm of the coronary artery
- Decreased or increased blood pressure

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Rare Risks

- Tearing, puncture, or rupture of the coronary artery
- Air, pieces of devices, or fragments of clots blocking the coronary or peripheral arteries
- Complete blockage of the coronary artery, which may require a repeat procedure to reopen the coronary artery
- Compression of the heart due to accumulation of blood around the heart
- Re-narrowing of the coronary artery
- Heart attack
- Damage to the stent or injury to the coronary artery, requiring emergency heart surgery
- Bleeding, requiring transfusion or surgery
- Allergic reaction (may include X-ray dye, cobalt, chromium, nickel, tungsten, everolimus, acrylic, and fluoropolymer)
- Infection
- Nerve injury
- Kidneys fail to function normally
- Aneurysm (weakening of a portion of the wall of a blood vessel)
- Shock
- Stroke
- Death

Potential adverse events related to taking everolimus daily by mouth (based on long-term everolimus drug studies in organ transplant patients) may include: Acne, decreased red or white blood cells, blood clotting abnormalities, diarrhea, water retention in the body, destruction of red blood cells, increased blood cholesterol, increased fat in the blood, increased blood pressure, decreased functioning of sexual organs in men, infections, liver function test abnormality, white blood cell abnormalities, nausea, pain, rash, destruction of the kidney tubules, surgical wound complication, decreased platelet cell count, blood clot in the vein, or vomiting.

Exposure to drug and polymer on the XIENCE V stent is directly related to the number and lengths of the stents implanted. The use of multiple XIENCE V stents will result in you receiving larger amounts of drug and polymer. It should be noted that a kidney transplant patient usually receives a daily dose of the drug

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everolimus by mouth that is about seven times more than the maximum dose of the drug contained on one XIENCE V stent.

Everolimus, when given by mouth daily to organ transplant patients, may interact with other drugs or substances. Please tell your physician about any medications you are taking.

The XIENCE V SPIRIT Family of Clinical Trials

There have been three clinical trials thus far that together have shown the safety and effectiveness of the XIENCE V drug eluting stent in patients with coronary artery disease. A short description of these trials, known as the XIENCE V SPIRIT Family of Trials, is detailed below:

SPIRIT FIRST

SPIRIT FIRST was the first clinical trial. This study had 60 patients and was performed outside the United States. The purpose of the study was to compare the XIENCE V stent that is coated with a drug to that of an approved metallic stent that is not coated with a drug. There were 28 patients who received the XIENCE V stent and 32 patients who received the metallic stent (patients who received the metallic stent are also known as the "control" group).

After six months, the XIENCE V stent was significantly better than the metallic stent at reducing the re-narrowing of the artery where the stent was placed. After three years, patients who had received the XIENCE V stent had fewer major adverse cardiac events (15.4%) compared to patients who received the metallic stent (25.0%).

SPIRIT II

The SPIRIT II clinical trial was the second study of the XIENCE V stent. The purpose of the study was to compare the XIENCE V stent to an approved drug-eluting stent, called TAXUS® EXPRESS²™ (TAXUS stent). The SPIRIT II study was conducted outside of the United States.

After six months, the XIENCE V stent was significantly better than the TAXUS stent at reducing the re-narrowing of the artery where the stent was placed. At two years, patients who had received the XIENCE V stent had a rate of major adverse cardiac events (6.6%) that was comparable to the TAXUS stent (11.0%).

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SPIRIT III

SPIRIT III was the third clinical study of the XIENCE V stent. This was a much bigger study than either the SPIRIT FIRST or SPIRIT II studies, and was conducted in the United States. In one part of this study, 1002 patients were given either the XIENCE V stent or the TAXUS® stent. There were 669 patients who received the XIENCE V stent and 333 patients who received the TAXUS stent.

After eight months, the XIENCE V stent was significantly better than the TAXUS stent at reducing the re-narrowing of the artery where the stent was placed. At two years, patients who had received the XIENCE V stent had a rate of major adverse cardiac events (7.7%) that was comparable to the TAXUS stent (13.8%).

For patients treated with the XIENCE V stent in ways not studied in these clinical trials, clinical results may vary. Very long-term (beyond 24 months) risks and benefits associated with the XIENCE V stent are currently unknown.

Your Drug Eluting Stent Procedure

How Do I Prepare for My Procedure?

In the days prior to your treatment, make sure you:

- Take all of your prescribed medicines
- Tell your doctor if you are taking any other medication
- Tell your doctor if, for any reason, you cannot take aspirin and/or Plavix®
- Make sure your doctor knows about any allergies you have
- Refrain from eating and drinking after midnight on the night before your treatment
- Follow all instructions given to you by your doctor or nurse

You may be given a mild sedative to help you relax, but you will not be put to sleep. There are two reasons for this. First, most people find they experience little to no discomfort from the procedure. Secondly, your doctor may need to ask you to take a deep breath while X-rays are being taken, to improve the quality of the pictures.

The procedure usually lasts about 90 minutes, during which time your doctor will ask you to remain very still. For the most part, you will be comfortable, but you

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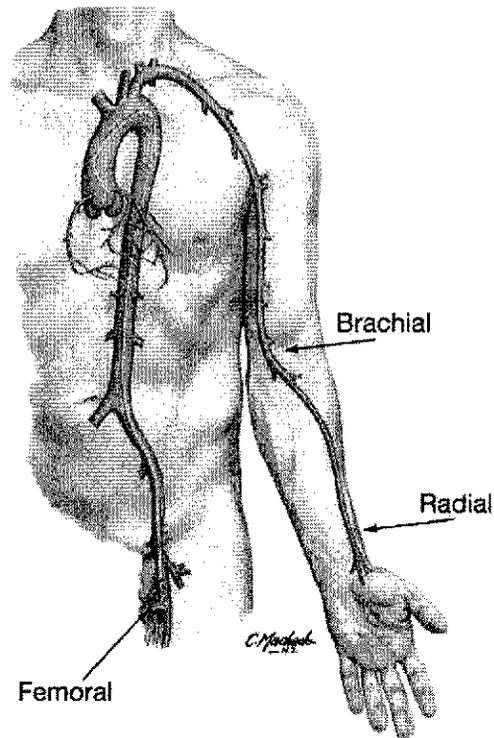
may feel some pressure or chest pain when the balloon is inflated. This is normal and will quickly fade when the balloon is deflated.

Your Drug-Eluting Stent Placement Procedure

Your procedure will be performed in a cardiac catheterization laboratory (cath lab). You will lie on the X-ray table, and an X-ray camera will move over your chest during the procedure. The staff will monitor your heart by attaching several small sticky patches to your chest and using a specialized ECG recorder and monitor.

The groin is the most common site for catheter introduction and requires a very small skin incision to be made on the inside of your upper thigh. The area will be shaved and cleaned with an antiseptic, and you will be given a local anesthetic to numb the area. This incision will allow an introducer sheath (short tube) to be inserted into your femoral artery (the main artery of the thigh, supplying blood to the leg). Your doctor will then insert a guiding catheter (long, flexible tube) into the introducer sheath and advance it to where the coronary arteries branch off to the heart. A guide wire is then advanced through the guiding catheter to the narrowing in the coronary artery. This helps carry all the necessary devices required during the stenting procedure.

Additional options for catheter introduction are the arm/brachial approach (incision is made on the inside of your elbow) and the transradial approach (incision is made on the inside of your wrist).



Blood vessel access for heart catheterization through the femoral, radial, or brachial artery

After the catheters are inserted, your doctor will inject a contrast dye through the guiding catheter into your artery to view the narrowing. Your doctor will watch the injection on an X-ray monitor, much like a TV screen. While these X-rays are being taken, your doctor may ask you to take a deep breath and hold it for a few seconds. You may also be asked to cough after the X-ray picture is completed to help speed the removal of the contrast dye from the arteries.

Using the guiding catheter, a balloon catheter is positioned in the narrowing in the coronary artery and the balloon is then inflated. This compresses the plaque and widens the coronary artery. This procedure is called pre-dilatation.

Step 1: The stent mounted on a balloon catheter is delivered to the narrowing in the coronary artery by a delivery catheter.

Step 2: The balloon is then inflated and this expands the stent, pressing it against the coronary artery wall. Your doctor may choose to expand the stent

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further by using another balloon so that the stent can make better contact with the artery wall. This is known as post-dilatation.

Step 3: Once in place, the XIENCE V stent will remain as a permanent implant in your coronary artery.

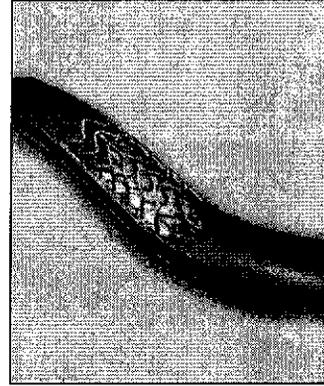
Step 1



Step 2



Step 3



Immediately after Procedure

You will be asked to lie flat for four to six hours following the procedure and to not bend your leg or arm, depending on which area your doctor used to insert the catheters. Pressure will also be placed on the area.

A vascular closure device may be used to seal the incision site in your groin or arm. You will be allowed to get up and walk around sooner if this type of device is used. Your hospital stay may range from one to three days.

Medications will be prescribed for you before and after stent placement. Antiplatelet medications such as aspirin and Plavix® are the most commonly prescribed. They help prevent a blood clot (thrombus) from forming and blocking the stent lumen. Your doctor or nurse will give you instructions about your medications before you leave the hospital.

CAUTION: If you have any chest pain, or discomfort or bleeding from your incision site, call your doctor immediately. If your doctor is unavailable, call for an ambulance to take you to the nearest hospital emergency room.

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Take All Medications as Instructed

After you leave the hospital, your cardiologist will instruct you to take a daily dose of aspirin and another antiplatelet drug such as Plavix. Your doctor will tell you how long you should continue taking the antiplatelet drugs. It is very important that you take these medications exactly as your doctor instructs you:

- Follow your medication schedule exactly to avoid possible complications after you receive your stent. Do not miss any doses.
- Call your doctor if you cannot keep taking your medications because of side effects such as rash, bleeding, or upset stomach.
- **CAUTION:** Do not stop taking your prescribed medications unless you are instructed to do so by the doctor who performed your stent procedure.
- **CAUTION:** Notify your cardiologist or family doctor if you are scheduled to see the dentist while on antiplatelet medication. Your doctor may prescribe antibiotics to avoid the potential of an infection. You should review with your doctor any recommendations from your dentist to stop your prescribed medications.
- **CAUTION:** Before undergoing implantation of a drug-eluting stent, if you plan to have any type of surgery, which may require you to stop taking antiplatelet medications, you and your cardiologist should discuss whether or not placement of a drug-eluting stent is the right treatment choice for you.

If surgery or dental work, which would require you to stop taking antiplatelet medications, is recommended after you have received the stent, you and your doctors should carefully consider the risks and benefits of this surgery or dental work versus the possible risks from early discontinuation of these medications.

If you do require discontinuation of antiplatelet medications because of significant bleeding, your cardiologist will carefully monitor you for possible complications. Once your condition has stabilized, your cardiologist may put you back on these medications.

Follow-Up Care

You will be discharged to the care of your cardiologist or family doctor. You should be able to return to your normal activities soon.

CAUTION: Notify your doctor immediately if you experience chest pain (angina), or notice any changes such as more severe or frequent chest discomfort,

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especially in the first month after a procedure. These symptoms may indicate a re-narrowing in your coronary arteries.

Your doctor will ask you to return for follow-up visits. The first visit is usually two to four weeks after your stent is implanted, with follow-up visits every six months for the first year. Be sure to keep all appointments for follow-up care, including blood tests.

Keep Your ID Card Handy

CAUTION: Show your identification card if you report to an emergency room. This card identifies you as a patient who has had a stent implanted.

If you require a magnetic resonance imaging (MRI) scan, tell your doctor or MRI technician that you have a stent implant. Test results indicate that patients with single or overlapped XIENCE V stents can undergo MRI scans safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 720 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning or less

The stent(s) should not migrate in this MRI environment, and MRI may be performed immediately following the implantation of the XIENCE V stent(s). Prior to undergoing an MRI scan, inform your doctor that you have a XIENCE V Everolimus Eluting Coronary Stent.

Preventing Coronary Artery Disease

Coronary artery disease can be treated effectively, but it has no cure. You can help to prevent your coronary artery disease from progressing by carefully following your doctor's advice. Your doctor may prescribe medications to help control your blood pressure, diabetes, and/or high cholesterol. Your doctor may also recommend some lifestyle changes. Among the healthy choices you can make:

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Stop smoking. If you smoke, quitting is the single most important thing you can do to lower your risk of coronary artery disease. Chemicals in cigarette smoke may make it easier for plaque to build up on your artery walls. And smoking increases your heart rate and blood pressure, raising your risk of heart attack and stroke. If you are ready to quit, ask your doctor for advice — he or she can recommend smoking cessation aids to help you quit.

Increase your activity and eat a healthy diet. A sedentary lifestyle increases your risk. Your doctor can recommend an activity program tailored for your situation. Regular exercise can help you lower your blood pressure and blood cholesterol and reach a healthy weight. It can also help you manage the daily stresses of modern life more easily. Choose a healthy diet. A diet low in saturated fats and cholesterol, and rich in lean protein, fresh fruits, vegetables, and whole grains, can help you achieve a healthy weight and control your blood pressure, and cholesterol levels.

Manage your stress. Stress is an inescapable aspect of modern day living, but you can help lessen its negative health effects by practicing the “relaxation response.” Research has shown that relaxation techniques can improve your ability to cope with stressful events while decreasing your heart rate, blood pressure, and stress hormone levels.

Frequently Asked Questions

How long will the stent stay in my body?

Stents are designed to stay in your body permanently.

What are the restrictions or cautions after I've received a stent?

If you require magnetic resonance imaging (MRI), tell your doctor or MRI technician that you have an implanted stent.

When can I resume my regular activities?

Your doctor will advise you. Many patients can return to work and follow their normal routine about a week after their stent procedure.

Will my stent set off the metal detector at airport security checkpoints?

No, your stent implant will not trigger alarms at security checkpoints.

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Will I be able to feel the stent inside me?

No, you will not be able to feel the stent once it has been implanted in your artery.

Could I have recurring symptoms?

Yes, it is possible that you will experience symptoms again, either due to a new blockage in the region treated with the stent or due to a blockage at another place in your coronary arteries. Your doctor will monitor your progress.

How can I help prevent a recurrence of symptoms?

While there is no sure way to prevent a recurrence of symptoms, you can reduce the risk through exercise, not smoking, and eating a healthy diet. Your doctor can advise you about lifestyle changes.

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Definition of Medical Terms

Angina: Chest pain caused by inadequate supply of blood to the heart.

Angioplasty (also referred to as PTCA): A minimally invasive procedure in which a balloon dilatation catheter is passed through to the blocked area of an artery. Once inflated the catheter compresses the plaque against the blood vessel wall and enlarges the vessel opening. An angioplasty can also be performed with placement of a stent.

Anticoagulant: A medication to prevent or slow the clotting of blood.

Antiplatelet: A substance to reduce clumping of platelets in the blood. An antiplatelet medicine helps thin the blood to prevent clot formation.

Atherosclerosis: A disease that causes narrowing or blockage of arteries caused by a build-up of fat (cholesterol) within the artery wall. The build-up is sometimes referred to as "plaque."

Cardiac Catheterization Laboratory (Cath Lab): A sterile X-ray theater in which heart catheterization is performed.

Catheter: A thin, hollow, flexible tube used to access the coronary arteries during an angiogram or during an angioplasty procedure. This catheter can be used to inject medication, fluids, or contrast dye during your procedure. Catheter is also used to describe the device used to deliver the balloon or stent during an angioplasty procedure.

Coronary Angiography (or Heart Catheterization or Cardiac Cath): A test in which contrast dye is injected to create images of the coronary arteries and the chamber of the heart. This allows the doctor to see the extent of the disease in the coronary arteries and make a decision on how to best treat the blockages.

Coronary Arteries: The blood vessels that carry oxygenated blood from the aorta to the heart muscle. There are four major coronary arteries: the left main, the right coronary artery, the left anterior descending, and the circumflex.

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Coronary Artery Bypass Graft Surgery (CABG): Open-heart surgery to treat CAD.

Coronary Artery Disease (CAD): The formation of blockages or atherosclerotic plaques within coronary arteries that result in restricted blood flow to the heart muscle.

Electrocardiogram (ECG/EKG): A test that records changes in the electrical activity of the heart. An ECG/EKG may show whether parts of the heart muscle are damaged due to decreased blood flow to the heart muscle.

Femoral Artery: The main artery of the thigh, supplying blood to the leg.

Fluoroscope: An X-ray device that creates an image of the body that can be viewed on a TV monitor. This permits the doctor to obtain real-time images of the internal structures of a patient.

In-stent Restenosis: Recurrent blockage or narrowing of a previously stented vessel.

Local Anesthetic: A substance used to numb the area to which it is applied.

Lumen: The inner channel or cavity of a vessel or tube. In a blood vessel, it is the opening through which blood flows.

Myocardial Infarction (MI): Also called a heart attack. Permanent damage of an area of the heart tissue, due to interruption in the blood flow to the heart muscle (myocardium).

Magnetic Resonance Imaging (MRI): A non-invasive diagnostic procedure used to obtain images of internal body structures through the use of magnets and radio waves.

Percutaneous: Performed through the skin.

Plaque: An accumulation or build-up of fatty deposits, calcium, white blood cells, and other substances in the wall of an artery that results in narrowing of the vessel lumen.

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Restenosis: A recurring blockage caused by the excessive growth of scar tissue inside the artery or stent, following an interventional procedure such as angioplasty.

Stent: A metallic mesh tube that is implanted into an artery during an angioplasty, providing a scaffold to help hold the artery open, ensuring blood flow to the heart muscle.

Transluminal: Through the inside opening of a vessel or artery.

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