

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug Eluting Coronary Stent System (NIQ)

Device Trade Name: XIENCE PRIME™ Everolimus Eluting Coronary Stent System
XIENCE PRIME™ LL Everolimus Eluting Coronary Stent System

Applicant's Name and Address: Abbott Vascular
3200 Lakeside Drive
Santa Clara, CA 95054

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110019

Date of FDA Notice of Approval: November 1, 2011

Expedited: Not Applicable

II. INDICATIONS FOR USE

The XIENCE PRIME stent system is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length \leq 32 mm) with reference vessel diameters of \geq 2.25 mm to \leq 4.25 mm.

III. CONTRAINDICATIONS

The XIENCE PRIME stent system 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 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 PRIME and XIENCE PRIME LL Everolimus Eluting Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The XIENCE PRIME family of stent systems includes:

- The XIENCE PRIME Everolimus Eluting Coronary Stent System (stent diameters 2.25, 2.5, 2.75, 3.0, 3.5, 4.0 mm, stent lengths 8, 12, 15, 18, 23 mm)
- XIENCE PRIME LL Everolimus Eluting Coronary Stent System (stent diameters 2.25¹, 2.5, 2.75, 3.0, 3.5, 4.0 mm, stent lengths 28, 33, 38 mm) Everolimus Eluting Coronary Stent Systems

Hereafter the XIENCE PRIME family of stent systems is referred to as the XIENCE PRIME stent or XIENCE PRIME stent system. The XIENCE PRIME stent systems are device/drug combination products consisting of a drug-coated stent and a balloon expandable delivery system. The stent is coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer, which is identical to the XIENCE V[®] Everolimus Eluting Coronary Stent System (XIENCE V EECSS) approved in P070015.

The device component consists of medical grade L-605 cobalt chromium (CoCr) drug-coated stent mounted onto the XIENCE PRIME stent delivery system. The device component characteristics are summarized in **Table 1**.

¹ The 2.25 mm stent diameter for XIENCE PRIME LL is only available in the 28 mm stent length.

Table 1 XIENCE PRIME and XIENCE PRIME LL Product Description

	XIENCE PRIME ECSS	XIENCE PRIME LL ECSS			
Available Stent Lengths (mm)	8, 12, 15, 18, 23	28, 33, 38			
Available Stent Diameters (mm)	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	2.25*, 2.75, 3.0, 3.5, 4.0			
Stent Material	A medical grade L-605 Cobalt Chromium (CoCr) alloy				
Drug Component	Stent Design	Diameters (mm)	Stent Length (mm)	Surface Area (cm ²)	Target Drug Amount (µg)
	Small	2.25, 2.5, 2.75, 3.0	8	0.3972	40
	Small	2.25, 2.5, 2.75, 3.0	12	0.6048	60
	Small	2.25, 2.5, 2.75, 3.0	15	0.7431	74
	Small	2.25, 2.5, 2.75, 3.0	18	0.8815	88
	Small	2.25, 2.5, 2.75, 3.0	23	1.0891	109
	Small	2.25, 2.5, 2.75, 3.0	28	1.3658	137
	Small	2.5, 2.75, 3.0	33	1.5734	157
	Small	2.5, 2.75, 3.0	38	1.8501	185
	Medium	3.5, 4.0	8	0.4979	50
	Medium	3.5, 4.0	12	0.7466	75
	Medium	3.5, 4.0	15	0.9124	91
	Medium	3.5, 4.0	18	1.1612	116
	Medium	3.5, 4.0	23	1.4099	141
	Medium	3.5, 4.0	28	1.7415	174
	Medium	3.5, 4.0	33	1.9903	199
Medium	3.5, 4.0	38	2.3219	232	
Delivery System Working Length	143 cm				
Delivery System Design	Single access port to inflation lumen; guide wire exit notch is located 25.5 cm from tip; designed for guide wires ≤ 0.014".				
Stent Delivery System Balloon	A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length				
Balloon Inflation Pressure	Rated Burst Pressure (RBP): 18 atm (1824 kPa)				
	Stent Diameter (mm)		In Vitro Stent Nominal Pressure (atm)		
	2.25		8		
	2.5		8		
	2.75		8		
	3.0		10		
	3.5		10		
4.0		10			
Guiding Catheter Inner Diameter	≥ 5F (0.056")				
Catheter Shaft Outer Diameter	Distal: 0.034" (0.86 mm)				
	Proximal: 0.031" (0.79 mm)				

* The 2.25 mm diameter stent for XIENCE PRIME LL is only available in the 28 mm stent length.

A. Device Component Description

The XIENCE PRIME stent system consists of the coated Cobalt Chromium (CoCr) alloy stent mounted on a delivery system. The XIENCE PRIME stent uses the identical stent and balloon materials, and the identical drug coating formulation and drug dose density (100ug/cm²) as the XIENCE V Everolimus Eluting Coronary Stent System (P070015 and supplements). The XIENCE PRIME stent design is similar to that of the XIENCE V stent with regard to the Multi-Link Vision Coronary Stent System (P020047 and supplements) stent design in strut thickness and similar metal to artery ratios that, when expanded, allows for similar drug dosing to the vessel. The XIENCE PRIME stent design has been slightly modified from that of the XIENCE V stent design in order to accommodate design improvements while not affecting the overall structural integrity of the design. These modifications include longer cell length and a modified proximal end ring.

The XIENCE PRIME stent delivery system utilizes the same principle of operations as other Abbott Vascular Rapid Exchange (RX) stent systems and dilatation catheters. The XIENCE PRIME stent delivery system materials are similar to those used in the XIENCE V EECSS and the Voyager NC Coronary Dilatation Catheter (DCD) (P810046/S226).

B. Drug Component Description

Identical to the XIENCE V stent, the XIENCE PRIME and XIENCE PRIME LL Everolimus Eluting Coronary Stents (XIENCE PRIME stent) are coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

B1. Everolimus

Everolimus is the active pharmaceutical ingredient in the XIENCE PRIME 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.

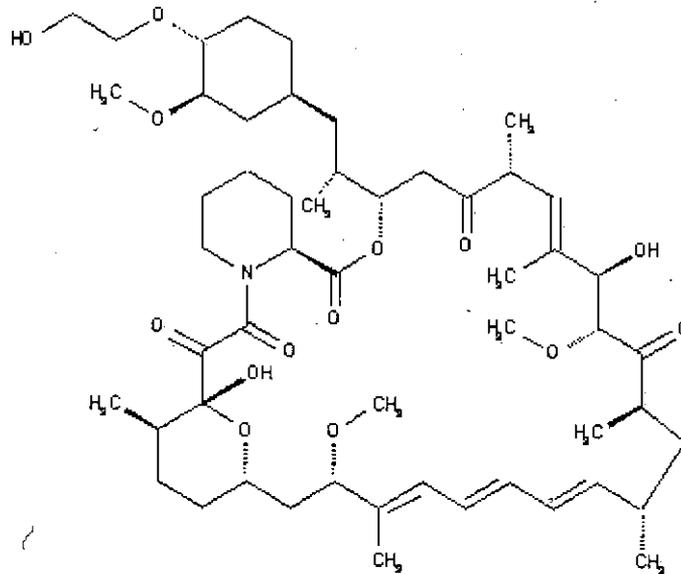


Figure 1 Chemical Structure of Everolimus

B2. Inactive Ingredients

The XIENCE PRIME stent contains inactive ingredients, including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA-coated stent surface. The drug load is 100 µg/cm². No topcoat layer is used. The polymer chemical structures are shown in Figure 2a and 2b below.

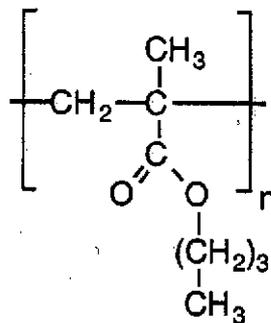


Figure 2a Chemical Structure of Poly (n-butyl methacrylate) (PBMA)

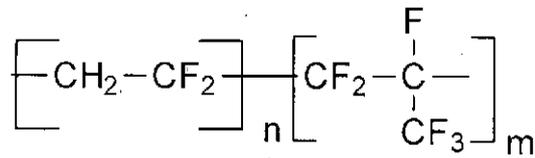


Figure 2b Formula for Vinylidene Fluoride and Hexafluoropropylene Copolymer (PVDF-HFP)

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

Table 2 XIENCE PRIME and XIENCE PRIME LL EECSS Product Matrix and Everolimus Content

XIENCE PRIME™ US and Japan Commercial Part #	Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
1011730-08	2.25	8	40
1011730-12	2.25	12	60
1011730-15	2.25	15	74
1011730-18	2.25	18	88
1011730-23	2.25	23	109
1011730-28	2.25	28	137
1011731-08	2.5	8	40
1011731-12	2.5	12	60
1011731-15	2.5	15	74
1011731-18	2.5	18	88
1011731-23	2.5	23	109
1011731-28	2.5	28	137
1011731-33	2.5	33	157
1011731-38	2.5	38	185
1011732-08	2.75	8	40
1011732-12	2.75	12	60
1011732-15	2.75	15	74
1011732-18	2.75	18	88
1011732-23	2.75	23	109
1011732-28	2.75	28	137
1011732-33	2.75	33	157
1011732-38	2.75	38	185
1011733-08	3.0	8	40
1011733-12	3.0	12	60
1011733-15	3.0	15	74
1011733-18	3.0	18	88
1011733-23	3.0	23	109
1011733-28	3.0	28	137
1011733-33	3.0	33	157
1011733-38	3.0	38	185

Table 2 XIENCE PRIME and XIENCE PRIME LL EECSS Product Matrix and Everolimus Content (cont'd)

XIENCE PRIME™ US and Japan Commercial Part #	Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
1011734-08	3.5	8	50
1011734-12	3.5	12	75
1011734-15	3.5	15	91
1011734-18	3.5	18	116
1011734-23	3.5	23	141
1011734-28	3.5	28	174
1011734-33	3.5	33	199
1011734-38	3.5	38	232
1011735-08	4.0	8	50
1011735-12	4.0	12	75
1011735-15	4.0	15	91
1011735-18	4.0	18	116
1011735-23	4.0	23	141
1011735-28	4.0	28	174
1011735-33	4.0	33	199
1011735-38	4.0	38	232

C. Mechanism of Action

The mechanism by which the XIENCE PRIME stent inhibits neointimal growth as seen in preclinical 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 PRIME and XIENCE PRIME LL Everolimus Eluting Coronary Stent System is commercially available in the following countries:

Afghanistan	France	Luxembourg	Serbia
Albania	French Polynesia	Macedonia	Singapore
Algeria	French Guyana	Malaysia	Slovakia
Aruba	Georgia	Malta	Slovenia
Australia	Germany	Martinique	South Korea
Austria	Greece	Mauritius	Spain
Bahamas	Guadeloupe	Morocco	Sri Lanka
Bahrain	Guatemala	Myanmar	Suriname
Bangladesh	Guyana	Netherlands	Sweden
Barbados	Honduras	New Caledonia	Switzerland
Belgium	Hong Kong	New Zealand	Syria
Belize	Hungary	Nicaragua	Thailand
Bermuda	Iceland	Niederl. Antill.	Trinidad and Tobago
Bolivia	India	Nigeria	Tunisia
Brazil	Indonesia	Norway	Turkey
British Virgin Islands	Iran	Oman	Uganda
Brunei	Iraq	Pakistan	Ukraine
Bulgaria	Ireland	Panama	United Arab Emirates.
Cambodia	Israel	Paraguay	United Kingdom
Cayman Islands	Italy	Philippines	Uruguay
Chile	Jamaica	Poland	Vietnam
Colombia	Jordan	Portugal	Zimbabwe
Cyprus	Kenya	Qatar	
Czech Republic	Kosovo	Rep. of Armenia	
Denmark	Kuwait	Rep. of Yemen	
Dominican Republic	Latvia	Réunion	
Egypt	Lebanon	Romania	
El Salvador	Libya	Russian Federation	
Estonia	Liechtenstein	San Marino	
Finland	Lithuania	Saudi Arabia	

The XIENCE PRIME and XIENCE PRIME LL EECSS have not been withdrawn from marketing in any country for any reason.

As of September 30, 2011, 472,860 XIENCE PRIME™ and XIENCE PRIME™ LL Everolimus Eluting Coronary Stent Systems have been distributed outside of the United States.

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 PRIME and XIENCE PRIME LL Everolimus Eluting Coronary Stent System.

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures, where coronary stents are used 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 (MI)
- Nausea and vomiting
- Palpitations

- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Renal failure
- Restenosis of the stented segment of the artery
- Shock/pulmonary edema
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of coronary artery
- Unstable or stable angina pectoris
- Vascular complications, including at the entry site, which may require vessel repair
- Vessel dissection

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

The following list includes the known risks of everolimus at the oral doses listed above:

- Abdominal pain
- Acne
- Anemia
- Anorexia
- Asthenia
- Coagulopathy
- Cough
- Diarrhea
- Dyspnea
- Dysgeusia
- Dry skin
- Edema peripheral
- Epistaxis
- Fatigue
- Headache
- Hemolysis
- Hypercholesterolemia
- Hyperglycemia
- Hyperlipidemia
- Hypertension
- Hypertriglyceridemia
- Hypogonadism male

- Infections: wound infection, urinary tract infection, pneumonia, pyelonephritis, sepsis and other viral, bacterial, and fungal infections
- Increased serum creatinine
- Leukopenia or lymphopenia
- Pruritus
- Pyrexia
- Liver function test abnormality
- Lung and breathing problems
- Lymphocele
- Mucosal inflammation
- Myalgia
- Nausea
- Non-infectious pneumonitis
- Pain in extremity
- Rash
- Renal tubular necrosis
- Stomatitis
- Surgical wound complication
- Thrombocytopenia
- Venous thromboembolism
- Vomiting

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

For the specific adverse events that occurred in the clinical studies, please see Section X. below.

IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies related to the XIENCE PRIME and XIENCE PRIME LL product were performed. Studies included those performed on the bare metal stent system (Multi-Link family — ML8, VISION and MINI VISION), the combination product XIENCE V or the finished combination product (XIENCE PRIME and XIENCE PRIME LL Stent Systems). Leveraging data from testing performed on the Multi-Link family is appropriate because the stent materials and manufacturing process are identical to the XIENCE PRIME for testing where it is appropriate to test bare metal stents.

A. Laboratory Studies

A1. Biocompatibility Studies

A series of GLP biocompatibility tests were conducted to demonstrate the components of the XIENCE PRIME and XIENCE PRIME LL Everolimus Eluting Coronary Stent System are non-toxic.

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 Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (April 18, 2010)
- 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 USP: Cytotoxicity ISO Elution Test (MEM Extract)	<ul style="list-style-type: none"> • Composite sample of XIENCE PRIME stent and 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: Maximization Test for Delayed Hypersensitivity (ISO)	<ul style="list-style-type: none"> • Composite sample of XIENCE PRIME stent and 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 USP: Intracutaneous (Intradermal) Reactivity Test (ISO)	<ul style="list-style-type: none"> • Composite sample of XIENCE PRIME stent and 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 USP: ISO Acute Systemic Toxicity	• Composite sample of XIENCE PRIME stent and delivery system: Pass (non-toxic)
	USP <88>: Systemic Injection Test (Mouse Injection)	• Polymer-only coated stent: Pass (non-toxic)
Hemocompatibility/Hemolysis*	ISO 10993-4: Hemolysis Test – Extraction Method	Composite sample of XIENCE PRIME stent and delivery system: Pass (non-hemolytic)
	ISO 10993-4: Hemolysis, Direct Contact (Rabbit Red Blood Cells)	• XIENCE V stent: Pass (non-hemolytic)
	ISO 10993-4: Hemolysis, Indirect Contact (Rabbit Red Blood Cells)	• XIENCE V stent: Pass (non-hemolytic)
Complement Activation	ISO 10993-4: Complement Activation Test (C3a and SC5b-9)	XIENCE PRIME stent: Pass XIENCE PRIME delivery system: Pass
Pyrogenicity	ISO 10993-11 USP : LAL Bacterial Endotoxins Test for Medical Devices – Chromogenic Method	Composite sample of XIENCE PRIME stent and delivery system: Pass (non-pyrogenic)
	ISO 10993-11: Systemic Toxicity (Material Mediated Rabbit)	Composite sample of XIENCE PRIME stent and delivery system: Pass (non-pyrogenic)
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	(2.6X XIENCE V stent: Pass (non-

	Reverse Mutation Assay (Ames test)	mutagenic)
	ISO 10993-3: <i>In Vitro</i> 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)

A2. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with FDA “*Guidance for and FDA Staff- Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*,” April 2010, was conducted on the XIENCE PRIME Stent except where the testing could be leveraged from the MULTI-LINK VISION, MULTI-LINK MINI VISION, or MULTI-LINK 8 stents, approved in P020047, P020047/S003, and P020047/017 respectively, or the XIENCE V stent, approved in P070017. Supplementary *in vitro* engineering tests were also performed on the XIENCE PRIME delivery systems containing the XIENCE PRIME 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.

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 ASTM standards (F90, A751, E1086, F1479, E1019, E112, F138, 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
Material 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	<p>Initial pitting corrosion testing conducted on the MULTI-LINK VISION stents (P020047) is leveraged to support the approval of the XIENCE PRIME Stent System. In addition, corrosion testing was conducted on MULTI-LINK 8 stents (P020047/S017) following 400 million cycles (ten year equivalent) of radial fatigue in an overlapped 15 mm static bend. The corrosion testing was conducted according to ASTM F2129 "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. All MULTI-LINK VISION and MULTI-LINK 8 stents tested exceeded the minimum acceptance criteria for rest potential and breakdown potential and therefore exhibited acceptable pitting corrosion resistance.</p> <p>Both bare metal and polymer-only coated XIENCE V stents were tested according to ASTM F2129 to demonstrate that the finished stents exhibit acceptable corrosion resistance.</p> <p>Since the XIENCE PRIME stent is similar in design to the MULTI-LINK VISION and XIENCE V stents, identical to the MULTI-LINK 8 stent, and has the identical material and manufacturing processes as all three stents, the corrosion test results can be leveraged in support of the XIENCE PRIME Stent System.</p>	PASS
Fretting Corrosion	XIENCE PRIME stents were evaluated following 400 million cycles (10 year equivalent) of radial fatigue testing in an overlapped 15mm static bend 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 PRIME 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 (17%) occurring at the smallest stent diameter (2.25 mm).	PASS

Table 4 In Vitro Engineering Studies

Test	Test Description	Results
Stent Uniformity of Expansion Test	Determines the uniformity of expansion along the stent length. XIENCE PRIME 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 XIENCE PRIME stents met product specifications.	PASS
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 XIENCE PRIME stents met product specifications.	PASS
Radial Stiffness	Radial stiffness was evaluated on the XIENCE PRIME stent for information only.	For characterization only
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 XIENCE PRIME stents met product specifications.	PASS
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 of the XIENCE PRIME stent will not likely occur.	PASS
Accelerated Structural Fatigue	<p>Testing was conducted to demonstrate structural durability of the XIENCE PRIME stent under expected in vivo cyclic loading conditions for an equivalent of 10 years (~400 million cycles) in an overlapped configuration on a static bend with a radius of 15 mm.</p> <p>The stents were expanded to the largest intended diameter, and 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.</p>	PASS

Table 4 In Vitro Engineering Studies

Test	Test Description	Results
Magnetic Resonance Imaging (MRI)	<p>Nonclinical testing has demonstrated that the XIENCE PRIME stent, in single and in overlapped configurations up to 71 mm in length, is MR Conditional. It can be scanned safely under the following conditions:</p> <ul style="list-style-type: none"> • Static magnetic field of 1.5 or 3 Tesla • Spatial gradient field of 2500 Gauss/cm or less • Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for up to 15 minutes of scanning for each sequence <p>The XIENCE PRIME stent should not migrate in this MRI environment. Nonclinical 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 PRIME stent.</p> <p>Stent heating was derived by using the measured nonclinical, in vitro temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil in combination with the local specific absorption rates (SARs) in a digitized human heart model. The maximum whole body averaged SAR was determined by validated calculation. At overlapped lengths of up to 71 mm, the XIENCE PRIME stent produced a nonclinical maximum local temperature rise of 3.3°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.</p> <p>The effects of MRI on overlapped stents greater than 71 mm in length or stents with fractured struts are unknown.</p> <p>As demonstrated in nonclinical testing, an image artifact can be present when scanning the XIENCE PRIME 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 PRIME stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of XIENCE PRIME stent.</p> <p>It is suggested that patients register the conditions under which the implant can safely be scanned with the MedicAlert Foundation (www.medicalert.org) or an equivalent organization</p>	PASS

Table 4 In Vitro Engineering Studies

Test	Test Description	Results
Radiopacity	Confirms that the XIENCE PRIME stent is adequately visible under fluoroscopic imaging equipment. Testing indicated that visibility of the XIENCE PRIME stent is comparable to that of the MULTI-LINK VISION and MULTILINK MINI VISION under fluoroscopy.	PASS
Delivery System Dimensional and Functional Attributes		
Catheter Dimensional Measurements	The following characteristics were tested to conform to the applicable specifications: Tip Length, Tip Seal Length, Tip Unsealed Length, Proximal Unsealed Balloon Shaft, Total Catheter Length & Distal Catheter Length, Guide Wire Lumen Dimensions (Tip Inner Diameter (ID) & Distal Shaft Junction Notch ID), Stent Placement, Balloon Shoulder to Marker Alignment, Balloon Working Length, Proximal Shaft Marker Locations (Femoral Marker & Brachial Marker), Delivery System Outer Diameters (Distal Shaft OD, Mid Shaft OD, Proximal Shaft OD, Tip Entry OD, Guide Wire Notch OD). All XIENCE PRIME Stent Systems met product specifications.	PASS
Delivery, Deployment, and Retraction	Design validations demonstrate that the XIENCE PRIME Stent System meets the user needs.	PASS
Balloon Rated Burst Pressure	Statistically demonstrates with 95% confidence, at least 99.9% of the XIENCE PRIME Stent 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 PRIME Stent Systems will not rupture below the maximum labeled compliance (MLC) pressure. All XIENCE PRIME Stent Systems met product specifications and confidence/reliability limits.	PASS
Unconstrained Balloon Fatigue	Statistically demonstrates with 95% confidence, at least 90% of the XIENCE PRIME Stent Systems will sustain 10 repeated inflations to the rated burst pressure inside the stent. All XIENCE PRIME Stent 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 XIENCE PRIME Stent Systems met product specifications.	PASS
Soft Tip Tensile	Determines the tensile strength of the soft tip. All XIENCE PRIME Stent Systems met product specifications.	PASS
Distal Delivery System Tensile	Determines the tensile strength of the distal portion of the delivery system. All XIENCE PRIME Stent Systems met product specifications.	PASS
Proximal Adaptation Tensile Strength	Determines the tensile strength of the proximal adaptation of the delivery system. All XIENCE PRIME Stent 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 XIENCE PRIME Stent 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. Inflation times were tested for information only. All XIENCE PRIME Stent Systems met product specifications for deflation times.	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 XIENCE PRIME Stent Systems met product specifications.	PASS

Table 4 In Vitro Engineering Studies

Test	Test Description	Results
Delivery System Guiding Catheter Pullback	Statistically demonstrates that with 95% confidence, at least 99% of the XIENCE PRIME Stent 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 XIENCE PRIME Stent Systems met product specifications and confidence/reliability limits.	PASS
Delivery System Preparation	Evaluates the ease of preparing the XIENCE PRIME Stent System using the aspiration method. All XIENCE PRIME Stent Systems met product specifications.	PASS
Delivery System Inner Member Collapse	Verifies that irreversible collapse of the inner member does not occur at or below 325 psi. All XIENCE PRIME Stent Systems met product specifications.	PASS
Delivery System Shaft Pressure (Proximal Adaption Pressure Integrity & Catheter Body Pressure Integrity).	Determines the pressure integrity of the catheter shaft proximal to the delivery system balloon. All XIENCE PRIME Stent Systems met product specifications.	PASS
Delivery System Coating Friction (Hydrophilic)	Determines the coefficient of frictions along the hydrophilic coated portion of the XIENCE PRIME catheter using an aorta lined fixture. All XIENCE PRIME Stent Systems met product specifications.	PASS
Delivery System Coating Dry Adhesion (Hydrophilic)	Determines the percent adhesion of the hydrophilic coating to the XIENCE PRIME catheter. The percent coating adhesion is determined by subtracting the percent coating removed from 100. All XIENCE PRIME Stent Systems met product specifications.	PASS
Catheter Kink and Flexibility Test	Determines the radius of curvature at which the delivery system kinks. All XIENCE PRIME Stent Systems met product specifications.	PASS
Catheter Torque Test - Turns to Failure	Determines the minimum number of rotations to break joints and/or materials or to lose functional integrity of the delivery system. All XIENCE PRIME Stent Systems met product specifications.	PASS

A3. Coating Characterization Testing

The coating Characterization testing conducted on the XIENCE PRIME 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: <ul style="list-style-type: none"> • 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, and • 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 PRIME 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 PRIME stent after balloon rupture within the stent. The stents were compared to control stents expanded to nominal diameter.	PASS
Accelerated Coating Fatigue	<p>Testing was conducted to demonstrate coating durability of the XIENCE PRIME stent under expected in vivo cyclic loading conditions for an equivalent of 10 years (~400 million cycles) in an overlapped configuration on a static bend with a radius of 15 mm.</p> <p>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 XIENCE PRIME stents met product specifications and confidence/reliability limits.</p>	PASS
Particulate Matter: Regulatory Tracking Method (Particulates: Stents on a bend)	Determines the particulate matter after navigating simulated, challenging vasculature followed by deployment in a 15 mm radius bend. The XIENCE PRIME 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
Particulate Matter: Beaker Method (Over Expansion)	Determines the particulate matter generated during deployment and over expansion of the XIENCE PRIME 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 particle quantities and sizes were counted and recorded. All stents met product specifications.	PASS

Test	Test Description	Results
Particulate Matter: Tracking on a Bend Method (Overlap Configuration)	Determines the particulate matter after navigating simulated, challenging vasculature followed by deployment of two stents in an overlapped configuration. The XIENCE PRIME system was tracked through tortuous artery model and the stent was deployed constrained to RBP on a bend of the tortuous path. A second stent was then deployed, overlapping the first. Water was drawn through the vasculature and the particle quantities and sizes were counted and recorded. All stents met product specifications.	PASS
Embolitic Fatigue (Overlap Configuration)	Investigates the embolic particle size and count from the XIENCE PRIME stent during an accelerated radial fatigue test. The test was performed under an accelerated pulsatile pressure loading with physiologic displacements for an equivalent of 10 years (~400 million cycles). The stents were tested on a static bend with a radius of 15 mm in an overlapped configuration by overlapping two stents of the same size with an overlapped length of 4 mm. Particle quantities and sizes were recorded from each pair of stents through the testing duration.	PASS

A4. Chemistry, Manufacturing & Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on the XIENCE PRIME 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/Shelf Life**.

Table 6 XIENCE PRIME Stent Release Testing

Test	Test Description
Appearance	A visual inspection is conducted to verify that the XIENCE PRIME meets product appearance specifications.
Identity	Assays are conducted to verify the identity of the drug substance, everolimus, on the XIENCE PRIME stent using two different methods
Total Content	Assay is conducted to quantitatively verify that the total amount of drug on the XIENCE PRIME stent met specification for finished good release.
Content Uniformity	Multiple stents are tested to verify that the uniformity of the drug content between individual stents was within specifications established for finished good release.
Degradation Products	Assays are conducted to quantitatively verify the amount and type of degradation products on the XIENCE PRIME stent.
USP <85> Bacterial Endotoxins Test	The amount of bacterial endotoxins is verified to be within the specification limits established for finished good release.
Sterility Biological Indicator	Release of each lot of XIENCE PRIME stents is based on verification that the individual lot complied with validated sterilization cycle parameters and satisfies the requirement for labeling the finished goods as sterile.
Drug Release	The in vitro drug release profile of the drug substance, everolimus, is measured on the XIENCE PRIME stent. The product meets specifications established for finished good release.
Residual Solvents	The amount of residual solvent is verified to be within the specification limits established for finished good release.
Particulate	Particulate levels are verified to meet product specifications.

A5. Stability/Shelf Life

A formal stability study was conducted to establish a shelf life / expiration date for the XIENCE PRIME Stent System. Testing included appearance, total content, drug release, degradation products, oxygen content, molecular weight and polydispersity, bubble leak test (packaging integrity), endotoxin (pyrogen), particulates, 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 9 months.

A6. Sterilization

The XIENCE PRIME Stent System is sterilized using ethylene oxide (EO) sterilization. The cycle is validated per the ISO 11135-1: 2007 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* Pharmacokinetics

One *in vivo* PK study was carried out in an animal model to evaluate the PK profile of the drug from the XIENCE PRIME stent system and to assess the bioequivalence between the XIENCE PRIME stent system and the XIENCE V Stent System by comparing their drug release profiles through biostatistic analysis.

A summary of the performed PK study to support product safety is included in **Table 4**.

B2. Drug Interactions

Formal drug interaction studies have not been conducted with the XIENCE PRIME stent. Everolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A) isozyme in the gut wall and liver and is a substrate for the countertransporter Pglycoprotein. 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 PRIME 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.

The two *in vivo* safety studies, conducted in the porcine coronary model at 28 and 180 days, demonstrate the safety of the XIENCE PRIME stent system and an overall comparability to the XIENCE V Stent System. The 28 and 180 day time points were selected as key time points to evaluate drug effect and vascular healing following stent implantation.

Summaries of the major animal studies performed to support product safety are included in **Table 7**.

Table 7 GLP Animal Studies for the XIENCE PRIME Stent System Findings

Study #	Stent Design	Animal Model (n)	# of Stents	Follow-up Duration	Endpoints
R0061003 KBP	<p>Test Article: XIENCE PRIME (3.0 x 12 mm, 100 µg/cm²)</p> <p>Control:</p> <ul style="list-style-type: none"> XIENCE V (3.0 x 12 mm, 100 µg/cm²) MULTI-LINK VISION (3.0 x 12 mm) <p>GLP: Yes</p>	Farm Swine (12) (LAD, LCX, RCA) 1 stent/vessel; 2 or 3 stents/animal	Test: 12 (XIENCE PRIME =12) Control: 23 (XIENCE V = 11, MULTI-LINK VISION =12)	28 days	<ul style="list-style-type: none"> Chronic vascular response Quantitative Coronary Angiography Histological & histomorphometric evaluations. Evaluation of degree of endothelialization by SEM
R0061002 KBP	<p>Test Article: XIENCE PRIME (3.0 x 12 mm, 100 µg/cm²)</p> <p>Controls:</p> <ul style="list-style-type: none"> XIENCE V (3.0 x 12 mm, 100 µg/cm²) MULTI-LINK VISION (3.0 x 12 mm) <p>GLP: yes</p>	Yucatan Swine (12) (LAD, LCX, RCA) 1 stent/vessel; 3 stents/animal	Test: 12 (XIENCE PRIME = 12) Control: 24 (XIENCE V = 12, MULTI-LINK VISION = 12)	180 days	<ul style="list-style-type: none"> Quantitative Coronary Angiography Histological & histomorphometric evaluations Evaluation of degree of endothelialization by SEM Chronic vascular response
R0061106 MJL	<p>Test Article: XIENCE PRIME (3.0 x 12 mm, 100 µg/cm²)</p> <p>GLP: yes</p>	Yucatan Swine (8) Farm Swine (16) (LAD, LCX, RCA) 1 stent/vessel 2 or 3 stents/animal	Test: 69 XIENCE PRIME	0.125, 1, 3, 7, 14, 28, 60, 90, 120, 180, 240, 300 days	<ul style="list-style-type: none"> <i>In vivo</i> pharmacokinetics Bioequivalence between XIENCE V and XIENCE PRIME

X. SUMMARY OF CLINICAL STUDIES

The XIENCE PRIME Stent System safety and effectiveness is derived from the SPIRIT PRIME clinical trial that was conducted under IDE #G090068. The SPIRIT PRIME clinical trial was designed to demonstrate the safety and effectiveness of the XIENCE PRIME family of stent systems in improving coronary luminal diameter in subjects with symptomatic heart disease due to a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. This global trial consists of two separate arms, the Core Size Registry and the Long Lesion Registry. One-year results are presented here and yearly follow-up for clinical parameters through 5 years is ongoing. Given the substantial similarities between the XIENCE PRIME and XIENCE V stent systems, clinical trials previously conducted on the XIENCE V stent are also relevant and included in the Instructions For Use (IFU). For additional details on the SPIRIT family of trials, see the SSED for P070015 (http://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015b.pdf).

A. Study Design

The SPIRIT PRIME clinical trial is a prospective, nonrandomized, open-label, multicenter study consisting of two separate arms, the Core Size Registry (stent diameters 2.25, 2.5, 3.0, 3.5, 4.0 mm with stent lengths 8, 18, and 28ⁱⁱ mm) and the Long Lesion Registry (stent diameters, 2.5, 3.0, 3.5, 4.0 mm with stent lengths 33 and 38 mm) in 505 subjects at up to 75 global sites. For clinical trial design purposes, the 28 mm length stent is included in the Core Size Registry because the historical data on XIENCE V used to develop the comparative performance goal includes stent lengths up to 28 mm. The Long Lesion Registry only includes subjects with at least one 33 and 38 mm length stents as there were limited data on these stent lengths from which to develop a comparative performance goal.

Each subject was to receive treatment in up to two *de novo* native coronary lesions, each lesion in a different epicardial vessel. Subjects in the Core Size Registry were allowed to have: one target lesion treated with the core size XIENCE PRIME stent systems (stent diameters 2.25-4.0 mm with stent lengths 8, 18, 28 mm) or two target lesions in separate epicardial vessels, treated with two core size XIENCE PRIME stent systems (stent diameters 2.25-4.0 mm with stent lengths 8, 18, 28 mm).

Subjects in the Long Lesion Registry were allowed to have: one target lesion treated with the XIENCE PRIME stent system (stent diameters 2.5-4.0 mm with stent lengths 33 or 38 mm) or two target lesions in separate epicardial vessels, treated with two XIENCE PRIME stent system (stent diameters 2.5-4.0 mm with stent lengths 33 or 38 mm) or one XIENCE PRIME stent system (stent diameters 2.5-4.0 mm with stent lengths 33 or 38 mm) and one XIENCE PRIME stent system (stent diameters 2.25-4.0 mm with stent lengths 8, 18, 28 mm). All subjects in the Long Lesion Registry were required to be treated with at least one XIENCE

ⁱⁱ The 28 mm length stent was studied in the XIENCE PRIME Core Size Registry. The results of the Core Size Registry are presented in Table 10.

PRIME stent of 33 or 38 mm in length. For both the Core Size Registry and Long Lesion Registry, planned overlap was not allowed, however overlap was allowed in case of bailout stenting.

The primary endpoint is target lesion failure (TLF) at one year, a composite endpoint of cardiac death, target vessel myocardial infarction (TV-MI), and clinically indicated target lesion revascularization (CI-TLR). The primary endpoint rates of TLF at 1 year (per protocol and per ARC definitions) were compared to a set of pre-specified performance goals (PGs) for both Core Size Registry and Long Lesion Registry as shown below.

The PG for the Core Size Registry was developed utilizing historical data from the SPIRIT III trial, while the PG for the Long Lesion Registry was developed based on a regression analysis conducted on the historical data from the pooled SPIRIT II and III trials. Although the SPIRIT PRIME trial defined TLF based on the ARC definition of MI, the historical SPIRIT II and III trials used to develop the initial PG were based on the per protocol definition of MI. In order to provide a comparison of outcomes using the same definitions for both the treatment arms and PGs, two subsequent analyses, with PGs developed using the same definitions (per protocol and per ARC), were developed and are presented in rows 2 and 3 of the table below.

Table 8 Analyses of the Primary Endpoint

TLF Primary Endpoint	Core Size Registry* Performance Goal	Long Lesion Registry** Performance Goal
TLF Cardiac Death, <i>ARC-Defined TV-MI, CI-TLR</i>	9.2% ¹	19.2% ¹
TLF Cardiac death, <i>Protocol-Defined TV-MI, CI-TLR</i>	9.2% ¹	19.2% ¹
TLF Cardiac death, <i>ARC-Defined TV-MI, CI-TLR</i>	15.3% ²	26.0% ²

¹ Performance goal developed based on per protocol-defined MI.

² Performance goal developed based on per ARC-defined MI.

* The Core Size Registry includes 2.25 - 4.0 mm stent diameters, 8, 18, 28 mm lengths

** The Long Lesion Registry includes 2.5 - 4.0 mm stent diameters, 33 and 38 mm stent lengths

The primary analysis of the SPIRIT PRIME data was performed on the Full Analysis Set (FAS) population which was defined as the subjects who received the XIENCE PRIME stent. The Intent to Treat (ITT) population was defined as the subjects enrolled into the study, regardless of the treatment actually received; this population excludes de-registered subjects.

The clinical trial design for SPIRIT PRIME is summarized in **Table 9**.

Table 9 SPIRIT PRIME Clinical Trial Design

	SPIRIT PRIME
Study Type/Design	<ul style="list-style-type: none"> • Prospective • Two-arm • Open-label • Multi-center • Registry
Number of Subjects Enrolled	Total 529 Core Size Registry 419 Long Lesion Registry 110
Treatment	Maximum of two <i>de novo</i> coronary lesions, each in a different epicardial vessel.
Lesion Size	<p>XIENCE PRIME, Core Size RVD: ≥ 2.25 mm and ≤ 4.25 mm Lesion Length: ≤ 22 mm</p> <p>XIENCE PRIME, Long Lesion RVD: ≥ 2.5 mm and ≤ 4.25 mm Lesion Length: > 22 mm and ≤ 32 mm</p>
Stent Sizes	<p>Core Size Registry Stent diameter: 2.25, 2.5, 3.0, 3.5, and 4.0mm Stent Lengths: 8, 18, and 28 mm</p> <p>Long Lesion Registry Stent diameter: 2.5, 3.0, 3.5, and 4.0 mm Stent Length: 33 and 38 mm</p>
Post-procedure Antiplatelet Therapy	Clopidogrel 12 months minimum (or ticlopidine per site standard), aspirin indefinitely
Primary Endpoint	Target lesion failure (TLF) defined as the composite rate of cardiac death, target vessel myocardial infarction (TV-MI) and clinically indicated target lesion revascularization (CI-TLR) at 1year.
Co-Primary Endpoint	None
Major Secondary Endpoint	None
Clinical Follow-up	30 days, 180 days, 1-5 years
Angiographic Follow-up	None
IVUS Follow-up	None
PK Study	None
Status	One year reported

1. Clinical Inclusion/Exclusion Criteria

Enrollment in the SPIRIT PRIME 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.

Angiographic Inclusion Criteria

- One or two *de novo* target lesions each in a different epicardial vessel.
- If there are two target lesions, both lesions must satisfy the angiographic eligibility criteria for that registry.
- Multiple focal *de novo* lesions in a target vessel that can be covered by a single stent are allowed.
- The target lesion(s) must be located in a major artery or branch with a visually estimated diameter stenosis of $\geq 50\%$ and $< 100\%$ with a TIMI flow of ≥ 1 .
- Target lesion(s) must be located in a native coronary artery with vessel diameter by visual estimation of:
 - ≥ 2.25 mm and ≤ 4.25 mm for treatment by the core size XIENCE PRIME stent
 - 2.5 mm and ≤ 4.25 mm for treatment by the XIENCE PRIME LL stent
- Target lesion(s) must be located in a native coronary artery with length by visual estimation of:
 - ≤ 22 mm for treatment by the core size XIENCE PRIME stent
 - >22 mm and ≤ 32 mm for treatment by the XIENCE PRIME LL stent

Angiographic Exclusion Criteria

All angiographic exclusion criteria are based on visual estimation.

- Target lesion located within an arterial or saphenous vein graft or distal to a diseased (vessel irregularity per angiogram and $> 20\%$ stenosed lesion) arterial or saphenous vein graft.
- Target lesion involving a bifurcation with a side branch ≥ 2 mm in diameter and/or ostial lesion $> 40\%$ stenosed or side branch requiring protection guide wire, or side branch requiring predilatation.
- Target lesion with total occlusion (TIMI flow 0), prior to crossing with wire.
- Another lesion requiring revascularization is located in the same epicardial vessel of the target lesion.
- Restenotic target lesion.
- Aorto-ostial target lesion (within 3 mm of the aorta junction).
- Target lesion is in a left main location.
- Target lesion located within 2 mm of the origin of the LAD or LCX.
- Extreme angulation ($\geq 90^\circ$) or excessive tortuosity (\geq two 45° angles) proximal to or within the target lesion.
- Heavy calcification proximal to or within the target lesion.
- Target vessel contains thrombus as indicated in the angiographic images.
- Target lesion has a high probability that a procedure other than pre-dilatation and stenting will be required at the time of index procedure for treatment of the target vessel (e.g. atherectomy, cutting balloon).
- Target vessel was previously treated with any type of PCI (e.g. balloon angioplasty, stent, cutting balloon, atherectomy) < 9 months prior to index procedure.

- Non-target vessel was previously treated with any type of PCI < 90 days prior to the index procedure.
- Additional clinically significant lesion(s) (e.g. %DS \geq 50%) in a target vessel or side branch for which PCI may be required < 90 days after the index procedure.

2. Follow-up Schedule

All subjects will be followed up to five years. All subjects were required to have a hospital or office follow-up visit at 30 days and 1 year. There was the option for an office or telephone follow-up visits at 180 days and 2-5 years.

3. Stent Thrombosis Definitions

Stent Thrombosis (ST) was defined in the protocol as clinical presentation of acute coronary syndrome with angiographic appearance of thrombus within or adjacent to a previously treated target lesion. In the absence of angiography, any unexplained death, or acute MI (ST segment elevation or new Q-wave in the distribution of the target lesion within 30 days. Stent thrombosis was categorized as acute (\leq 1day), subacute ($>$ 1day \leq 30 days) and late ($>$ 30 days).

Stent thrombosis was defined by ARC criteria as:

- Definite (angiographic confirmation with at least one of the following: acute onset of ischemic symptoms at rest, new ischemic changes suggestive of acute ischemia, typical rise and fall of cardiac biomarkers, or non-occlusive or occlusive thrombus)
- Probable (any unexplained death within the first 30 days or, irrespective of the time after the index procedure, any MI related to documented acute ischemia in the territory of the stent without angiographic confirmation), and
- Possible (any unexplained death from 30 days to end of trial follow-up).

Timing:

- Acute ST: 0 to 24 hours post stent implantation
- Subacute ST: $>$ 24 hours - 30 days post stent implantation
- Late ST: 30 days to 1 year post stent implantation
- Very late ST: $>$ 1 year post stent implantation

Level of probability:

- Definite ST - considered to have occurred by either angiographic or pathologic confirmation.
- Probable ST - considered to have occurred after intracoronary stenting in the following cases:
 1. Any unexplained death within the first 30 days.

2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.
- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up.ⁱⁱⁱ

4. Clinical Endpoints

The SPIRIT PRIME clinical trial primary endpoint was TLF at 1 year, defined as the composite of:

1. Cardiac death
2. Target Vessel Myocardial Infarction (TV-MI)
3. Clinically-indicated Target Lesion Revascularization (TLR).

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

- Acute Success: (combined clinical and angiographic)
- Clinical Device Success (Lesion basis)
- Clinical Procedural Success (Subject basis)
- Procedure time (from insertion to withdrawal of guide catheter)
- Clinical Endpoint in hospital and at each clinical follow-up time point (30 days, 180 days, 1,2,3,4 and 5 years):
 - All Death (Cardiac, Vascular, Non-cardiovascular)
 - TV-MI - Q-wave and non Q-wave (defined as MI not clearly attributable to a non-target vessel)
 - Non-target vessel MI (Q-wave, Non Q-wave)
 - CI-TLR
 - Clinically indicated Target Vessel Revascularization (TVR = TLR and non-TLR in TV)
 - All TLR (CI and non-CI)
 - All TVR (CI and non-CI)
 - All Coronary Revascularization (TVR and non-TVR)
 - Cardiac Death/All MI
 - Cardiac Death/All MI/CI-TLR
 - All Death/All MI/All Coronary Revascularization
 - Stent Thrombosis (per protocol and per ARC)

ⁱⁱⁱ All data presented as definite + probable only.

B. Accountability of Subjects

SPIRIT PRIME Core Size Registry: The Core Size Registry analysis population had a total of 419 subjects. The ITT population consisted of 415 subjects, as four subjects were de-registered. The FAS population (only subjects receiving a XIENCE PRIME stent with stent diameters 2.25 - 4.0 and stent lengths 8, 18, 28 mm) consisted of 413 subjects. Only subjects with available cardiac enzyme data in window (between 8 hours post-procedure and hospital discharge) were included in the main data analysis of the primary and secondary endpoints in the FAS and ITT, resulting in a population of 401. The 401 subjects in the FAS population received a total of 484 XIENCE PRIME stent with stent diameters 2.25 - 4.0 and stent lengths 8, 18, 28 mm. Of the 401 subjects 88.3% (354/401) of these subjects were single target lesion subjects and 11.7% (47/401) were dual target lesion subjects.

SPIRIT PRIME Long Lesion Registry: The Long Lesion Registry analysis population had a total of 110 subjects. The ITT population consisted of 110 subjects and the FAS population (only subjects receiving at least one XIENCE PRIME stent with stent diameters 2.5 - 4.0 mm and stent lengths 33 and 38 mm) consisted of 107 subjects. Only subjects with available cardiac enzyme data in window (between 8 hours post-procedure and hospital discharge) were included in the main data analysis of the primary and secondary endpoints in the FAS and ITT, resulting in an ITT population of 106 and a FAS population of 104. The 104 subjects in the FAS population received a total of 105 XIENCE PRIME stent with stent diameters 2.5 - 4.0 mm and stent lengths 33 and 38 mm and 46 XIENCE PRIME stent with stent diameters 2.25 - 4.0 and stent lengths 8, 18, 28 mm. Of the 104 subjects, 80.8% (84/104) were single target lesion subjects and 19.2% (20/104) were dual target lesion subjects.

C. Study Population Demographics and Baseline Parameters

SPIRIT PRIME Core Size Registry: In the Core Size Registry, the mean age was 62.70 ± 10.23 years, 70.3% (282/401) were male, 29.7% (119/401) were female and 92.3% (346/375) were white. The average body mass index (BMI) was 30.86 ± 5.83 kg/m² and 50.3% (192/382) of subjects were obese, with a BMI ≥ 30 . Regarding medical risk factors in the Core Size Registry, 19.2% (77/401) were tobacco users, 76.6% (307/401) were hypertensive requiring medication, and 80.3% (322/401) were hypercholesterolemic requiring medication. There were 11.1% (44/397) of subjects having had a prior cardiac intervention on the target vessel and 23.0% (91/395) had a prior MI. In addition, there were 45.6% (183/401) of subjects with stable angina and 24.9% (100/401) of subjects with unstable angina. Furthermore, the Core Size Registry consisted of 34.9% (140/401) diabetics, 29.9% (120/401) diabetics requiring medication and 3.5% (14/401) diabetics requiring diet and exercise only.

SPIRIT PRIME Long Lesion Registry: In the Long Lesion Registry, the mean age was 63.46 ± 9.44 years, 62.5% (65/104) were male, 37.5% (39/104) were female and 91.7% (88/96) were white. The average body mass index (BMI) was 30.67 ± 5.84 kg/m², and 49.5% (50/101) of subjects were obese, with a BMI ≥ 30 . Regarding medical risk factors in

the Long Lesion Registry, 26.9% (28/104) were tobacco users, 75.0% (78/104) were hypertensive requiring medication, and 80.8% (84/104) were hypercholesterolemic requiring medication. There were 11.8% (12/102) of subjects having had a prior cardiac intervention on the target vessel and 22.5% (23/102) had a prior MI. In addition, there were 49.0% (51/104) of subjects with stable angina and 23.1% (24/104) of subjects with unstable angina. Furthermore, the Long Lesion Registry consisted of 35.6% (37/104) diabetics, 31.7% (33/104) diabetics requiring medication and 1.9% (2/104) diabetics requiring diet and exercise only.

D. Safety and Effectiveness Results

The results are presented in **Table 10** (Primary endpoint), **Table 11** (Core Size Registry Clinical Results), and **Table 12** (Long Lesion Registry Clinical Results). The primary endpoints and the components are presented in **Figure 3** and **Figure 4** for the Core Size Registry and in **Figure 5** and **Figure 6** for the Long Lesion Registry. These analyses are based on the Full Analysis Set (FAS). The FAS population is defined as subjects who have received at least one XIENCE PRIME stent including bailout. SPIRIT PRIME Core Size and Long Lesion Registries met all pre-specified PGs with statistical significance. The observed TLF rate at one year was 4.5% (18/399) (per protocol defined MI) and 6.5% (26/399) (per ARC defined MI) in the Core Size Registry, and 7.7% (8/104) (per protocol defined MI) and 12.5% (13/104) (per ARC defined MI) in the Long Lesion Registry respectively.

Table 10 SPIRIT PRIME Primary Endpoint Results

Core Size Registry*	XIENCE PRIME (N=401)	Performance Goal	P-Value¹
1 Year TLF Cardiac Death, <i>ARC-Defined TV-MI, CI-TLR</i>	6.5% (26/399)	9.2% [§]	0.0338
1 Year TLF Cardiac Death, <i>Protocol-Defined TV-MI, CI-TLR</i>	4.5% (18/399)	9.2% [§]	0.0003
1 Year TLF Cardiac Death, <i>ARC-Defined TV-MI, CI-TLR</i>	6.5% (26/399)	15.3% [#]	< 0.0001
Long Lesion Registry**	XIENCE PRIME (N=104)	Performance Goal	P-Value¹
1 Year TLF Cardiac Death, <i>ARC-Defined TV-MI, CI-TLR</i>	12.5% (13/104)	19.2% [§]	0.0484
1 Year TLF Cardiac Death, <i>Protocol-Defined TV-MI, CI-TLR</i>	7.7% (8/104)	19.2% [§]	0.0009
1 Year TLF Cardiac Death, <i>ARC-Defined TV-MI, CI-TLR</i>	12.5% (13/104)	26.0% [#]	0.0006

Notes:

- N is the total number of subjects.
- Population for SPIRIT PRIME consists of those subjects who were treated with at least one PRIME stent and had cardiac enzyme data between 8 hour post index procedure and hospital discharge.
- TLF includes cardiac death, target vessel MI and clinically indicated TLR.
- Time Frame includes follow-up window (365 + 28 days).
- ¹ One-sided p-value against pre-specified performed goals, to be compared at a 0.05 significance level.
- [§] Performance Goal developed based on per-protocol definition MI.
- [#] Performance Goal developed based on per-ARC definition MI.
- * The Core Size Registry includes 2.25 - 4.0 mm stent diameters, 8, 18, 28 mm lengths
- ** The Long Lesion Registry includes 2.5 - 4.0 mm stent diameters, 33 and 38 mm stent lengths

Table 11 SPIRIT PRIME Core Size Registry Clinical Results*

	OUTCOMES AT 1-YEAR Core Size Registry (N=401)
COMPOSITE EFFECTIVENESS & SAFETY	
TLF (per protocol)	4.5% (18/399)
TLF (per ARC)	6.5% (26/399)
EFFECTIVENESS	
CI-TLR	2.5% (10/399)
CI-TLR, CABG	0.3% (1/399)
CI-TLR, PCI	2.5% (10/399)
CI-TVR	4.5% (18/399)
SAFETY	
All Death	0.8% (3/399)
Cardiac Death	0.3% (1/399)
Non-Cardiac Death	0.5% (2/399)
Target Vessel MI (per protocol)	1.8% (7/399)
Target Vessel QMI (per protocol)	0.3% (1/399)
Target Vessel NQMI (per protocol)	1.5% (6/399)
All MI (per protocol)	1.8% (7/399)
QMI (per protocol)	0.3% (1/399)
NQMI (per protocol)	1.5% (6/399)
Target Vessel MI (per ARC)	4.0% (16/399)
Target Vessel QMI (per ARC)	0.3% (1/399)
Target Vessel NQMI (per ARC)	3.8% (15/399)
All MI (per ARC)	4.5% (18/399)
QMI (per ARC)	0.3% (1/399)
NQMI (per ARC)	4.3% (17/399)
Cardiac Death or All protocol MI	2.0% (8/399)
Cardiac Death or All ARC MI	4.8% (19/399)
ARC Definite + Probable Stent Thrombosis	
Cumulative through 1 year	0.5% (2/399)
Acute/Subacute (0 – 30 days)	0.5% (2/401)
Late (31 days – 1 year)	0.0% (0/399)

Notes:

- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI, and clinically-indicated TLR.
- Population for SPIRIT PRIME Core Size Registry consists of those subjects who were treated with at least one PRIME stent and had cardiac enzyme data between 8 hour post index procedure and hospital discharge.
- ARC: Academic Research Consortium
- * The Core Size Registry includes 2.25 - 4.0 mm stent diameters, 8, 18, 28 mm lengths

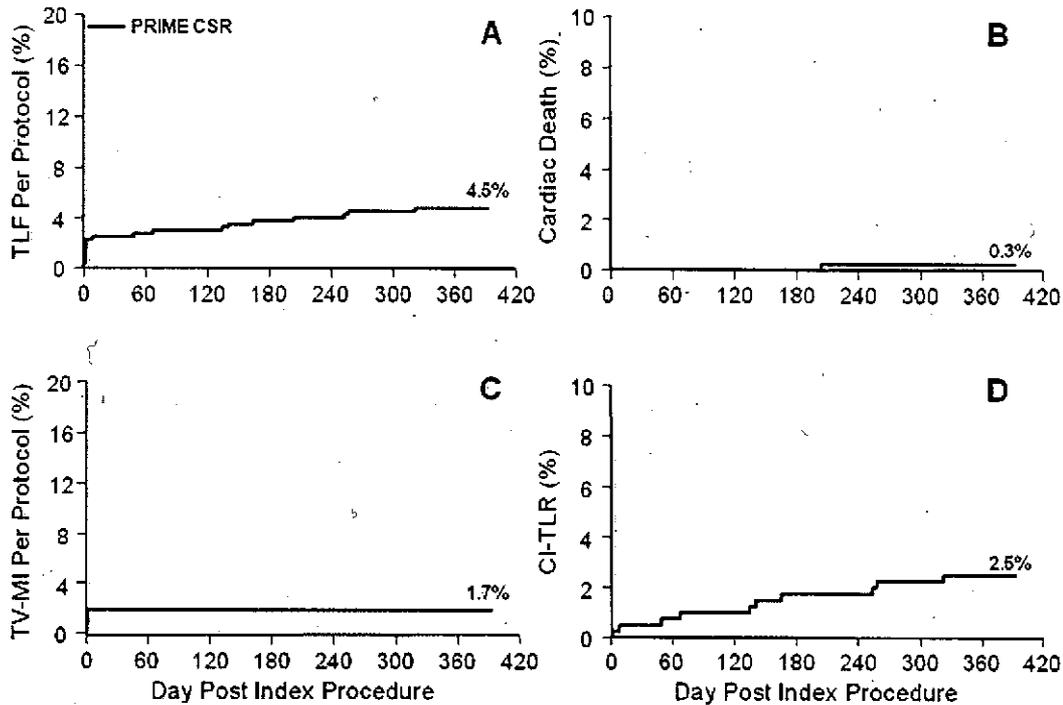


Figure 3 Core Size Registry Primary endpoint-TLF at 1 year per protocol (A) and its components of cardiac death (B), TV-MI per protocol (C) and CI-TLR (D)

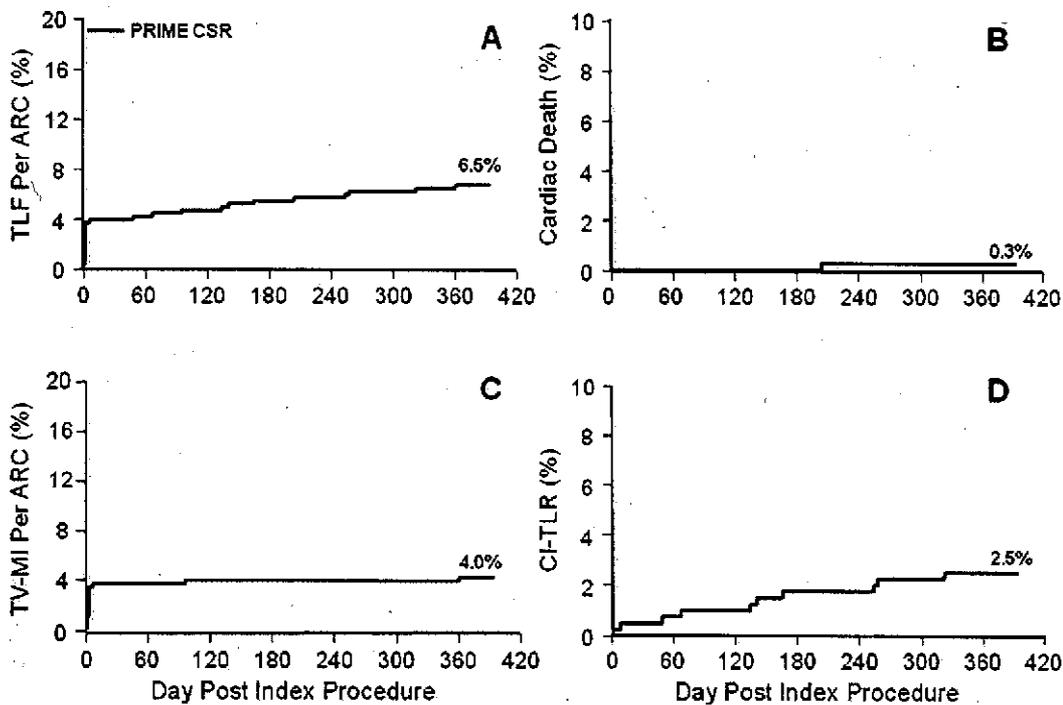


Figure 4 Core Size Registry-Primary endpoint-TLF at 1 year per ARC (A) and its components of cardiac death (B), TV-MI per protocol (C) and CI-TLR (D)

Table 12 SPIRIT PRIME Long Lesion Registry Clinical Results*

	OUTCOMES AT 1 YEAR Long Lesion Registry (N=104)
COMPOSITE EFFECTIVENESS & SAFETY	
TLF (per protocol)	7.7% (8/104)
TLF (per ARC)	12.5% (13/104)
EFFECTIVENESS	
CI-TLR	2.9% (3/104)
CI-TLR, CABG	0.0% (0/104)
CI-TLR, PCI	2.9% (3/104)
CI-TVR	4.8% (5/104)
SAFETY	
All Death	1.0% (1/104)
Cardiac Death	0.0% (0/104)
Non-Cardiac Death	1.0% (1/104)
Target Vessel MI (per protocol)	4.8% (5/104)
Target Vessel QMI (per protocol)	1.9% (2/104)
Target Vessel NQMI (per protocol)	2.9% (3/104)
All MI (per protocol)	4.8% (5/104)
QMI (per protocol)	1.9% (2/104)
NQMI (per protocol)	2.9% (3/104)
Target Vessel MI (per ARC)	10.6% (11/104)
Target Vessel QMI (per ARC)	1.9% (2/104)
Target Vessel NQMI (per ARC)	8.7% (9/104)
All MI (per ARC)	10.6% (11/104)
QMI (per ARC)	1.9% (2/104)
Cardiac Death or All protocol MI	4.8% (5/104)
Cardiac Death or All ARC MI	10.6% (11/104)
ARC Definite + Probable Stent Thrombosis	
Cumulative through 1 year	0.0% (0/104)
Acute/Subacute (0 – 30 days)	0.0% (0/104)
Late (31 days – 1 year)	0.0% (0/104)

Notes:

- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI, and clinically-indicated TLR.
- Population for SPIRIT PRIME Core Size Registry consists of those subjects who were treated with at least one PRIME stent and had cardiac enzyme data between 8 hour post index procedure and hospital discharge.
- ARC: Academic Research Consortium
- * The Long Lesion Registry includes 2.5 - 4.0 mm stent diameters, 33 and 38 mm stent lengths

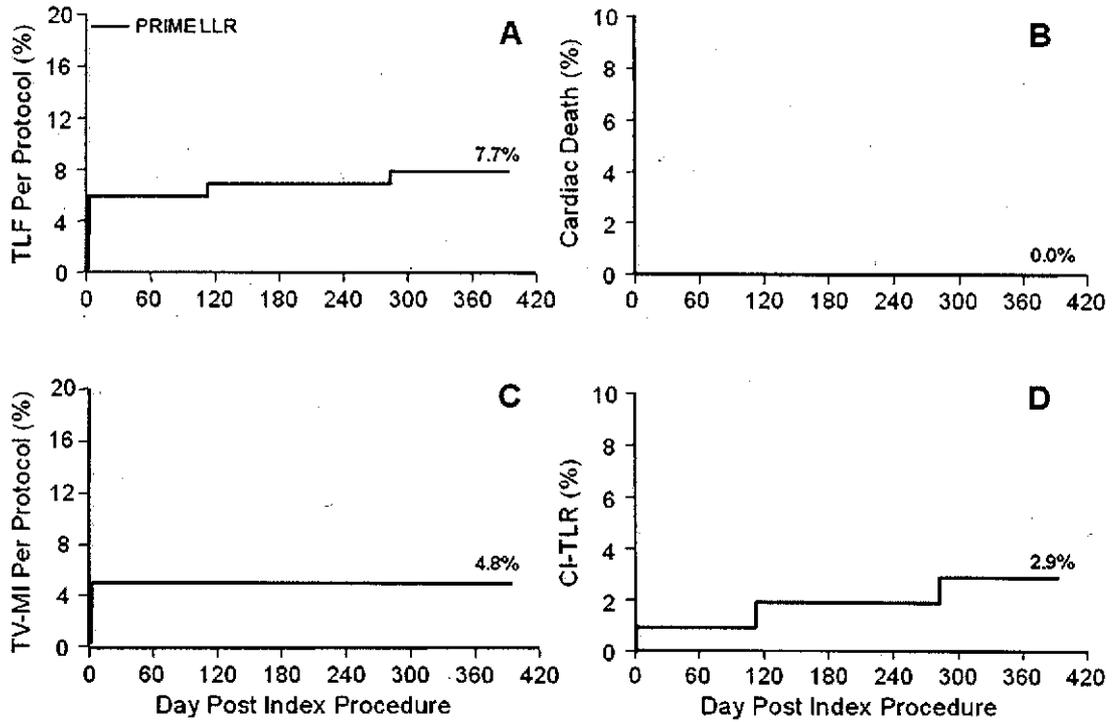


Figure 5 Long Lesion Registry Primary endpoint-TLF at 1 year per protocol (A) and its components of cardiac death (B), TV-MI per protocol (C) and CI-TLR (D)

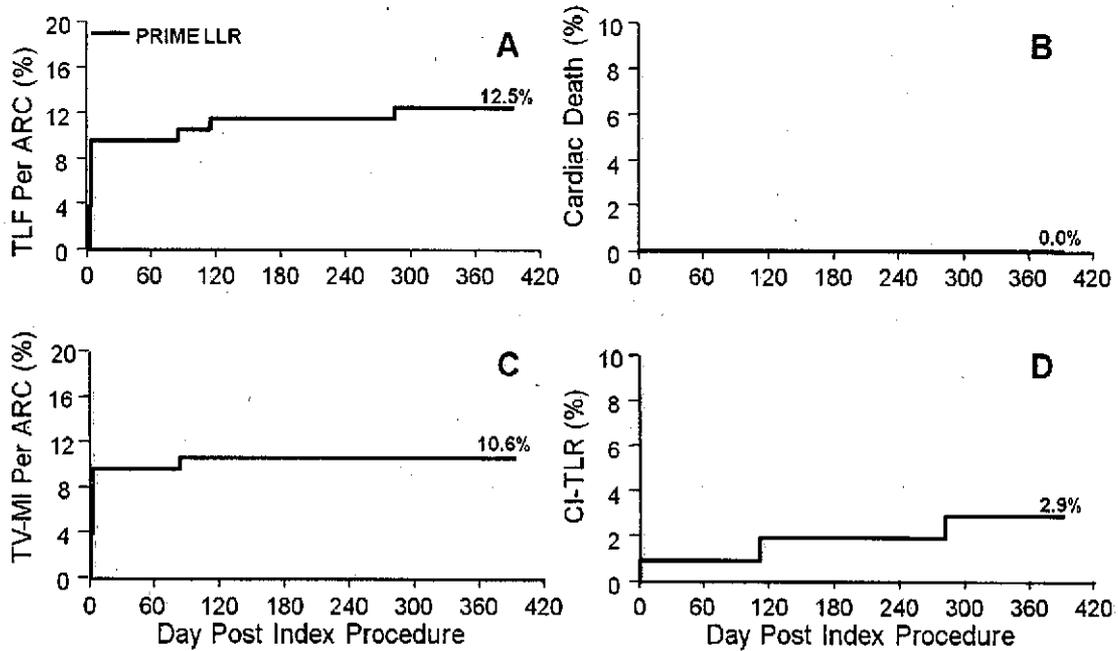


Figure 6 Long Lesion Registry Primary endpoint-TLF at 1 year per ARC (A) and its components of cardiac death (B), TV-MI per protocol (C) and CI-TLR (D)

Geriatric Use: The XIENCE PRIME clinical trial did not have an upper age limit. Among the 401 patients in the SPIRIT PRIME Core Size Registry, 167 were older than age 65 and 234 were age 65 or younger. Among the 104 patients in the SPIRIT PRIME Long Lesion Registry, 48 patients were older than age 65 and 56 were age 65 or younger. A post hoc analysis showed no clinically significant differences in clinical endpoints between patients older than age 65 compared to those age 65 years or younger.

XI. Gender-Based Analysis

Abbott Vascular performed a post hoc evaluation of the SPIRIT PRIME clinical trial for possible sex-based differences in baseline characteristics and clinical outcomes, as well as for any interaction between treatment and sex/gender. The SPIRIT PRIME trial was not designed or powered to study safety or effectiveness differences between sexes, so these analyses are considered exploratory without definitive conclusions.

In the Core Size Registry, 119/401 (29.7%) subjects were female and 282/401 (70.3%) were male. In the Long Lesion Registry, 39/104 (37.5%) subjects were female and 65/104 (62.5%) were male. In comparison, the prevalence of coronary artery disease (CAD) is estimated at 9.2 million in males and 8.4 million in females for adults age 20 and older the United States (i.e., the CAD population is estimated to be 52.2% males and 47.7% females). The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology, which may lead to under-diagnosis and under-referral of female patients with CAD. The gender proportions enrolled in this trial are similar to other drug-eluting stent trials.^{1,2}

Table 13 presents the baseline demographics, risk factors, and angiographic characteristics by gender for subjects in the Core Size Registry. As is consistent with previous literature, female patients at baseline were numerically older and had a higher BMI. Additionally, more females than males had hypertension requiring medication and diabetes mellitus. Table 14 presents the baseline demographics, risk factors, and angiographic characteristics by gender for subjects in the Long Lesion Registry

Table 13 Demographics, Risk Factors, and Baseline Angiographic Characteristics for SPIRIT PRIME Core Size Registry Subjects *

Subject/Lesion Characteristics	Male (N=282) (M=315)	Female (N=119) (M=132)	Total (N=401) (M=447)	P-Value
Baseline Demographics, Mean ± SD (n)				
Age (year)	61.63 ± 10.37 (282)	65.23 ± 9.47 (119)	62.70 ± 10.23 (401)	0.0009 ¹
Baseline Risk Factors, % (No./total)				
All Diabetes	31.9% (90/282)	42.0% (50/119)	34.9% (140/401)	0.0663 ²
Diabetes Treated with Insulin	7.4% (21/282)	14.3% (17/119)	9.5% (38/401)	0.0400 ²
Current Tobacco Use	19.1% (54/282)	19.3% (23/119)	19.2% (77/401)	1.0000 ²
Hypertension Requiring Medication	73.4% (207/282)	84.0% (100/119)	76.6% (307/401)	0.0278 ²
Hypercholesterolemia Requiring Medication	80.9% (228/282)	79.0% (94/119)	80.3% (322/401)	0.6815 ²
Stable Angina	44.0% (124/282)	49.6% (59/119)	45.6% (183/401)	0.3244 ²
Unstable Angina	25.2% (71/282)	24.4% (29/119)	24.9% (100/401)	0.9001 ²
Prior MI	25.0% (69/276)	18.5% (22/119)	23.0% (91/395)	0.1927 ²
Target Vessel, % (No./total)				
LAD	44.1% (139/315)	46.2% (61/132)	44.7% (200/447)	0.7545 ²
Circumflex or Ramus	23.8% (75/315)	25.8% (34/132)	24.4% (109/447)	0.7174 ²
RCA	31.7% (100/315)	28.0% (37/132)	30.6% (137/447)	0.5001 ²
LMCA	0.0% (0/315)	0.0% (0/132)	0.0% (0/447)	NA
Pre-Procedure QCA Analysis, Mean ± SD (m)				
Lesion Length (mm)	13.91 ± 5.10 (315)	13.06 ± 4.75 (132)	13.66 ± 5.01 (447)	0.0940 ¹
Pre-Procedure RVD (mm)	2.76 ± 0.48 (315)	2.63 ± 0.45 (132)	2.72 ± 0.48 (447)	0.0067 ¹
Pre-Procedure MLD (mm)	0.82 ± 0.40 (315)	0.81 ± 0.26 (132)	0.81 ± 0.36 (447)	0.7352 ¹
Pre-Procedure Percent Diameter Stenosis (%DS)	70.01 ± 12.87 (315)	68.58 ± 8.53 (132)	69.59 ± 11.76 (447)	0.1676 ¹

* Subjects with Cardiac Enzyme Data in Window

1 From T-test.

2 From Fisher's exact test.

Note: All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.

Note: N is the total number of subjects.

Note: M is the total number of target lesions.

Note: This table contains only subjects with post index procedure cardiac enzyme data in window (between 8 hours post index procedure and hospital discharge).

Table 14 Demographics, Risk Factors, and Baseline Angiographic Characteristics for SPIRIT PRIME Long Lesion Registry Subjects*

Subject/Lesion Characteristics	Male (N=65) (M=80)	Female (N=39) (M=44)	Total (N=104) (M=124)	P-Value
Baseline Demographics, Mean ± SD (n)				
Age (year)	63.64 ± 9.97 (65)	63.15 ± 8.60 (39)	63.46 ± 9.44 (104)	0.7927 ¹
Baseline Risk Factors, % (No./total)				
All Diabetes	32.3% (21/65)	41.0% (16/39)	35.6% (37/104)	0.4027 ²
Diabetes Treated with Insulin	9.2% (6/65)	10.3% (4/39)	9.6% (10/104)	1.0000 ²
Current Tobacco Use	26.2% (17/65)	28.2% (11/39)	26.9% (28/104)	0.8232 ²
Hypertension Requiring Medication	76.9% (50/65)	71.8% (28/39)	75.0% (78/104)	0.6418 ²
Hypercholesterolemia Requiring Medication	81.5% (53/65)	79.5% (31/39)	80.8% (84/104)	0.8023 ²
Stable Angina	43.1% (28/65)	59.0% (23/39)	49.0% (51/104)	0.1563 ²
Unstable Angina	27.7% (18/65)	15.4% (6/39)	23.1% (24/104)	0.2289 ²
Prior MI	25.0% (16/64)	18.4% (7/38)	22.5% (23/102)	0.4753 ²
Target Vessel, % (No./total)				
LAD	41.3% (33/80)	40.9% (18/44)	41.1% (51/124)	1.0000 ²
Circumflex or Ramus	27.5% (22/80)	18.2% (8/44)	24.2% (30/124)	0.2803 ²
RCA	31.3% (25/80)	40.9% (18/44)	34.7% (43/124)	0.3261 ²
LMCA	0.0% (0/80)	0.0% (0/44)	0.0% (0/124)	NA
Pre-Procedure QCA Analysis, Mean ± SD (m)				
Lesion Length (mm)	26.62 ± 7.89 (80)	25.17 ± 6.83 (44)	26.10 ± 7.53 (124)	0.2872 ¹
Pre-Procedure RVD (mm)	2.80 ± 0.46 (80)	2.66 ± 0.40 (44)	2.75 ± 0.44 (124)	0.0864 ¹
Pre-Procedure MLD (mm)	0.75 ± 0.28 (80)	0.79 ± 0.31 (44)	0.77 ± 0.29 (124)	0.5067 ¹
Pre-Procedure Percent Diameter Stenosis (%DS)	72.05 ± 8.74 (80)	68.76 ± 9.60 (44)	70.88 ± 9.15 (124)	0.0632 ¹

* Subjects with Cardiac Enzyme data in Window

1 From T-test.

2 From Fisher's exact test.

Note: All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.

Note: N is the total number of subjects.

Note: M is the total number of target lesions.

Note: This table contains only subjects with post index procedure cardiac enzyme data in window (between 8 hours post index procedure and hospital discharge).

A post hoc analysis was conducted on the composite primary safety and effectiveness endpoint of TLF, per protocol and per ARC, to assess for heterogeneity of treatment effect across sex/gender (using Fisher's Exact Test). Table 15 and Table 16 present the clinical results for the Core Size Registry and Long Lesion Registry respectively. Due to the modest sample size (Core Size Registry 282 males vs. 119 females and Long Lesion Registry 65 males vs. 39 females), these analyses and interpretation are limited.

Table 15 Clinical Results for All Female and All Male Subgroups in the SPIRIT PRIME Core Size Registry through 1 year*

SPIRIT PRIME	Male (N=282)	Female (N=119)	Total (N=401)	P-Value [†]
All Death	1.1% (3/280)	0.0% (0/119)	0.8% (3/399)	0.5576
Cardiac Death	0.4% (1/280)	0.0% (0/119)	0.3% (1/399)	1.0000
Non-Cardiac Death	0.7% (2/280)	0.0% (0/119)	0.5% (2/399)	1.0000
Target Vessel MI per Protocol	1.8% (5/280)	1.7% (2/119)	1.8% (7/399)	1.0000
Cardiac Death or Target Vessel MI per Protocol	2.1% (6/280)	1.7% (2/119)	2.0% (8/399)	1.0000
Target Vessel MI per ARC	3.2% (9/280)	5.9% (7/119)	4.0% (16/399)	0.2639
Cardiac Death or Target Vessel MI per ARC	3.6% (10/280)	5.9% (7/119)	4.3% (17/399)	0.2906
Major Bleeding Complication	2.9% (8/280)	1.7% (2/119)	2.5% (10/399)	0.7298
Stent Thrombosis				
Protocol defined	0.7% (2/280)	0.0% (0/119)	0.5% (2/399)	1.0000
ARC definite + probable	0.7% (2/280)	0.0% (0/119)	0.5% (2/399)	1.0000
TLF				
per Protocol	5.4% (15/280)	2.5% (3/119)	4.5% (18/399)	0.2941
per ARC	6.4% (18/280)	6.7% (8/119)	6.5% (26/399)	1.0000
Ischemia-Driven TLR	3.2% (9/280)	0.8% (1/119)	2.5% (10/399)	0.2931
Ischemia-Driven TVR, non TL	2.9% (8/280)	2.5% (3/119)	2.8% (11/399)	1.0000

* Subjects with Cardiac Enzyme data in Window

† From Fisher's exact test.

Note: All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.

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

Note: N is the total number of subjects.

Note: This table contains only subjects with post index procedure cardiac enzyme data in window (between 8 hours post index procedure and hospital discharge).

Table 16 Clinical Results for All Female and All Male Subgroups in the SPIRIT PRIME Long Lesion Registry through 1 year*

SPIRIT PRIME	Male (N=65)	Female (N=39)	Total (N=104)	P-Value
All Death	1.5% (1/65)	0.0% (0/39)	1.0% (1/104)	1.0000
Cardiac Death	0.0% (0/65)	0.0% (0/39)	0.0% (0/104)	NA
Non-Cardiac Death	1.5% (1/65)	0.0% (0/39)	1.0% (1/104)	1.0000
Target Vessel MI per Protocol	4.6% (3/65)	5.1% (2/39)	4.8% (5/104)	1.0000
Cardiac Death or Target Vessel MI per Protocol	4.6% (3/65)	5.1% (2/39)	4.8% (5/104)	1.0000
Target Vessel MI per ARC	13.8% (9/65)	5.1% (2/39)	10.6% (11/104)	0.2024
Cardiac Death or Target Vessel MI per ARC	13.8% (9/65)	5.1% (2/39)	10.6% (11/104)	0.2024
Major Bleeding Complication	1.6% (1/63)	2.6% (1/39)	2.0% (2/102)	1.0000
Stent Thrombosis				
Protocol defined	0.0% (0/65)	0.0% (0/39)	0.0% (0/104)	NA
ARC definite + probable	0.0% (0/65)	0.0% (0/39)	0.0% (0/104)	NA
TLF				
per Protocol	9.2% (6/65)	5.1% (2/39)	7.7% (8/104)	0.7069
per ARC	16.9% (11/65)	5.1% (2/39)	12.5% (13/104)	0.1242
Ischemia-Driven TLR	4.6% (3/65)	0.0% (0/39)	2.9% (3/104)	0.2900
Ischemia-Driven TVR, non TL	3.1% (2/65)	2.6% (1/39)	2.9% (3/104)	1.0000

* Subjects with Cardiac Enzyme data in Window

1 From Fisher's exact test.

Note: All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.

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

Note: N is the total number of subjects.

Note: This table contains only subjects with post index procedure cardiac enzyme data in window (between 8 hours post index procedure and hospital discharge).

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

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

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

A. Safety Conclusions

The biocompatibility testing, *in vivo* pharmacokinetics evaluation and *in vivo* animal testing conducted on the XIENCE PRIME stent system demonstrate that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery systems or appropriately leveraged from the XIENCE V stent 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 and functional shelf life testing demonstrated that the product can be labeled with a shelf life of 9 months.

B. Effectiveness Conclusions

The SPIRIT PRIME clinical trial consisted of two cohorts, the Core Size Registry and the Long Lesion Registry. The results of the SPIRIT PRIME clinical trial showed that the primary composite endpoint of target lesion failure (TLF, defined as cardiac death, target vessel myocardial infarction (TV-MI), and clinically indicated target lesion revascularization (CI-TLR)) at one year was 6.5%, with an upper limit of the one-sided 95% confidence interval of 8.9%, which met the prespecified performance goal of $\leq 9.2\%$ ($p < 0.0338$) for the Core Size Registry. The rate of TLF at one year in the Long Lesion Registry was 12.5%, with an upper limit of the one-sided 95% confidence interval of 19.1%, which met the prespecified performance goal of $\leq 19.2\%$ ($p < 0.0484$) for the LLR. Both major secondary endpoints were also met. The composite endpoint of TLF contains both safety and effectiveness components.

The SPIRIT PRIME trial demonstrated that the XIENCE PRIME Everolimus Eluting Coronary Stent System provides a reasonable assurance of safety and effectiveness when used in accordance with the instructions for use.

C. Overall Conclusions

XIV. CDRH DECISION

CDRH issued an approval order on November 1, 2011. The final conditions of approval cited in the approval order are described below.

1. *Continued Follow-up of Premarket Cohort:* You must conduct a post-approval study to continue follow-up of the premarket cohorts, consisting of 500 patients (Core Size Registry -400 participants; Long Lesion Registry-100 participants). You should collect clinical outcomes through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death) in the SPIRIT PRIME clinical trial. This study will be conducted as per protocol submitted with the revised statistical analysis plan provided in Amendment 3 of the PMA. A comparison of primary and secondary endpoints of the CSR and the XIENCE V arm of the SPIRIT II, III, and IV trials (pooled data), will be provided. For the LLR cohort, the comparison endpoints will be made with the SPIRIT IV overlapping cohort due to lack of overlapping data in SPIRIT II and SPIRIT III and unavailability of the 33 and 38mm XIENCE V stents.
2. The issue of the optimal duration of dual antiplatelet therapy following PCI with drug-eluting stents (DES) remains a critical question that is currently being studied in the DAPT trial. FDA acknowledges that you are participating in this trial to address a condition of approval for the Xience V DES (P070015). As the duration of dual antiplatelet therapy is also relevant for the Xience Prime EECS, you must fulfill your commitment to the condition of PMA approval for P070015. When appropriate or as requested by FDA, you should submit PMA supplements to the Xience PRIME PMA (P110019) requesting approval to update your IFU to include the data collected in the DAPT trial. If you do not fulfill the condition of approval for P070015, you must conduct or participate in a separate clinical trial that will develop data to study the duration of dual antiplatelet therapy following implantation of the Xience PRIME DES and subsequently submit PMA supplements to this PMA requesting approval to include these data in an IFU update.
3. Within 12 months of PMA approval, you should submit a PMA supplement requesting approval to tighten the in-process coating weight gain specifications or implementing procedures to re-coat stents with less than 95% coating weight gain upon in-process inspection.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions of use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Lansky AJ, Costa RA, Mooney M, et al. Gender-Based Outcomes After Paclitaxel-Eluting Stent Implantation in Patients With Coronary Artery Disease. *J Am Coll Cardiol* 2005 45: 1180-5.
2. Solinas E, Nikolsky E, Lansky AJ, et al. Gender-Specific Outcomes After Sirolimus-Eluting Stent Implantation. *J Am Coll Cardiol* 2007;50:2111-6.