SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Coronary Stent System (NIQ)
Device Trade Name:	XIENCE V Rapid Exchange (RX) Everolimus Eluting Coronary Stent System XIENCE V Over-the-Wire (OTW) Everolimus Eluting Coronary Stent System
Device will also be distributed as:	PROMUS Rapid Exchange (RX) Everolimus Eluting Coronary Stent System PROMUS Over-the-Wire (OTW) Everolimus Eluting Coronary Stent System
Applicant's Name and Address:	Abbott Vascular, Cardiac Therapies 3200 Lakeside Drive Santa Clara, CA 95054
Date of Panel Recommendation:	November 29, 2007
Premarket Approval Application (PMA) Number:	P070015
Date of FDA Notice of Approval:	July 2, 2008
Expedited:	Not Applicable

II. INDICATIONS FOR USE

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 ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

III. CONTRAINDICATIONS

The XIENCE V stent is contraindicated for use in patients:

- Who cannot receive anti-platelet and/or anti-coagulant therapy
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system

- With known hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the XIENCE V Everolimus Eluting Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V EECSS or XIENCE V stent) is a device/drug combination product comprised of two regulated components:

- A device (MULTI-LINK VISION® Coronary Stent System or MULTI-LINK MINI VISION® Coronary Stent System)
- A drug coating (formulation of everolimus in a polymer coating)

The characteristics of the XIENCE V EECSS are described in Table 1 below.

Table 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 largest 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 to designate the stent placement on the balloon.	
Balloon Inflation Pressure	Nominal inflation pressure: 8 atm for the 2.5 and 2.75 mm diameters; 9 atm for the 3.0, 3.5, and 4.0 mm diameters Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes	
Guiding Catheter Inner Diameter	≥ 5F (0.056")	
Catheter Shaft Outer Diameter (nominal)	2.5-3.0 mm / 3.5-4.0 mm Distal: 0.032" / 0.035" Proximal: 0.026" / 0.026"	2.5 mm / 2.75 x 8 - 3.5 x 18 / 3.5 x 23 - 4.0 x 28 Distal: 0.032" / 0.034" / 0.036" Proximal: 0.042" / 0.042" / 0.042"

A. Device Component Description

The device component is comprised of the balloon-expandable MULTI-LINK VISION or MULTI-LINK MINI VISION coronary stent pre-mounted onto either the MULTI-LINK VISION or MULTI-LINK MINI VISION delivery systems consisting of either the Rapid Exchange (RX) or the Over-the-Wire (OTW) platform. The MULTI-LINK VISION RX and OTW delivery systems were approved for deployment of the bare metal MULTI-LINK VISION stent in P020047 (approved July 16, 2003). The MULTI-LINK MINI-VISION RX and OTW delivery systems were approved for deployment of the bare metal MULTI-LINK MINI-VISION stent in P020047/S003 (approved September 10, 2004).

The small XIENCE V stent design (2.5, 2.75, and 3.0 mm diameters) is identical to the MULTI-LINK MINI VISION stent for the 2.5 diameter, and the MULTI-LINK VISION stent for the 2.75 mm and 3.0 mm diameter. The medium XIENCE V stent design is identical to the medium MULTI-LINK VISION stent for the 3.5 mm and 4.0 mm diameters. All stent diameters will be available in 8-28 mm lengths.

B. Drug Component Description

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

B1. Everolimus

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

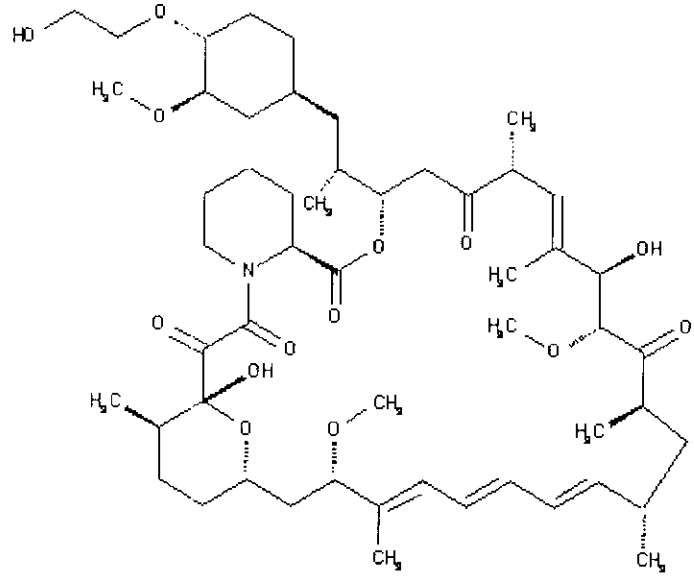

Figure 1 Chemical Structure of Everolimus

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B2. Interactive Ingredients

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

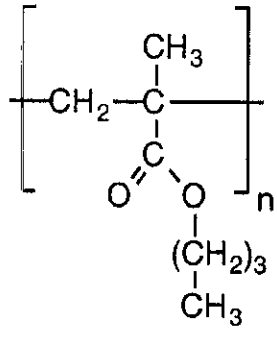

Figure 2a Chemical Structure of Poly (n-butyl methacrylate) (PBMA)

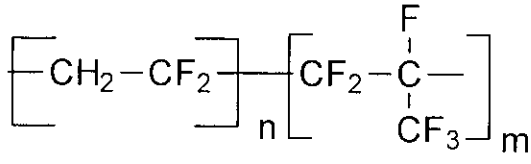

Figure 2b Formula for Poly(Vinylidene Fluoride-Co-Hexafluoropropylene) (PVDF-HFP)

The product matrix, including nominal dosages of everolimus in each XIENCE V stent is described in Table 2. The nominal everolimus content is based on stent design and length.

Table 2 XIENCE V EECSS Product Matrix and Everolimus Content

Model Number (RX)	Model Number (OTW)	Stent Diameter (mm)	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

C. 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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of patients with coronary artery disease including exercise, diet, drug therapy, percutaneous coronary interventions (i.e., balloon angioplasty, atherectomy, bare metal stents, coated stents, and other drug-eluting stents), and coronary artery bypass grafting (CABG) surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The XIENCE V Everolimus Eluting Coronary Stent System is commercially available in the following countries:

Argentina	France	Lithuania	Slovakia
Australia	Germany	Luxembourg	Slovenia
Austria	Greece	Malaysia	Spain
Bangladesh	Hong Kong	Macau	Sri Lanka
Belgium	Hungary	Malta	Sweden
Brazil	Iceland	Macedonia	Syria
Bulgaria	India	Netherlands	Switzerland
Colombia	Indonesia	New Zealand	Thailand
Costa Rica	Ireland	Norway	Ukraine
Croatia	Israel	Panama	United Arab Emirates
Cyprus	Italy	Philippines	United Kingdom
Czech Republic	Jordan	Poland	Uruguay
Denmark	Kuwait	Portugal	Tunisia
Egypt	Latvia	Romania	Turkey
Estonia	Lebanon	Russian Federation	Venezuela
Finland	Liechtenstein	Singapore	Vietnam
Thailand	Serbia	Peru	Taiwan
			South Korea

As of May 31, 2008, over 252,818 XIENCE V Stent systems have been distributed outside of the United States. The XIENCE V EECSS has not been withdrawn from marketing in any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the XIENCE V stent.

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

- Abrupt closure
- Access site pain, hematoma or hemorrhage
- Acute myocardial infarction
- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm
- 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
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- 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

For the specific adverse events that occurred in the clinical studies, please see Section X, Summary of Primary Clinical Study, below.

IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies related to the XIENCE V product were performed. Studies included those performed on the bare metal stent system (MULTI-LINK VISION or MULTI-LINK MINI VISION stent mounted on the stent delivery system), the coated stent alone (the XIENCE V stent), the polymer-only coated stent alone (the MULTI-LINK VISION or MULTI-LINK MINI VISION with the PBMA primer layer and PVDF-HFP polymer layer), or the finished combination product (XIENCE V EECSS).

A. Laboratory Studies

A1. Biocompatibility Testing

A series of Good Laboratory Practices (GLP) biocompatibility tests were conducted to demonstrate the components of the XIENCE V EECSS are non-toxic. Tests were conducted on ethylene oxide-sterilized XIENCE V RX EECSSs, XIENCE V coated stents, or polymer-only coated stents. These test articles were processed in a similar manner as the finished XIENCE V product, except in the case of the polymer-only coated stent that did not contain the active pharmaceutical ingredient. Some portion of biocompatibility testing was conducted on the XIENCE V EECSS contained a drug dose approximately 2.6 times (2.6X) the amount of the commercial product. Additional testing of the XIENCE V stent was evaluated at appropriate extract dosing levels near the toxicity threshold of everolimus as confirmed through cell culture testing. Testing was also performed on polymer-only coated stents with the same total coating weight as the drug eluting stents.

All biocompatibility testing was conducted in accordance with one or more of the following general regulations and guidance documents:

- Guidance for Industry and FDA Staff, Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems; published by the Interventional Cardiology Devices Branch, Division of Cardiovascular Devices, Office of Device Evaluation on January 13, 2005.
- Draft Guidance for Industry, Coronary Drug-Eluting Stents- Nonclinical and Clinical Studies; published by the Interventional Cardiology Devices Branch, Division of Cardiovascular Devices, Office of Device Evaluation on March 2008.
- Good Laboratory Practices Regulations (21 CFR § 58)
- ISO 10993, Biological Evaluation of Medical Devices
- USP <85> Bacterial Endotoxin Test
- USP <87/88> Biological Reactivity Tests
- USP <161> Transfusion and Infusion Assemblies and Similar Medical Devices

Table 3 describes the biocompatibility testing.

Table 3 Biocompatibility Test Summary

Test Name	Description of Test	Test Article and Results
Cytotoxicity	ISO 10993-5: In Vitro Cytotoxicity (L929 MEM Elution)	• XIENCE V Stent and OTW delivery system: Pass (non-cytotoxic) • 2.6X Stent and RX delivery system: Pass (non-cytotoxic) • XIENCE V Stent: Pass (non-cytotoxic below toxicity threshold of everolimus) • Polymer-only coated stent: Pass (non-cytotoxic)
Sensitization	ISO 10993-10: Sensitization (Guinea Pig Maximization)	• XIENCE V Stent and OTW delivery system: Pass (non-sensitizing) • 2.6X Stent and RX delivery system: Pass (non-sensitizing) • XIENCE V Stent: Pass (non-sensitizing below toxicity threshold of everolimus) • Polymer-only coated stent: Pass (non-sensitizing)
Intracutaneous Reactivity	ISO 10993-10: Irritation (Rabbit Injection)	• XIENCE V Stent and OTW delivery system: Pass (non-irritating) • 2.6X Stent and RX delivery system: Pass (non-irritating) • XIENCE V Stent: Pass (non-irritating below toxicity threshold of everolimus) • Polymer-only coated stent: Pass (non-irritating)
Systemic Toxicity	ISO 10993-11: Systemic Toxicity, Acute (Mouse Injection)	• XIENCE V Stent and OTW delivery system: Pass (non-toxic) • 2.6X Stent and RX delivery system: Pass (non-toxic)
	USP <88>: Systemic Injection Test (Mouse Injection)	• Polymer-only coated stent: Pass (non-toxic)
Pyrogenicity	Bacterial Endotoxin (LAL)	• XIENCE V Stent and OTW delivery system: Pass (non-pyrogenic) • 2.6X Stent and RX delivery system: Pass (non-pyrogenic)
	ISO 10993-11: Systemic Toxicity (Material Mediated Rabbit)	• XIENCE V Stent and OTW delivery system: Pass (non-pyrogenic) • 2.6X Stent and RX delivery system: Pass (non-pyrogenic)
Hemocompatibility/ Hemolysis*	ISO 10993-4: Hemolysis, Direct Contact (Rabbit Red Blood Cells)	• 2.6X Stent and RX delivery system: Pass (non-hemolytic) • XIENCE V stent: Pass (non-hemolytic)
	Thrombosis (fulfilled through Hemolysis and *in vivo* animal testing)	• XIENCE V Stent and OTW delivery system: Pass (non-hemolytic) • 2.6X Stent and RX delivery system: Pass (non-hemolytic)
	ISO 10993-4: Hemolysis, Indirect Contact (Rabbit Red Blood Cells)	• XIENCE V Stent and OTW delivery system: Pass (non-hemolytic) • XIENCE V stent: Pass (non-hemolytic)
	ISO 10993-4: Clotting, PT (Human Plasma)	• 2.6X Stent and RX delivery system: Pass (non-hemolytic)
	ISO 10993-4: Partial Thromboplastin Time, PTT (Human Plasma)	• 2.6X Stent and RX delivery system: Pass (non-hemolytic)

* See discussion of hemocompatibility testing below.

Table 3 Biocompatibility Test Summary (cont'd)

Test Name	Description of Test	Test Article and Results
Implantation	ISO 10993-6: 90-day (Rabbit, Intramuscular)	• 2.6X XIENCE V stent: Pass
	Sub-chronic Toxicity (fulfilled through 90-day implant)	
	USP <88> 7-day (Rabbit, Intramuscular)	• Polymer-only coated stent: Pass
Genotoxicity	ISO 10993-3: Bacterial Reverse Mutation Assay (Ames test)	• 2.6X XIENCE V stent: Pass (non-mutagenic)
	ISO 10993-3: *In Vitro* Chromosomal Aberration (Chinese Hamster Ovary cells)	• 2.6X XIENCE V stent: Pass (non-mutagenic)
	ISO 10993-3: Clastogenicity in Mammalian Cells (CHO/HGPRT forward mutation)	• 2.6X XIENCE V stent: Pass (non-mutagenic)
	ISO 10993-3: Mammalian Erythrocyte Micronucleus Test	• 2.6X XIENCE V stent: Pass (non-mutagenic)
Reproductive Toxicity (Teratology)	ISO 10993-3: Reproductive and Developmental Toxicity	• XIENCE V stent: Pass (non-teratogenic)
Carcinogenicity	ISO 10993-3: Carcinogenicity	• XIENCE V stent: Pass (non-carcinogenic)

The applicant completed multiple tests to assess hemocompatibility, with the exception of complement activation testing. The applicant provided a scientific rationale for the omission of this testing. Although complement activation was not specifically studied in the SPIRIT III clinical trial, adverse cardiac events were reviewed through the first 37 days (30 day clinical follow-up ± 7 days) to assess any potential for complement activation in the adverse cardiac event profile of the XIENCE V product. No differences between treatment groups were observed and no manifestations of complement activation were revealed. In addition to adverse cardiac events, immediate hypersensitivity, a potential manifestation of complement activation, was evaluated through 37 days. Using the list of adverse events suggested by Nebeker *et al.*[1] to be manifestations of hypersensitivity, a search of the SPIRIT III subject database revealed no reports of allergy or hypersensitivity reactions to the stent in either study arm, and a comparable incidence of hypersensitivity reactions without an identified etiology between the two arms. Given these analyses, the omission of complement activation testing is acceptable.

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

[1] Nebeker JR, Barach P, Samore M. Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting. Ann Intern Med 2004; 140: 795-801.

Stent). The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. 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.

In addition, a teratology (reproductive toxicity) study was conducted to demonstrate that implantation of XIENCE V Stents in female Sprague-Dawley rats does not affect their fertility or reproductive capability as well as to show a lack of any teratology effect 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 teratologic effects in the offspring in this study.

In vivo animal and pharmacology studies have been completed on the XIENCE V stent to provide information about systemic, regional and local toxicity, and dose-related toxicity. Abbott Vascular completed a series of *in vivo* pharmacokinetic studies of the XIENCE V stent. The animal PK studies are summarized in Section IX.B1. *In Vivo* Pharmacokinetics below. In addition, clinical pharmacokinetic studies have been performed on the XIENCE V stent. The human PK studies are described in Section X.D. Global Pharmacokinetics.

There is no evidence to suggest that any chemical interactions, which would result in the formation of a new intermediate or molecular entity, occur between everolimus or the polymers used in the XIENCE V stents. Long term biocompatibility of the drug/polymer coating on the stent in humans is unknown.

A2. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with the FDA "Guidance for Industry and FDA Staff – Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems," January 2005 and "Draft Guidance for Industry, Coronary Drug-Eluting Stents- Nonclinical and Clinical Studies," March 2008, was conducted on the XIENCE V Stent except where the testing could be leveraged from the MULTI-LINK VISION or MULTI-LINK MINI VISION Stent, which were approved in P020047 and P020047/S003, respectively. Supplementary *in vitro* engineering tests were also performed on the XIENCE V delivery systems containing the XIENCE V stent mounted on a delivery catheter. This testing is summarized in Table 4. "Pass" denotes that the test results met product specifications and/or the recommendations in the above referenced guidance document.

Additional tests were conducted to support the integrity of the coating on the XIENCE V Stent and are summarized separately in Section IX.A3. Coating Characterization Testing.

Table 4 *In Vitro* Engineering Studies

Test	Test Description	Results
Material Characterization Testing		
Material Analysis	Evaluations were conducted on the stent tubing provided by the material supplier prior to any processing to confirm chemical analysis, grain size, and inclusion content per relevant ASTMs (F90, A751, E1086, E1479, E1019, F138, E112, F2527, E45). In addition, SEM analysis was conducted on bare metal stents to identify and analyze trace contaminants which may be present on the stent.	PASS
Mechanical Properties: Tensile Strength and Elongation	Tensile strength and elongation testing was performed on the stent tubing prior to any processing. The tensile strength and elongation met acceptance criteria.	PASS
Corrosion Testing	Both bare metal and polymer-only coated stents were tested according to ASTM F2129-01 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" to demonstrate that the finished stents exhibit acceptable corrosion resistance. Testing was also conducted to evaluate the relative susceptibility to pitting/crevice corrosion. Results were comparable to the marketed MULTI-LINK VISION stents and met the specifications requirements.	PASS
Fretting Corrosion	Overlapped XIENCE V Stents and overlapped MULTI-LINK VISION stents were evaluated post fatigue testing to determine the potential for fretting corrosion. The results met all acceptance criteria and indicated that the stents possess a high resistance to fretting corrosion.*	PASS
Galvanic Corrosion	Testing was conducted on marketed stainless steel (MULTI-LINK TETRA) and CoCr (MULTI-LINK VISION) overlapped in a passive manner, and overlapped in an active manner (with disruption of the oxide layer) to determine the potential for galvanic corrosion. The results met the acceptance criteria and indicated a high resistance to galvanic corrosion.	PASS
Stent Dimensional and Functional Attributes		
Stent Dimensional Inspection	Measurements were taken of the bare metal stent strut width, thickness, and length. All stents met product specifications.	PASS
Stent Percent Surface Area	Determines the metal-to-artery ratio of the nominal XIENCE V stent using a theoretical calculation that divides the total vessel contact metal surface area of the stent by the theoretical surface area of the vessel at the desired diameter. Metal to artery percentage ratios were calculated for each stent diameter, with the highest surface to artery ratio (14.89%) occurring at the smallest stent diameter (2.5 mm).	Descriptive only
Stent Uniformity of Expansion Test	Determines the uniformity of expansion along the stent length. Units were inflated to either nominal or post-dilated inner diameters, deflated, and diameter measurements were taken at various points along the stent length. Measurements were averaged and all stents met product specifications.	PASS

* The applicant has agreed to provide additional fretting corrosion testing out to 400 million cycles on overlapped stents placed in a 15 mm bend configuration postapproval.

Table 4 *In vitro* Engineering Studies (cont'd)

Test	Test Description	Results
Stent Dimensional and Functional Attributes (cont'd)		
Stent Percent Length Change (Foreshortening) Test	Determines the difference in stent length pre-and post-expansion to either nominal or post-dilated inner diameters. All stents met product specifications.	PASS
Stent Percent Recoil Test	Quantifies the amount of recoil of the stent after balloon expansion. The system was inflated to either nominal or post-dilated diameters and measurements were taken of the stent diameter at various locations along the stent length. The system was then deflated and the same measurements taken. The percent recoil is calculated by subtracting the average stent inner diameter (ID) without the balloon from the average stent ID with the balloon, dividing by the average stent ID with the balloon and multiplying by 100. All stents met product specifications.	PASS
Stent Radial (Hoop) Strength Test	Testing was conducted to determine the radial strength of the stent under compression force. Stents were expanded to either nominal or post-dilated diameters, placed in an Instron tester, and subjected to incrementally increasing compression forces. The pressure at which deformation is no longer completely reversible was recorded. All stents met product specifications.	PASS
Radial Stiffness	Radial stiffness was evaluated on the XIENCE V stent compared to the MULTI-LINK VISION stent	Descriptive only
Finite Element Analysis (FEA)	An in-depth analysis of the stent was conducted to ensure that the implant conditions to which the stent will be subjected would not result in failure due to fatigue. The FEA evaluated the structural integrity of the stent when subjected to the expected loading conditions generated in coronary arteries. The analysis took into account manufacturing, delivery, implantation and clinical loading over the implant life, and predicted that fatigue failures will not likely occur.	PASS
Accelerated Fatigue Testing	Determines that the system can adequately withstand expected *in vivo* cyclic loading conditions. Accelerated fatigue testing was conducted on the following configurations: • Radial Fatigue Testing: Single Configuration • Radial Fatigue Testing: Overlapped Configuration • Radial Fatigue Testing: Overlapped Configuration on Static 20 mm Bend (to 400 million cycles) • Radial Fatigue Testing: Overlapped Configuration on Static 15 mm Bend (to 30 million cycles)** to ensure that the stent, when expanded to its largest intended diameter, will not show fatigue failure during simulated 10 year testing. The stents were dynamically cycled in a simulated vessel for 400 million cycles. Following cycling, stents were visually inspected under 40X magnification. No signs of strut cracking or breaking were detected.	PASS

** The applicant has agreed to provide structural cyclic fatigue testing out to 400 million cycles on overlapped stents placed in a 15 mm bend configuration postapproval.

Table 4 *In vitro* Engineering Studies (cont'd)

Test	Test Description	Results
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 is 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 this implant.	PASS
Radiopacity	Confirms that the XIENCE V stent is adequately visible under fluoroscopic imaging equipment. The XIENCE V stent is comparable to that of the MULTI-LINK VISION and MULTI-LINK MINI VISION under fluoroscopy.	PASS
Delivery System Dimensional and Functional Attributes		
Balloon Rated Burst Pressure	Statistically demonstrates with 95% confidence, at least 99.9% of the XIENCE V systems will not rupture below the rated burst pressure (RBP) and to demonstrate that at a 95% confidence level, at least 99% of the XIENCE V systems will not rupture below the maximum labeled compliance (MLC) pressure. All systems met product specifications and confidence/reliability limits.	PASS

Table 4 *In vitro* Engineering Studies (cont'd)

Test	Test Description	Results
Unconstrained Balloon Fatigue	Statistically demonstrates with 95% confidence, at least 90% of the XIENCE V systems will sustain 10 repeated inflations to the rated burst pressure inside the stent. All systems met product specifications.	PASS
Stent Diameter vs. Balloon Pressure (Compliance)	Determines how the diameter of a deployed balloon varies with applied balloon pressures. All systems met product specifications.	PASS
Soft Tip Tensile	Determines the tensile strength of the soft tip. All systems met product specifications.	PASS
Distal Delivery System Tensile	Determines the tensile strength of the distal portion of the delivery system. All systems met product specifications.	PASS
Proximal Delivery System Tensile	Determines the tensile strength of the proximal portion of the delivery system. All systems met product specifications.	PASS
Delivery System Crossing Profile Crimped Stent Outer Diameter	Determines the crimped stent outer diameter. Measurements were taken at various locations along the length of the stent and averaged to calculate the mean outer diameter. All systems met product specifications.	PASS
Delivery System Balloon Inflation/Deflation Times	Determines the amount of time required to inflate or deflate the delivery catheter balloon. All systems met product specifications for deflation times. Inflation times were tested for information only.	PASS
Stent Dislodgement	Determines the amount of force required to displace a stent in both distal and proximal direction from its original, crimped position on the delivery system balloon after a pre-conditioning step where the system is tracked through a tortuous artery model. All systems met product specifications.	PASS
Delivery System Guiding Catheter Pullback	Statistically demonstrates that with 95% confidence, at least 99% of the XIENCE V systems can be successfully retracted back into a 5F guiding catheter after tracking through a simulated tortuous model prior to the deployment of the stent. All systems met product specifications and confidence/reliability limits.	PASS
Delivery, Deployment, and Retraction	Design validations demonstrate that the XIENCE V system meets the user needs.	PASS
Delivery System Preparation	Evaluates the ease of preparing the XIENCE V system using the aspiration method. All systems met product specifications.	PASS
Delivery System Shaft Pressure	Determines the pressure integrity of the XIENCE V catheter shaft proximal to the delivery system balloon. All systems met product specifications.	PASS
Delivery System Inner Member Collapse	Verifies that irreversible collapse of the inner member does not occur at or below 300 psi. All systems met product specifications.	PASS

Table 4 *In vitro* Engineering Studies (cont'd)

Test	Test Description	Results
Delivery System Dimensional and Functional Attributes (cont'd)		
Delivery System Coating Friction (Hydrophilic)	Determines the coefficient of friction along the hydrophilic coated portion of the XIENCE V catheter using an aorta lined fixture. All systems met product specifications.	PASS
Delivery System Coating Dry Adhesion (Hydrophilic)	Determines the percent adhesion of the hydrophilic coating to the XIENCE V catheter. The percent coating adhesion is determined by subtracting the percent coating removed from 100. All systems met product specifications.	PASS

A3. Coating Characterization Testing

The following methods were developed to characterize and set initial specifications for the XIENCE V stent. The coating characterization testing conducted on the XIENCE V stent is summarized in Table 5.

Table 5 Coating Characterization Testing

Test	Test Description	Results
Stent Coating Durability		
Coating Physical Structure and Chemical Properties	Characterizes various aspects of the coated stent including: • the coating thickness along the length of the stent and the drug density and its distribution in the stent coating • the cross section of the coated stent struts • the content uniformity along the length of the stent • adhesion of the coating to the delivery system balloon • physical microstructure.	PASS
Coating Adhesion	Evaluates adhesion properties between the coating and the metal stent with shear stress analysis using a Nano-Scratch Tester.	PASS
Coating Surface Integrity	Determines the stent coating surface integrity of the XIENCE V stent after tracking through a tortuosity fixture, expansion, and post-dilated to RBP. Defect quantities and sizes were recorded. The compromised coating area was calculated as a percentage of entire coated stent surface. All stents met product specifications.	PASS
Coating Integrity after Balloon Rupture	Evaluates the stent coating surface integrity of the XIENCE V stent after balloon rupture within the stent. The stents were compared to control stents expanded to nominal diameter.	PASS

Table 5 Coating Characterization Testing (cont'd)

Test	Test Description	Results
Stent Coating Durability (cont'd)		
Accelerated Coating Fatigue	Demonstrates the coating durability of the XIENCE V stent under expected *in vivo* cyclic loading conditions for an equivalence of 10 years (~400 million cycles). Accelerated coating fatigue testing was conducted on the following configurations: • Coating Fatigue Testing: Single Configuration • Coating Fatigue Testing: Overlapped Configuration • Coating Fatigue Testing: Overlapped Configuration on Static 20 mm Bend (to 400 million cycles) • Coating Fatigue Testing: Overlapped Configuration on Static 15 mm Bend (to 30 million cycles)* The stents were deployed and post-dilated to the largest intended diameter. The drug was eluted from the coating. The stents were evaluated under SEM and then loaded into tubing and the fatigue tester. The stents were dynamically cycled within simulated vessel conditions for 400 million cycles. The stents were removed and visually inspected under SEM for changes to coating morphology in the documented anomalies that were captured prior to fatigue testing. All stents met product specifications and confidence/reliability limits.	PASS
Particulate - Beaker Method (Over-expansion)	Determines the particulate matter generated during deployment and over expansion of the XIENCE V stent in a beaker of water. The distal end (balloon and stent) was inserted into glassware filled with clean water. The stents were deployed and post-dilated to the maximum stent diameter. After agitation, aliquots of the water were withdrawn and the particles quantities and sizes were counted and recorded. All stents met product specifications.	PASS
Particulate – Tracking Method (Simulated Use)	Determines the particulate matter after navigating simulated, challenging vasculature followed by deployment. The XIENCE V system was tracked through a simulated tortuous artery model and the stent was deployed unconstrained to RBP inside simulated vasculature. Water was drawn through the vasculature and the particle quantities and sizes were counted and recorded. All stents met product specifications.	PASS

* The applicant has agreed to provide coating integrity testing out to 400 million cycles on overlapped stents placed in a 15 mm bend configuration.

Table 5 Coating Characterization Testing (cont'd)

Test	Test Description	Results
Stent Coating Durability (cont'd)		
Embolic Fatigue (Overlap Configuration)	Investigates the embolic particle size and count from the XIENCE V stent during an accelerated radial fatigue test through multiple time points. Pre-condition units and deploy into tubing with a 4 mm overlap. Particle quantities and sizes were recorded from each pair of stents through the testing duration. Testing was done for the following configurations and time points: • Overlapped Straight Configuration through 9.3 million cycles • Overlapped Configuration on 20 mm Bend through 37.8 million cycles • Overlapped Configuration on 15 mm Bend through 30 million cycles**	PASS

** The applicant has agreed to provide additional embolic fatigue data for overlapped stents placed in a 15 mm bend configuration. This new testing will be carried out to 10 years equivalent or at a minimum two years equivalent if the test data demonstrates a clear plateau.

A4. Chemistry, Manufacturing & Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on the XIENCE V stent as part of CMC. This testing is summarized in Table 6. Information to support the stability of the XIENCE V stent is summarized separately in Section IX.A5 Stability.

Table 6 XIENCE V Stent Release Testing

Test	Description of Test
Appearance	A visual inspection was conducted to verify that the XIENCE V meets product appearance specifications.
Identity	Assays were conducted to verify the identity of the drug substance, everolimus, on the XIENCE V stent using two different methods.
Content Uniformity	Multiple stents were tested to verify that the uniformity of the drug content between individual stents was within specifications established for finished good release.
Total Content	Assay was conducted to quantitatively verify that the total amount of drug on the XIENCE V stent met specification for finished good release.
Drug Release	The *in vitro* drug release profile of everolimus was measured on the XIENCE V stent. The product met specifications established for finished good release.
Degradation Products	Assays were conducted to quantitatively verify the amount and type of degradation products on the XIENCE V stent.
USP <85> Bacterial Endotoxins Test	The amount of bacterial endotoxins was verified to be within the specification limits established for finished good release.
Particulate	Particulate levels were verified to meet product specifications.

A5. Stability/Shelf Life

Manufacturing site-specific stability studies were conducted to establish a shelf life/expiration date for the XIENCE V stent system. Testing included appearance, total content, drug release, degradation products, and butylated hydroxytoluene (BHT) content. Testing to establish container closure integrity was conducted to ensure sterility was maintained during the shelf life of the product. Functional testing of the stent system was conducted on aged product. The data generated to-date support a shelf life of 1 year.

A6. Sterilization

The XIENCE V stent system is sterilized using ethylene oxide (EtO) sterilization and has been validated per AAMI/ISO 11135:1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization."

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, the amount of bacterial endotoxins was verified to be within the specification limits.

B. *In Vivo* Animal Studies

B1. *In Vivo* Pharmacokinetic Studies

In vivo preclinical pharmacokinetic studies were performed in the porcine coronary artery model to determine: the percent drug release of everolimus from the XIENCE V stent over time, the tissue concentrations of everolimus over time, and the impact, if any, of systemic maximum dose of everolimus on platelet function. The pharmacokinetic data demonstrate that everolimus is delivered to the arterial wall in a controlled and reproducible manner. Also, blood and tissue levels were within safe levels when compared to therapeutic levels achieved in organ rejection therapy. Platelet function was not adversely affected at maximum doses of everolimus eluted from the XIENCE V stent. In summary, the XIENCE V EECSS has a safe pharmacokinetic profile as demonstrated in the porcine animal model.

B2. Drug Interactions

Formal drug interaction studies have not been conducted with the XIENCE V stent. Everolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A) isozyme 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 affect these pathways. Coadministration of strong CYP3A inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampicin, rifabutin) should be avoided. Coadministration of moderate CYP3A inhibitors (such as erythromycin, fluconazole, calcium channel blockers) and inducers (such as carbamazepine, phenobarbital, phenytoin) should be accompanied by everolimus therapeutic drug monitoring. The

pharmacokinetic interaction between orally administered everolimus and concomitantly administered drugs is described in the XIENCE V stent system Instructions for Use.

B3. Animal Safety Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials, so a series of animal studies were conducted to evaluate safety, efficacy (proof of concept dosing), and overall product performance.

Twenty four (24) major supportive studies were carried out in a porcine non-atherosclerotic coronary artery model and rabbit iliac artery model at time points out to 2 years to determine the clinical dose of everolimus to incorporate into the XIENCE V stent, to determine the pharmacokinetics of the XIENCE V stent, and to evaluate the safety of and vascular response to the XIENCE V stent. Additionally, animal studies were conducted to evaluate the safety of overlapping two XIENCE V stents. To establish a drug safety margin, a maximum dose (~8X) XIENCE V stent was also assessed. Studies were also performed to evaluate the safety of the polymer alone at both an equivalent loading to that in the XIENCE V stent and a bulk polymer system. Supportive safety data and overlapping stent safety data have also been generated in a rabbit non-atherosclerotic iliac artery model. The results of these tests support the safety of the XIENCE V stent.

A majority of these studies were conducted in accordance with 21 CFR 58 (Good Laboratory Practices). A rationale was provided for the non-GLP animal studies to demonstrate that appropriate animal care procedures were followed and data integrity were maintained. Summaries of the major supportive animal studies performed to support product safety are included in Table 7.

Table 7 Summary of Major Supportive Animal Studies

Study #	Stent Design	Animal Model (n)	# of Stents	Follow-up Duration	Endpoints
R040703-CW	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) • XIENCE (3.0 x 12 mm, 200 μg/cm^2) • XIENCE (3.0 x 12 mm, 260 μg/cm^2) **Control:** BMS **GLP:** no	Farm Swine (19) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 34 (100 =11, 200 =11, 260 =12) Control: 8	28 days	Evaluation of dose response of various everolimus formulations. •Angiography •Histological & histomorphometric evaluations. •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response •Dosing study (B:A = 1.3:1.0)
R051004-MJL	**Test Article:** XIENCE (3.0 x 12 mm, 100 μg/cm^2) **GLP:** yes	Farm Swine (18) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 52 (Target: 6/time point)	15, 30, 45, 60, 90, 120, 150, 180 minutes and 12 hours (blood levels only) 3 and 6 hours, 3, 14, 28, 60, 90, and 120 days (other evaluations)	Evaluation of % drug released, arterial and other tissue drug levels & systemic blood levels over time
R050503-PDD	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) • XIENCE (3.0 x 12 mm, 200 μg/cm^2) • XIENCE (3.0 x 12 mm, 260 μg/cm^2) **Controls:** • Polymer (3.0 x 12 mm) 515μg • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (24) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 37 (100 =12, 200 =12, 260 =13) Control: 32 (BMS =21, Polymer = 11)	28 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R081704-KHB	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (12) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 12 Control: 12	28 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R100704-KHB	**Test Article:** • XIENCE (2.5 x 8 mm, 100 μg/cm^2) **Controls:** • BMS (2.5 x 8 mm) **GLP:** yes	New Zealand White Rabbit (7) (Left & Right Iliac) 1 stent/vessel 2 stents/animal	Test: 7 Control: 7	28 days	•Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response

Table 7 Summary of Major Supportive Animal Studies (cont'd)

Study #	Stent Design	Animal Model (n)	# of Stents	Follow-up Duration	Endpoints
R042403-PDD	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) • XIENCE (3.0 x 12 mm, 200 μg/cm^2) • XIENCE (3.0 x 12 mm, 260 μg/cm^2) **Controls:** • Polymer (3.0 x 12 mm) 515μg • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (24) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 36 (100 =12, 200 =12, 260 =12) Control: 34 (BMS =22, Polymer = 12)	90 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R042204-PDD	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (12) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 12 Control: 12	90 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R081103-PDD	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) • XIENCE (3.0 x 12 mm, 200 μg/cm^2) • XIENCE (3.0 x 12 mm, 260 μg/cm^2) **Controls:** • Polymer (3.0 x 12 mm) 836μg • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (24) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 35 (100 =11, 200 =12, 260 =12) Control: 33 (BMS =21, Polymer = 12)	180 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R041504-PDD	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (13) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 12 Control: 12	180 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R042904-KHB	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (12) (LAD, LCX, RCA) 2 stents/vessel; 2 stent pairs/animal	Test: 24 (12 stent pairs) Control: 24 (12 stent pairs)	28 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response

Table 7 Summary of Major Supportive Animal Studies (cont'd)

Study #	Stent Design	Animal Model (n)	# of Stents	Follow-up Duration	Endpoints
R100604-KHB	**Test Article:** • XIENCE (2.5 x 8 mm, 100 μg/cm^2) **Controls:** • BMS (2.5 x 8 mm) **GLP:** yes	New Zealand White Rabbit (8) (Left & Right Iliac) 2 stents/vessel; 2 stent pairs/animal	Test: 16 (8 stent pairs) Control: 16 (8 stent pairs)	28 days	•Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response
R042604-KHB	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (12) (LAD, LCX, RCA) 2 stents/vessel; 2 stent pairs/animal	Test: 24 (12 stent pairs) Control: 24 (12 stent pairs)	90 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R041904-KHB-01	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (12) (LAD, LCX, RCA) 2 stents/vessel; 2 stent pairs/animal	Test: 24 (12 stent pairs) Control: 24 (12 stent pairs)	180 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R051503-DMH	**Test Article:** • XIENCE (3.0 x 12 mm, 803 μg/cm^2) **Controls:** • Polymer (3.0 x 12 mm) 905μg • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (14) (LAD, LCX, RCA) 1 stent/vessel: 3 stents/animal	Test: 13 Control: 25 (BMS = 12, bulk polymer = 13)	28 days	Evaluation of maximum dose everolimus and bulk polymer. •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R050503-DMH	**Test Article:** • XIENCE (3.0 x 12 mm, 803 μg/cm^2) **Controls:** • Polymer (3.0 x 12 mm) 905μg • BMS (3.0 x 12 mm) **GLP:** yes	Farm Swine (14) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 12 Control: 21 (BMS = 9, bulk polymer = 12)	90 days	Evaluation of maximum dose everolimus and bulk polymer. •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response

Table 7 Summary of Major Supportive Animal Studies (cont'd)

Study #	Stent Design	Animal Model (n)	# of Stents	Follow-up Duration	Endpoints
R032204-PDD	**Test Article:** • XIENCE (3.0 x 12 mm, 803 μg/cm^2) **Controls:** • Polymer (3.0 x 12 mm) 891 μg • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (13) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 10 Control: 25 (BMS = 13, bulk polymer = 12)	180 days	Evaluation of maximum dose everolimus and bulk polymer. •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R041904-KHB-02	**Test Article:** • Polymer (3.0 x 12 mm) 329 μg **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (12) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 12 Control: 12	180 days	•Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R093004-KHB-01	**Test Article:** • XIENCE (2.5 x 8 mm, 100 μg/cm^2) **Controls:** • BMS (2.5 x 8 mm) **GLP:** yes	New Zealand White Rabbit (6) (Left & Right Iliac) 1 stent/vessel 2 stents/animal	Test: 6 Control: 6	90 days	•Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response
R093004-KHB	**Test Article:** • XIENCE (2.5 x 8 mm, 100 μg/cm^2) **Controls:** • BMS (2.5 x 8 mm) **GLP:** yes	New Zealand White Rabbit (8) (Left & Right Iliac) 2 stents/vessel; 2 stent pairs/animal	Test: #16 (8 stent pairs) Control: 16 (8 stent pairs)	90 days	•Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response
R050304-PDD Part I	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (6) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 6 Control: 6	1 year	•Angiography •Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response
R050504-KHB Part I	**Test Article:** • Polymer (3.0 x 12 mm) 329 μg **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (6) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 6 Control: 6	1 year	Evaluation of polymer safety. •Angiography •Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response

Table 7 Summary of Major Supportive Animal Studies (cont'd)

Study #	Stent Design	Animal Model (n)	# of Stents	Follow-up Duration	Endpoints
R050304-PDD Part II	**Test Article:** • XIENCE (3.0 x 12 mm, 100 μg/cm^2) **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (6) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 6 Control: 6	2 years	•Angiography •Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response
R050504-KHB Part II	**Test Article:** • Polymer (3.0 x 12 mm) 329 μg **Controls:** • BMS (3.0 x 12 mm) **GLP:** yes	Yucatan Swine (5) (LAD, LCX, RCA) 1 stent/vessel; 2 stents/animal	Test: 5 Control: 5	2 years	Evaluation of polymer safety. •Angiography •Histological & histomorphometric evaluations •Acute delivery •Chronic vascular response
R0060228-MJL	**Test Article:** XIENCE (3.0 x 12 mm, 800 μg/cm^2) **GLP:** yes	Farm Swine (32) (LAD, LCX, RCA) 1 stent/vessel; 2-3 stents/animal	Test: 70 (Target: 10/time point)	1, 3, 7, and 14 days (platelet function), 15,30,45,60, 90,120, 150,180 minutes, 6 and 12 hours (blood levels only) 3, 6 and 24 hours, 3,14,28, 60 days (all other evaluations)	Evaluate the effect of high dose everolimus eluting stents on platelet function and to evaluate the systemic exposure of everolimus following stent-based delivery of >700 μg of everolimus by determining the concentration of everolimus in blood and selected key organs.

X. SUMMARY OF PRIMARY 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 heart disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in Table 8.

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^{2}™ 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 D - Global Pharmacokinetics). 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 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 RCT[2] and the 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. 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, control, multi-center first-in-man study. This trial was the first human study to evaluate the safety and performance of the XIENCE V stent. Sixty (60) 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 assessed in the per-treatment evaluable population, and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 180 days based on IVUS analysis of the per-treatment evaluable population. Follow-up through 3 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

Table 8 summarizes the clinical trial designs for the SPIRIT family of trials.

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

Table 8 XIENCE V SPIRIT Clinical Trial Designs

	SPIRIT III clinical trial		SPIRIT II clinical trial	SPIRIT FIRST clinical trial
	RCT	Registries		
Study Type/Design	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Single-arm • Open-label	• Multi-center • Randomized • Single-blinded • Active-Control	• Multi-center • Randomized • Single-blinded • Control
Planned Number of Subjects	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
Treatment	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Single *de novo* lesion
Lesion Size	RVD: ≥ 2.5 ≤ 3.75 mm Length: ≤ 28 mm	4.0 mm RVD: > 3.75 ≤ 4.25 mm Length: ≤ 28 mm Japan RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm	RVD: ≥ 2.5 ≤ 4.25 mm Length: ≤ 28 mm	RVD: 3 mm Length: ≤ 12 mm
Stent Sizes (XIENCE V)	D: 2.5, 3.0, 3.5 mm L: 8, 18, 28 mm	4.0 mm D: 4.0 mm L: 8, 18, 28 mm Japan D: 2.5, 3.0, 3.5, 4.0 mm L: 8, 18, 28 mm	D: 2.5, 3.0, 3.5, 4.0 mm L: 8, 18, 28 mm	D: 3.0 mm L: 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
Primary Endpoint	In-segment late loss at 240-days	In-segment late loss at 240-days	In-stent late loss at 180-days	In-stent late loss at 180-days
Co-Primary Endpoint	TVF at 270-days	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
Angiographic Follow-up	240 days (N=564)	240 days (All registry)	180-day (all), 2-years (N=152)	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)
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		Minimum 15 subjects with single lesion, maximum 20 with dual lesions	None
Status	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

* Only pharmacokinetic substudy results included (see Section D – Global Pharmacokinetics)

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A. SPIRIT III Pivotal Clinical Trial

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS^{2}™ 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 sub-study in a subject subset derived from the RCT[3] and Japan non-randomized arm (see Section D Global Pharmacokinetics). 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.

Study Design

SPIRIT III Randomized Clinical Trial (RCT)
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 at 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).

SPIRIT III RCT patients were randomized into follow-up coronary imaging subgroups:

Group A: (N=240)
Follow-up angiography at 240 days during their office/hospital visit follow-up was specified for 160 subjects enrolled in the XIENCE V arm and 80 subjects enrolled in the TAXUS arm. These subjects were also to be enrolled in the IVUS group (N=240)

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

at fixed number of pre-determined clinical sites and were to have follow-up IVUS at 240 days.

Group B: (N=324)
Follow-up angiography at 240 days during their office/hospital visit without follow-up IVUS at 240 days was specified for approximately 216 subjects enrolled in the XIENCE V arm and 108 subjects in the TAXUS arm.

Group C: (N=438)
No follow-up angiography or IVUS at 240 days was specified for 292 subjects in the XIENCE V arm and 146 subjects in the TAXUS arm.

SPIRIT III US 4.0 Arm
This was a prospective, single-arm, multi-center, clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V stent compared to the TAXUS stent arm in the SPIRIT III Randomized Control Trial (RCT). At the time of database lock on June 14, 2007, a total of 69 of the 73 subjects that were enrolled into the SPIRIT III 4.0 mm arm had reached their primary endpoint. Therefore, 69 subjects were included in the interim analysis.

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 in subjects who received a bailout stent at baseline and 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).

Clinical Inclusion and Exclusion Criteria
Enrollment in the SPIRIT III RCT and 4.0 mm arms was limited to subjects who met the eligibility criteria and who provided a signed informed consent form prior to enrollment. Subjects had to be at least 18 years old, with evidence of myocardial ischemia based on the presence of angina, silent ischemia, a positive functional study or reversible ECG changes consistent with ischemia. Female subjects with childbearing potential had to have a negative pregnancy test within 7 days of the index procedure.

Key angiographic inclusion criteria included a maximum of two *de novo* native coronary artery lesions, each within a different epicardial vessel. For the SPIRIT III RCT arm, the reference vessel diameter (RVD) had to be $\geq$ 2.5 mm and $\leq$ 3.75 mm, and for the SPIRIT III 4.0 mm arm, the RVD had to be > 3.75 mm and $\leq$ 4.25 mm. For both the RCT and the 4.0 mm arm, lesion length had to be $\leq$ 28 mm by visual estimation, percent diameter stenosis (%DS) $\geq$ 50% and < 100%, and TIMI flow $\geq$ 1.

Subjects were not permitted to enroll in the SPIRIT III RCT and 4.0 mm arms if their lesions met any of the following key angiographic exclusion criteria: aorto-ostial location, left main location, excessive tortuosity, extreme angulation ($\geq$ 90°), heavy

calcification, target vessel containing thrombus, and other significant lesions (> 40 %DS) in the target vessel or side branch for which intervention was required within 9 months.

If two target lesions were treated, each of these lesions had to meet all angiographic inclusion/exclusion criteria.

Follow-up Schedule
All subjects were scheduled to return postoperatively for a follow-up office/hospital visit at 30 days, telephone call/office visit follow-up at 180 and 270 days, an office/hospital visit at 240 days for angiographic follow-up, and an office/hospital visit or telephone call/office visit at 1, 2, 3, 4, and 5 years.

Stent Thrombosis Definitions
Protocol defined stent thrombosis (ST) was categorized as acute (< 1 day), subacute (1 - 30 days) and late (> 30 days) and was defined as any of the following[4]:

- 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)[5] 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)[6]. 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.

[4] 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.
[5] Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.
[6] 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.

2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up.[7]

Clinical Endpoints

SPIRIT III Randomized Clinical Trial (RCT)
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 RVD ≥ 2.5 mm to ≤ 3.75 mm. If non-inferiority was demonstrated, it was pre-specified that testing for superiority could be conducted.

SPIRIT III US 4.0 Arm
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 RCT.

Accountability of Subjects

SPIRIT III Randomized Clinical Trial (RCT)
A total of 1002 subjects (intent-to-treat) were randomized and enrolled into the SPIRIT III RCT. At the time of database lock on June 14, 2007, 997 subjects (99.5%) completed the 30-day follow-up; 987 subjects (98.5%) completed the 180-day follow-up; 972 subjects (97.0%) completed the 270-day follow-up, and 962 (96.0%) subjects completed the one-year follow-up.

It should be noted that 973 subjects completed the 270-day follow-up. This result is based on the database which was locked on March 10, 2007 for the 270-day report. One TAXUS subject had the 270-day follow-up completed, but the study completion form for this subject was not updated in the database until it was locked on June 14, 2007 for the one-year report. Therefore, this subject was considered to be lost to follow-up at Day 214 post index procedure. Thus, the 270-day follow-up is reduced to 972 subjects (97.0%).

A total of 947 subjects were included in the per-treatment evaluable population. As of June 14, 2007, 945 subjects (99.8%) completed the 30-day follow-up; 937 subjects (98.9%) completed the 180-day follow-up; 923 subjects (97.5%) completed the 270-day follow-up, and 913 (96.4%) subjects completed the one-year follow-up.

[7] All data within this Instructions for Use is presented as definite + probable only.

SPIRIT III US 4.0 Arm

At the time of database lock on June 14, 2007, a total of 69 of the 73 subjects that were enrolled into the SPIRIT III 4.0 mm arm had reached their primary endpoint. Therefore, 69 subjects were included in the interim analysis. As of June 14, 2007, 69 subjects (100%) completed the 30-day follow-up; 67 subjects (97.1%) completed the 180-day, 270-day and one-year follow-ups.

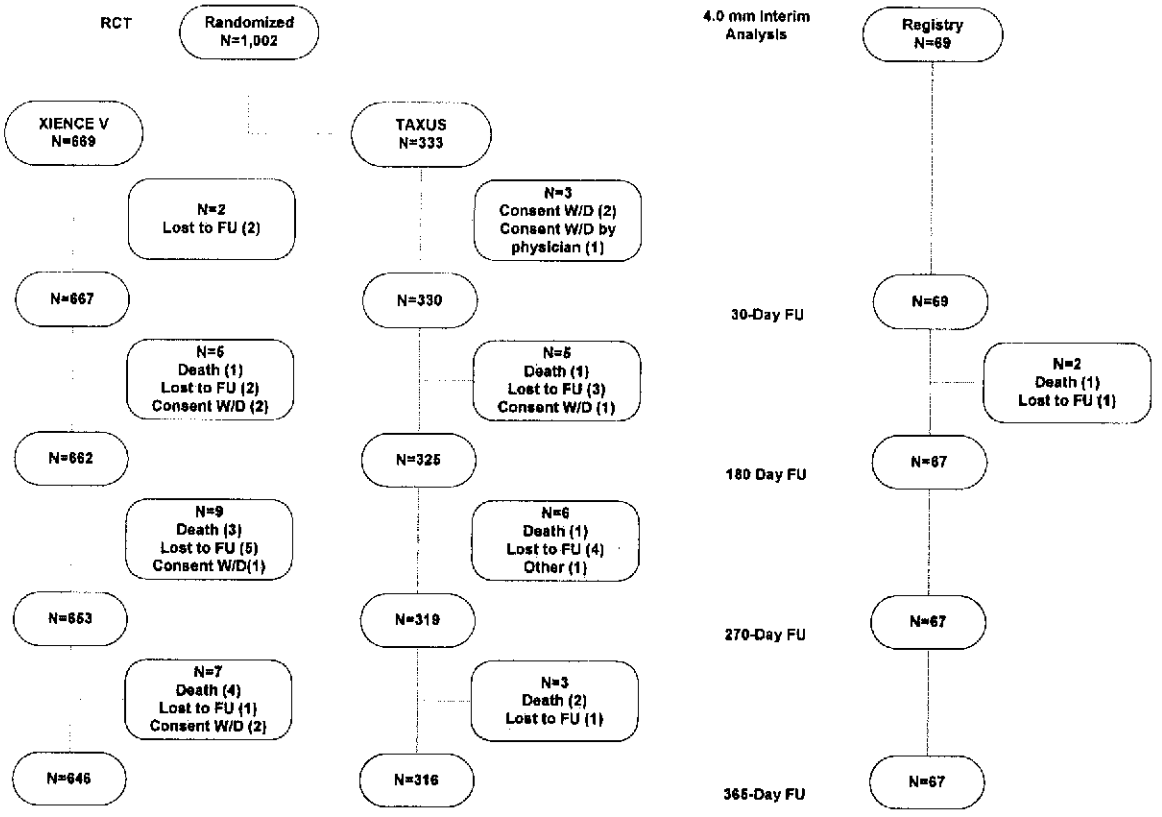


Figure 3 SPIRIT III 1-Year Clinical Follow-Up Subject Disposition (Intent-to-Treat)

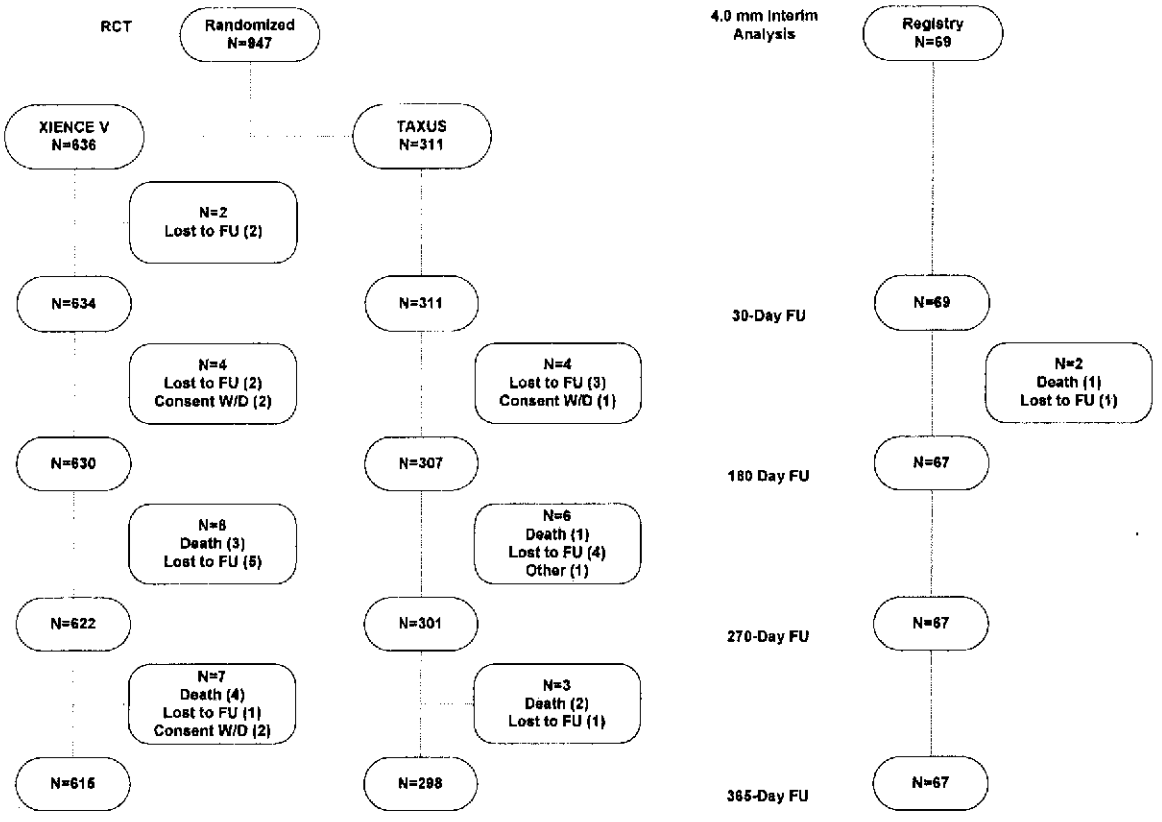


Figure 4 SPIRIT III 1-Year Clinical Follow-Up Subject Disposition (Per-Treatment Evaluable)

Study Population Demographics and Baseline Parameters

SPIRIT III Randomized Clinical Trial (RCT)

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) subjects with prior cardiac interventions and the TAXUS arm had to 29.5% (98/332). The XIENCE V arm had 29.6% (198/669) subjects with a history of diabetes and the TAXUS arm had 27.9% (92/330). The XIENCE V had 15.4% (103/669) 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.

SPIRIT III US 4.0 Arm

The mean age was 61.9 years for the XIENCE V 4.0 mm arm, with 72.5% (50/69) males, 21.7% (15/69) subjects with prior cardiac interventions, and 30.4% (21/69) subjects with a history of diabetes.

Safety and Effectiveness Results

SPIRIT III Randomized Clinical Trial (RCT)

The results are presented in Table 9 (Primary endpoints), Table 10 (Clinical Results), Table 11 (Angiographic and IVUS Results), Figure 5 (TVF Free Survival) and Table 12 (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 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 10 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 11 SPIRIT III 8 Month Angiographic and IVUS Results

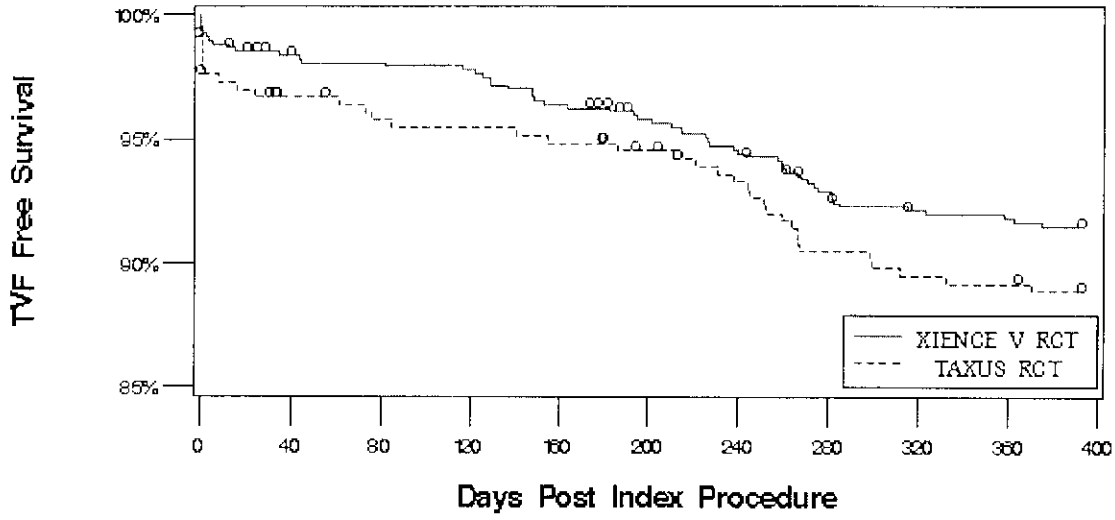
	XIENCE V (N=376) (M_{ANGIO}=427) (M_{IVUS}=181)	TAXUS (N=188) (M_{ANGIO}=220) (M_{IVUS}=93)	Difference [95% CI][1]
ANGIOGRAPHIC RESULTS			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment 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)	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 5 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)
[1]P-value based on log rank and not adjusted for multiple comparisons

Table 12 SPIRIT III RCT ARC defined Definite+Probable Stent Thrombosis[1] Through 1 Year

	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI][2]
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] See definitions above - ***Stent Thrombosis Definitions***
[2]Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only

SPIRIT III US 4.0 mm Arm

The results are presented in Table 13 (Primary endpoints), Table 14 (Clinical Results), Table 15 (Angiographic Results), and Table 16 (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 13 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 14 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 15 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 16: SPIRIT III 4.0mm ARC defined Definite+Probable Stent Thrombosis[1] 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)
[1] See definitions above - ***Stent Thrombosis Definitions***

B. SPIRIT II Clinical Trial

Study 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.

Clinical Inclusion and Exclusion Criteria

Enrollment in the SPIRIT II clinical trial was limited to subjects who met the eligibility criteria and who provided a signed informed consent form prior to enrollment. Subjects had to be at least 18 years old, with evidence of myocardial ischemia based on the presence of angina, silent ischemia, a positive functional study or reversible ECG changes consistent with ischemia. Female subjects with childbearing potential had to have a negative pregnancy test within 7 days of the index procedure.

Key angiographic inclusion criteria included a maximum of two *de novo* native coronary artery lesions, each within a different epicardial vessel. For the SPIRIT III RCT arm, the reference vessel diameter (RVD) had to be ≥ 2.5 mm and ≤ 3.75 mm, and for the SPIRIT III 4.0 mm arm, the RVD had to be > 3.75 mm and ≤ 4.25 mm. For both the RCT and the 4.0 mm arm, lesion length had to be ≤ 28 mm by visual estimation, percent diameter stenosis (%DS) ≥ 50% and < 100%, and TIMI flow ≥ 1.

Follow-up Schedule

All subjects were scheduled to have clinical follow-up at 30, 180, 270 days and 1, 2, 3, 4 and 5 years, and angiographic follow-up at baseline and 180 days.. A subgroup of 152 consecutive subjects were enrolled at selected sites were scheduled to have IVUS follow-up at baseline, 180 days, 2 years, and angiographic follow-up at 2 years.

Stent Thrombosis Definitions

The protocol and ARC definitions used in SPIRIT II were the same as those described in "***Stent Thrombosis Definitions***

" above.

Clinical Endpoint

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 compared to the TAXUS stent in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. If non-inferiority was demonstrated, it was pre-specified that testing for superiority could be conducted.

Accountability of Subjects

A total of 300 subjects (intent-to-treat) were randomized and enrolled into the SPIRIT II study. At the time of database lock on February 16, 2007, all subjects (100%) completed the 30-day follow-up; 298 subjects (99.3%) completed the 180-day follow-up; 296 subjects (98.7%) completed the 270-day and 365-day follow-up.

A total of 292 subjects (per-treatment evaluable) were enrolled into the SPIRIT II study. At the time of database lock on February 16, 2007, all subjects (100%) completed the 30-day follow-up; 290 subjects (99.3%) completed the 180-day follow-up; 288 subjects (98.6%) completed the 270-day and 365-day follow-up.

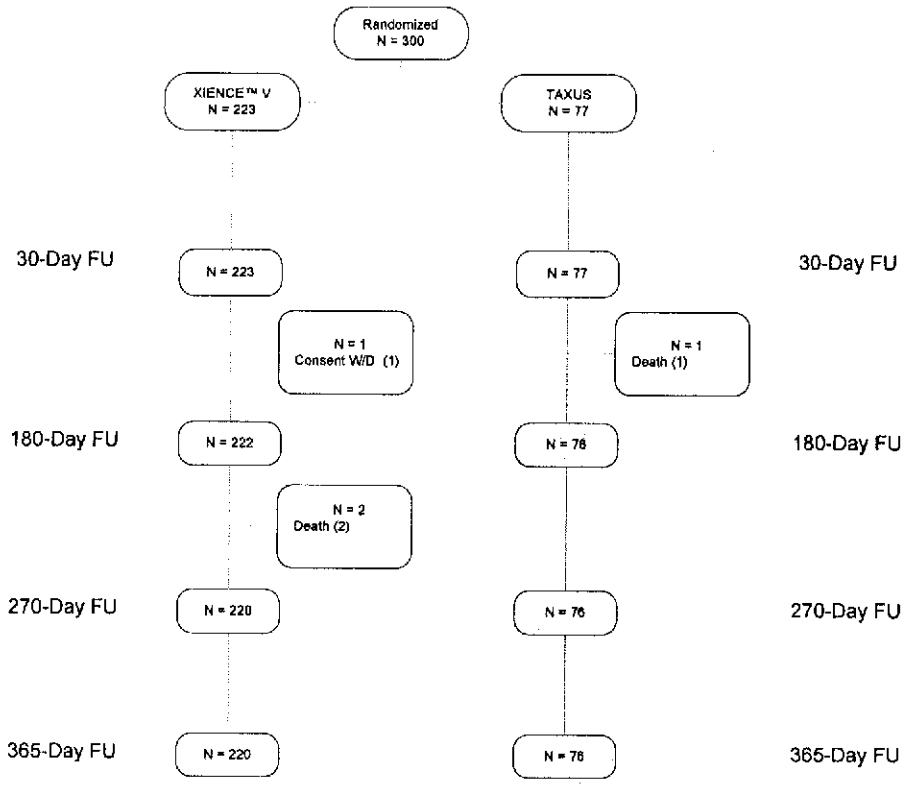


Figure 6 SPIRIT II 1-Year Clinical Follow-Up Subject Disposition (Intent-to-Treat)

Study Population Demographics and Baseline Parameters

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) subjects with prior cardiac interventions and the TAXUS arm had to 22.1% (17/77). The XIENCE V arm had 22.9% (51/223) subjects with a history of diabetes and the TAXUS arm had 23.7% (18/76). The XIENCE V had 16.6% (37/223) 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 XIENCEV arm and the TAXUS arm.

Safety and Effectiveness Results

The results are presented in Table 17 (Primary endpoint), Table 18 (Clinical Results), Table 18 (Angiographic and IVUS Results), and Table 20 (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 17 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.

[1]By normal approximation.
[2]One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16 mm, to be compared at a 0.0448 significance level
[3]P-value from two-sided t-test

Table 18 SPIRIT II Clinical Results

	OUTCOMES AT 180 DAYS			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]

Note:
- 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 19 SPIRIT II 180 Days 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]

Note:
- 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 20 SPIRIT II ARC Defined Definite+Probable Stent Thrombosis[1] Through 2 Years

	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI][2]
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] See definitions above - ***Stent Thrombosis Definitions***
[2] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only

C. 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 21 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 21 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

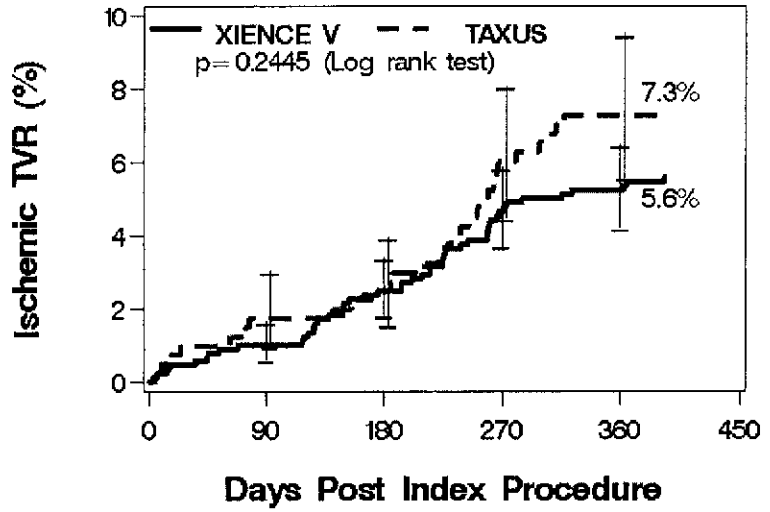
It is acknowledged that these retrospective pooled analyses are exploratory and hypothesis-generating. Definitive proof of the presence or absence of any differences between such sub-groups requires prospectively powered assessment in dedicated clinical trials. The pooled

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 7, 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.

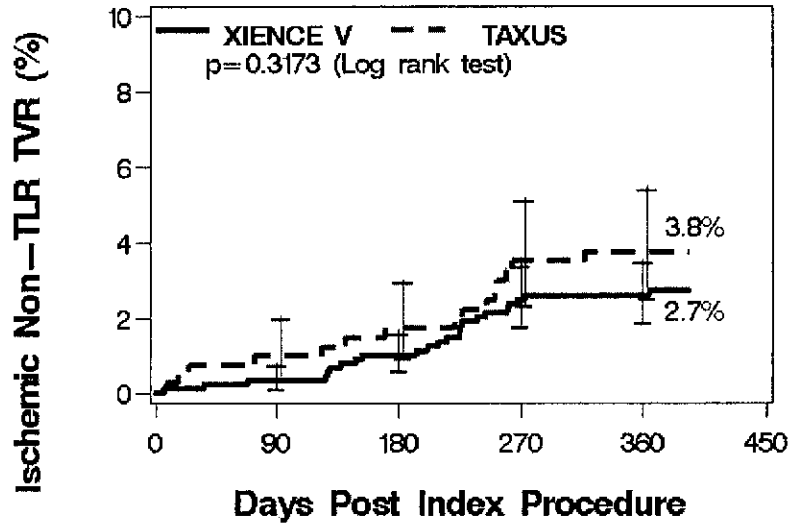
Figure 7 Kaplan Meier Hazard Curves for Time to First TVR or TLR event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

TVR (Includes TLR and Non-TLR TVR)



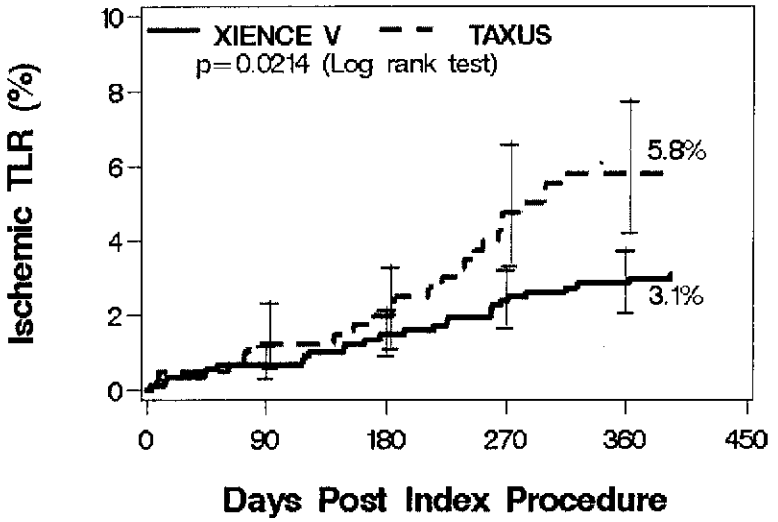
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Non-TLR TVR



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

TLR

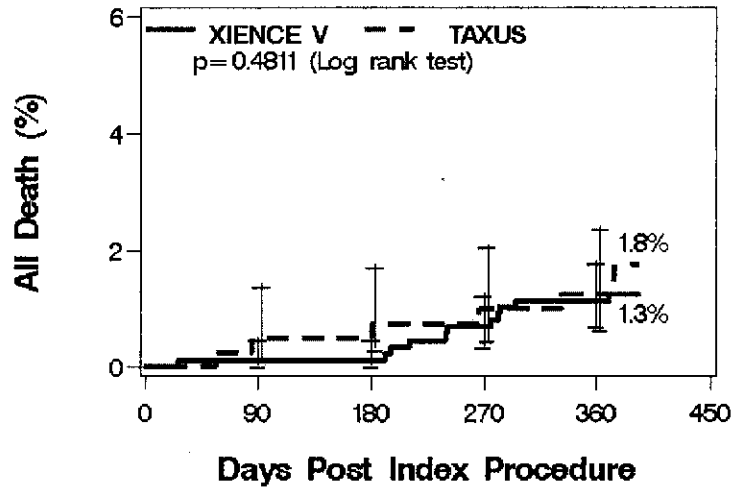


Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of all death, cardiac death, and non-cardiac death through 1 year are shown in Figure 8.

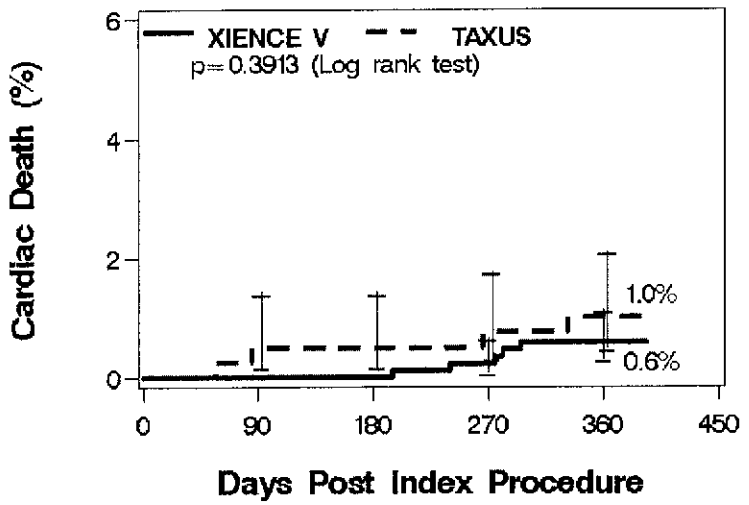
Figure 8 Kaplan Meier Hazard Curves for Time to Death through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

All Death



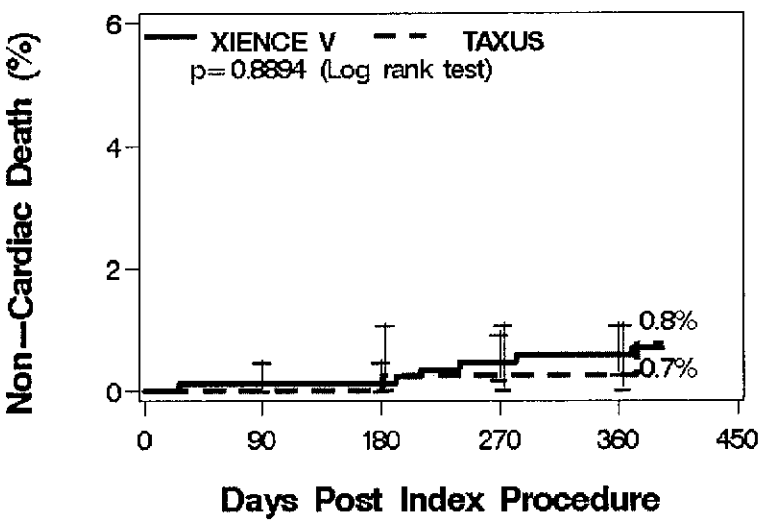
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Cardiac Death



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

Non-Cardiac Death

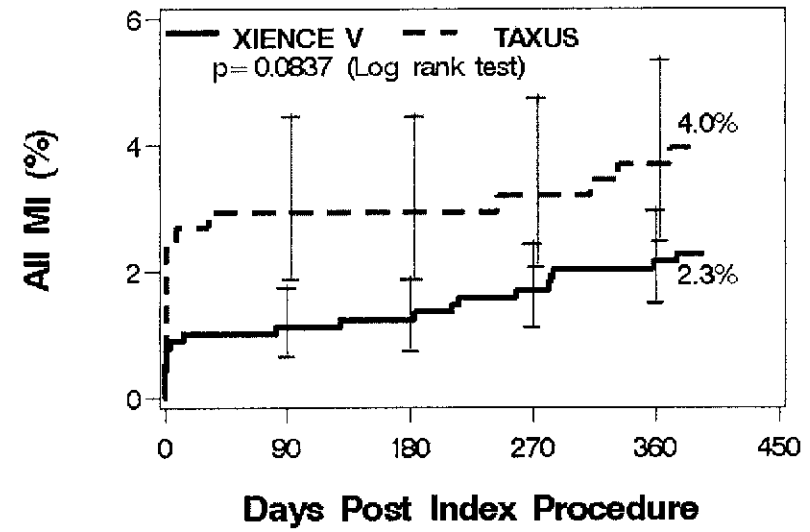


Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of MIs through 1 year are shown in Figure 9.

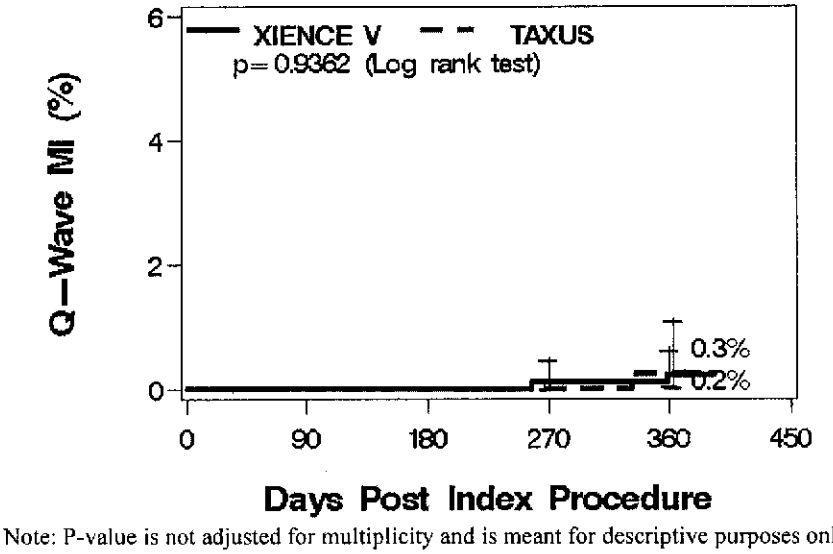
Figure 9 Kaplan Meier Hazard Curves for Time to First MI Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

All MI



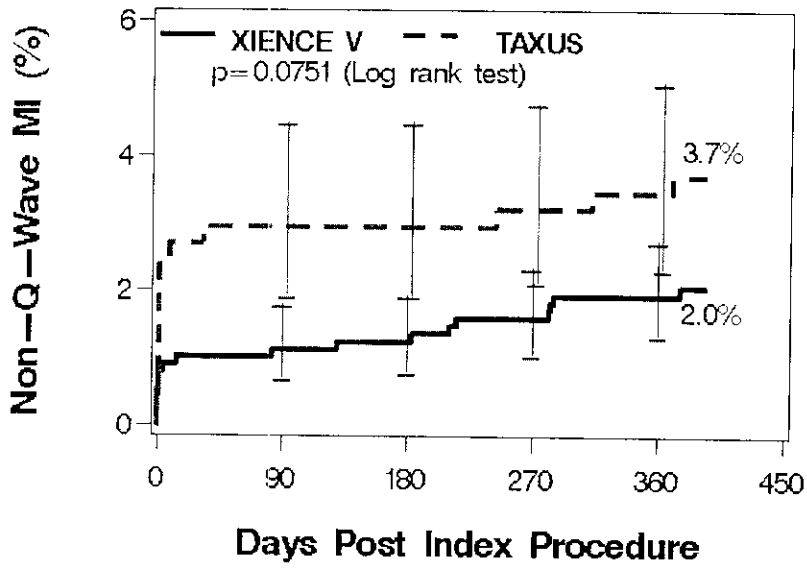
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Q-Wave MI



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

Non-Q-Wave MI



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

C1. Stent Thrombosis in SPIRIT II and SPIRIT III Pooled Analysis

The results for the pooled analysis rates of stent thrombosis are shown below in Figure 11 at one year. Rates were low for both treatments in this pooled analysis and consistent with the published literature[8]. The rates of stent thrombosis were evaluated based on the SPIRIT II and III protocol defined definition and the ARC definition for definite + probable stent thrombosis (see definitions above in ***Stent Thrombosis Definitions***
). The results for protocol and ARC definitions of stent thrombosis over time are summarized in Table 22.

Table 22 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%]

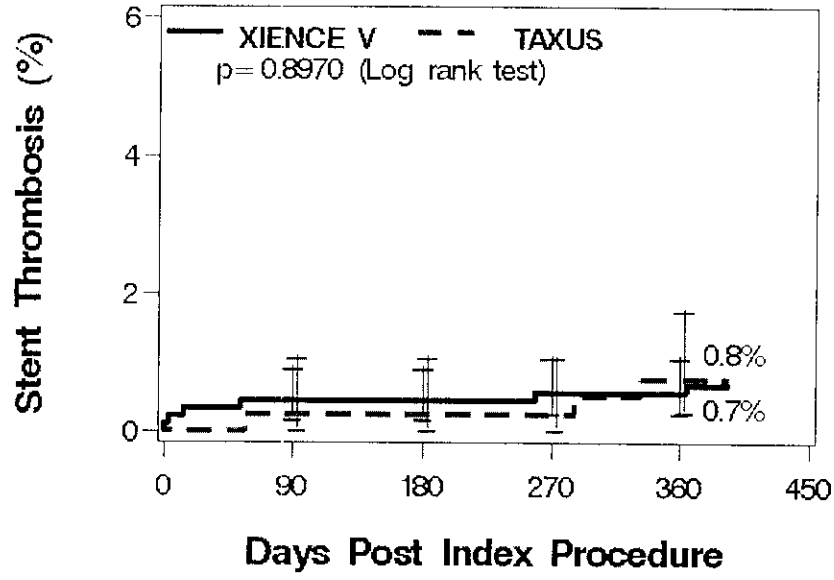
Note: timeframe for 1 year includes the follow-up window (365 + 28 days)

[8] 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.

[1] By Clopper-Pearson Exact Confidence Interval.

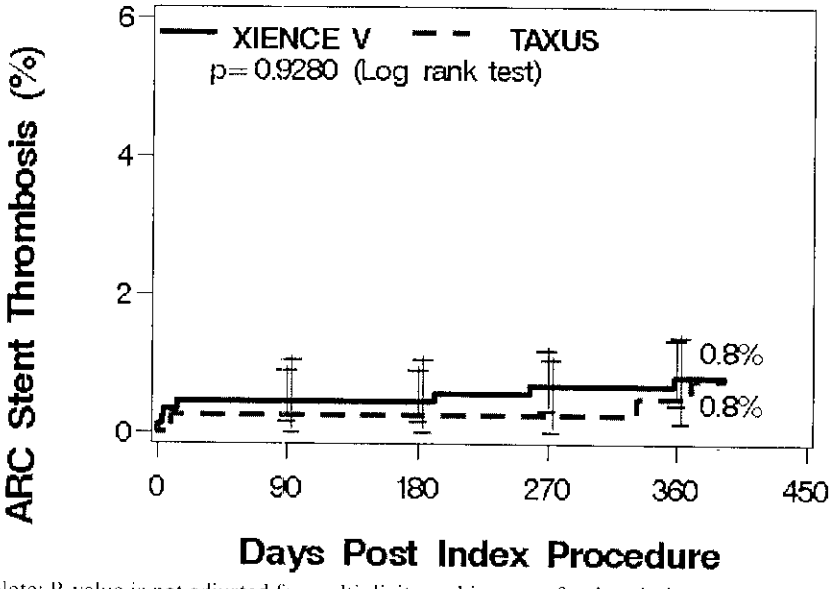
Figure 11 Kaplan Meier Hazard Curves for Time to First Stent Thrombosis Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)

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.

C2. 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 hypothesis or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in diabetic individuals.

Table 23 shows the clinical outcomes through 1 year in subjects pooled from SPRIT 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 are 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 conclusion can be drawn from these post-hoc analyses.

Table 23 Clinical Results in Diabetics and Non-Diabetics through 1 year (SPIRIT II and SPIRIT III RCT Pooled Population)

Non-Hierarchical	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	4.9% (31/629)	9.0% (26/290)	7.4% (18/244)	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% (2/629)	1.4% (4/290)	1.2% (3/244)	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 24 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	4.9% (31/629)	7.4% (18/244)	8.1% (5/62)	7.1% (13/182)
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)

	Non-Diabetics (N=643)	All Diabetics (N=249)	Insulin-Dependent Diabetics (N=63)	Non-Insulin-Dependent Diabetics (N=186)
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)

C3. 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 25 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 conclusion can be drawn from this post-hoc analysis.

Table 25 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	4.9% (36/735)	5.7% (19/333)	9.4% (13/138)	15.6% (10/64)
All Death	1.5% (11/739)	1.2% (4/333)	0.0% (0/138)	4.6% (3/65)
Cardiac Death	0.7% (5/735)	0.6% (2/333)	0.0% (0/138)	3.1% (2/64)
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)
Stent Thrombosis				
Protocol defined	0.3% (2/729)	0.6% (2/332)	2.9% (4/138)	1.6% (1/62)
ARC definite + probable	0.5% (4/730)	0.6% (2/332)	2.2% (3/138)	1.6% (1/62)

D. Global Pharmacokinetics

Study Design

Subjects enrolled at pre-specified sites in the SPIRIT III and SPIRIT II studies were invited to participate in the pharmacokinetic substudy. The global pharmacokinetic data includes a total of 73 subjects (SPIRIT III US, n=17; SPIRIT III Japan, n=17; SPIRIT II OUS, n=39). This includes patients with both single vessel/lesion treatment and dual vessel/lesion treatment. Venous blood was scheduled to be drawn at baseline (prior to 1st stent implant), at 10, 30 minutes, and at 1, 2, 4, 6, 12, 24, 36, 48, 72, 168 and 720 hours (30 days) post-stent implantation.

Endpoints

The primary objective of the pharmacokinetic substudies was to demonstrate the elution of everolimus from the XIENCE V stent in three different geographies. Both SPIRIT II conducted in Europe and SPIRIT III conducted in the United States (Randomized Control Trial - RCT) and Japan (registry) contained pharmacokinetic substudies.

Methods

Whole blood samples were temporarily stored at -30°C or lower at investigational sites and were shipped to a central core laboratory, regardless of the study region. The methodology for everolimus extraction from whole blood and LC-MS/MS analysis was prepared and provided by the core laboratory. Pharmacokinetic analysis of the everolimus blood concentration-time data was conducted using non-compartmental methods.

Study Population Demographics

Patients eligible for participation in the SPIRIT III and SPIRIT II studies were eligible to enroll in the pharmacokinetic substudy. The characteristics of the US pharmacokinetic substudy participants are similar to the characteristics of the entire population that participated in the US RCT.

Results

The results of the pharmacokinetic studies are presented in Table 26 below. In the SPIRIT family of clinical studies, everolimus blood levels were not detected beyond 168 hours post stent implantation except in one patient where blood levels were detected at 720 hours (30 days) post stent implantation. An analytical method with a lower limit of quantitation (LLOQ) of 0.1 ng/mL was used to detect everolimus blood levels in these studies. These findings are consistent with the results of preclinical studies using multiple stents with total everolimus doses above the dose present in clinically available stent systems using a similar assay with LLOQ of 0.1 ng/mL. In all three geographies, the C_{max} never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination; $t_{½}$, AUC_{0-t}, AUC_{last}, AUC_{∞},

and CL could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

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

Table 26 Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation

	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]
SPIRIT III RCT and 4.0 Arm							
		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

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XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

SPIRIT FIRST Randomized Clinical Trial

Study 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) in subjects with *de novo* native coronary artery lesions. Sixty (60) subjects were enrolled in the study with a per-treatment evaluable population of 56 patients.

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, 180 days and 1 year.

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).

Clinical Endpoint

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 *de novo* native coronary artery lesions. This study compared the XIENCE V stent to a matched uncoated metallic stent control (MULTI-LINK VISION).

Study Population Demographics and Baseline Parameters

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 well-matched between the XIENCE V arm and the VISION arm.

Safety and Effectiveness Results

The results are presented in Table 27 (Primary endpoint), Table 28 (Clinical Results), Table 29 (Angiographic and IVUS Results), and Table 30 (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 27 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.
[1]By normal approximation.
[2]One-tailed p-value by t-test, to be compared to a 5% significance level

Table 28 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:

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

[1] 6 month and 3 year time frames include follow-up window (180 +14 days and 730 + 28 days) respectively.

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

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

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

Table 29 SPIRIT FIRST 6 Month 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.

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

Table 30 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

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on November 29, 2007, the Circulatory Systems Devices Panel recommended by a vote of 9 to 1 that Abbott's PMA for the XIENCE V Everolimus Eluting Stent System be approved subject to the submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

1. A post-approval study, the details of which to be worked out between the FDA and the applicant.

2. Labeling that includes language regarding dual antiplatelet therapy use consistent with FDA's proposed changes to currently approved drug-eluting stent labeling following the December 2006 Circulatory System Devices Panel meeting. Specifically, the labeling should describe the use of antiplatelet therapy in the clinical trials and suggest that use through one year may be beneficial per the published consensus guidelines.

B. FDA's Post-Panel Action

CDRH concurred with the Panel's recommendations of November 29, 2007.

Abbott has developed a postapproval study proposal with FDA that addresses the Panel's first recommendation. Specifically, the XIENCE V USA study will evaluate clinical outcomes in a cohort of real world patients receiving the XIENCE V stent during commercial use by various physicians with a range of coronary stenting experience, evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications, determine clinical device and procedural success during commercial use, and evaluate patient health status (symptoms, physical function, and quality of life) by the Seattle Angina Questionnaire.

At least 5000 patients will be consecutively enrolled at up to 275 sites in the United States of America. The primary endpoint of the XIENCE V USA study is stent thrombosis rates annually through to 5 years as defined by Academic Research Consortium (ARC). The co-primary endpoint is a composite endpoint of cardiac death and any myocardial infarction (MI) at 1 year. Data will be analyzed separately for the patients enrolled in accordance with the labeled indication and collectively for all patients enrolled in the study.

To address the Panel's second recommendation, Abbott has provided labeling that describes the use of dual antiplatelet therapy in the SPIRIT family of trials and further states that "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)."

Additionally, Abbott has agreed to conduct or participate in a study that will develop clinical data to identify the optimal duration of dual antiplatelet therapy following percutaneous intervention with the XIENCE V drug-eluting stent.

XIII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of the XIENCE V Everolimus Eluting Coronary Stent System is based on the results obtained from biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing; and clinical studies. These test results revealed the following:

- The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal testing that were conducted demonstrated that the acute and chronic *in vivo* performance characteristics of the product are safe and acceptable for clinical use.
- The *in vitro* engineering testing conducted on the stent and delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the everolimus/polymer coating.
- The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.
- The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 12 months.
- The clinical pharmacokinetics studies provided adequate characterization of the systemic levels of everolimus reached following XIENCE V stent implantation. These data demonstrated that the C_{max} never reached the minimum therapeutic value necessary for effective systemic administration to prevent organ rejection.
- Clinical studies demonstrated that the product provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the Instructions for Use. Specifically, the XIENCE V stent was shown to be non-inferior to an

approved drug-eluting stent with respect to clinical outcomes and superior with respect to angiographic results.

XIV. CDRH DECISION

CDRH issued an approval order on July 2, 2008. The final conditions of approval cited in the approval order are described below.

1. The applicant should collect and report to the Agency on an annual basis clinical outcomes through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death) from SPIRIT FIRST, SPIRIT II, SPIRIT III, and SPIRIT IV. When appropriate or as requested by FDA, the applicant should submit PMA supplements requesting approval to update your Instructions for Use (IFU) to include these data.

2. The applicant should collect clinical data on the implantation of the PMA-approved, commercially-distributed XIENCE V product in the U.S. The trial should be statistically powered to evaluate the annual rates of stent thrombosis, and the rate of cardiac death plus myocardial infarction (MI) through five years in patients treated with the XIENCE V stent according to its labeled indications. These data are needed to evaluate whether the rate of stent thrombosis plateaus or increases over time, and to evaluate the impact of stent thrombosis on rates of cardiac death and MI. These data are also needed to evaluate the potential for rare adverse events related to the drug substance and/or drug carrier that could not be detected in your initial clinical trials. The applicant should also collect additional data on clinical outcomes (including target lesion revascularization rates at 12 months post-implantation) associated with use of the XIENCE V 4.0 mm diameter stent to confirm the outcomes observed in the 4.0 mm Arm of the SPIRIT III trial.

   The applicant has proposed collecting these data from at least 5000 patients enrolled in the XIENCE V USA Postmarket Registry. FDA agrees that the registry protocol submitted in Supplement 97 of the applicant's Investigational Device Exemption (IDE), G050050, with the planned modifications to the statistical analysis plan, is acceptable. Please provide progress reports at 6, 12, 18, and 24 months and annually thereafter through 5 years with data from the U.S. registry. When appropriate or as requested by FDA, the applicant should submit PMA supplements requesting approval to update the IFU to include these data. Please note that if subsequent data analyses identify areas of significant off-label use, the applicant should submit an IDE to conduct an appropriate study to evaluate the off-label use.

3. The applicant should conduct or participate in a study that will develop clinical data to identify the optimal duration of dual antiplatelet therapy following percutaneous intervention with the XIENCE V drug-eluting stent.

   The issue of the optimal duration of dual antiplatelet therapy following PCI with

drug-eluting stents (DES) remains a key question that has not been addressed by any clinical trials conducted to date on the Cordis Cypher DES, the Boston Scientific Taxus Express^2 DES, the Endeavor DES, or the XIENCE V DES. At the December 7 – 8, 2006 meeting of FDA's Circulatory System Devices Advisory Panel meeting on DES thrombosis, the Panel recommended that the labeling for all marketed DES include the then-current ACC/AHA/SCAI guidelines for dual anti-platelet therapy, which specified that patients should receive aspirin indefinitely and clopidogrel for a minimum of 3 or 6 months for the Cypher or Taxus stents, respectively, after implantation, with this duration extended to 12 months in patients who are at low risk for bleeding complications.

However, it is important to recognize that the current recommendation for an extended duration of clopidogrel use reflects a consensus opinion among experts within cardiovascular professional societies based on limited data, rather than on rigorous randomized clinical trials. Further, it is not clear that 12 months is the optimal maximum duration of a dual anti-platelet therapy. In fact, the ACC/AHA/SCAI guidelines were recently revised to specify that patients with low bleeding risks should receive clopidogrel for at least 12 months post-procedure. While extending the duration of clopidogrel use may decrease the risk of very late stent thrombosis events, this strategy may also result in an increased risk for major bleeding complications and involves lifestyle modifications, such as deferral of surgical and dental procedures that may affect a patient's health and overall quality of life. Finally, it is known that stent thrombosis can occur in some individuals despite the continued use of dual antiplatelet therapy. With these considerations in mind, it is imperative that the risks and benefits of continued clopidogrel use be evaluated to determine with greater precision the optimal duration of dual anti-platelet therapy to ensure that these patients receive the best care possible.

Based on the important public health impact of this information, as stated above, the applicant should collect clinical data to identify the optimal duration of dual anti-platelet therapy following PCI with the XIENCE V stent. Such an evaluation should encompass a consecutively enrolled patient population or utilize an approach to enroll patients representative of the actual use of your commercialized product. The applicant may wish to limit the investigation to the XIENCE V stent, or the study may involve pooling with other approved drug-eluting stents. The applicant may also choose to collect these data in a manner that would satisfy, wholly or in part, condition #2 above. When appropriate or as requested by FDA, the applicant should submit PMA supplements requesting approval to update the IFU to include these data. The applicant should submit a proposed plan to address this issue within six months of the date of this letter.

As FDA views the investigation of the optimal duration of dual anti-platelet therapy as a DES class effect, we are requesting that manufacturers of other approved DES collect the same information.

4. The applicant should comply with the commitments made in Amendment 11 related to the implementation of updated final product testing methodologies.

The applicant's manufacturing and sterilization facilities were inspected and found to be in compliance with the device Quality System (QS) regulations (21 CFR 820) and pharmaceutical current Good Manufacturing Practice (cGMP) regulations.

XV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

Hazard to Health from Use of the Product: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.