

SECTION 8.0
XIENCE V EECSS
SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Product Generic Name:	Drug Eluting Coronary Stent System (NIQ)
Product Trade Name:	XIENCE™ V Rapid Exchange (RX) Everolimus Eluting Coronary Stent System
	XIENCE™ V 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
Premarket Approval (PMA) Number:	P070015

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

The XIENCE V EECSS is contraindicated for use in patients with the following:

- patients in whom anti-platelet and / or anti-coagulant therapy is contraindicated
- lesions that prevent complete angioplasty balloon inflation
- 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. PRODUCT DESCRIPTION

The XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V EECSS) 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 EECSS 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 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)	<table border="0"> <tr> <td></td> <td><u>2.5-3.0 mm</u></td> <td><u>3.5-4.0 mm</u></td> </tr> <tr> <td>Distal:</td> <td>0.032”</td> <td>0.035”</td> </tr> <tr> <td>Proximal:</td> <td>0.026”</td> <td>0.026”</td> </tr> </table>		<u>2.5-3.0 mm</u>	<u>3.5-4.0 mm</u>	Distal:	0.032”	0.035”	Proximal:	0.026”	0.026”	<table border="0"> <tr> <td></td> <td><u>2.5 mm</u></td> <td><u>2.75 x 8 - 3.5 x 18</u></td> <td><u>3.5 x 23 - 4.0 x 28</u></td> </tr> <tr> <td>Distal:</td> <td>0.032”</td> <td>0.034”</td> <td>0.036”</td> </tr> <tr> <td>Proximal:</td> <td>0.042”</td> <td>0.042”</td> <td>0.042”</td> </tr> </table>		<u>2.5 mm</u>	<u>2.75 x 8 - 3.5 x 18</u>	<u>3.5 x 23 - 4.0 x 28</u>	Distal:	0.032”	0.034”	0.036”	Proximal:	0.042”	0.042”	0.042”
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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 EECSS. 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.

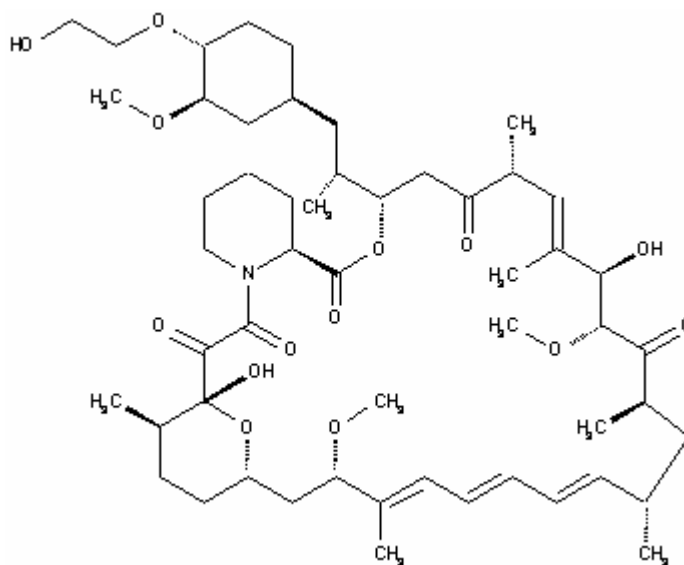
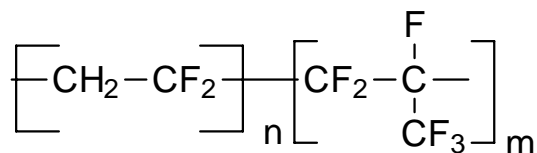


Figure 1 Chemical Structure of Everolimus

B2. Inactive Ingredients

The XIENCE V EECSS contains inactive ingredients including an acrylic polymer primer that adheres to the stent and drug coating, and a non-erodible semi-crystalline random copolymer made from vinylidene fluoride and hexafluoropropylene monomers (PVDF-HFP) as the drug matrix layer containing everolimus. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire primer coated stent surface. No topcoat layer is used. The chemical structure of PVDF-HFP is shown in Figure 2 below.



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

The product matrix, including nominal dosages of everolimus in each XIENCE V EECSS 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 (or mechanisms) by which the XIENCE V EECSS affects neointimal production as seen in clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation in a reversible manner. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the

presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1, two key players in the initiation of protein synthesis, is inhibited. Although not formally proven, it is thought that the everolimus-FKBP-12 complex may bind and interfere with FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian Target Of Rapamycin) - a protein that governs cell metabolism, growth and proliferation, and regulates phosphorylation of both p70 S6 kinase and 4E-BP1. This is supported by modeling results using published X-ray structure information which suggest that there is no impediment to the ternary FKBP-12/everolimus/FRAP complex formation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Treatment of patients with coronary artery disease may include exercise, diet, drug therapy, percutaneous coronary interventions (ie, balloon angioplasty, atherectomy, bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass grafting (CABG) surgery.

VII. MARKETING HISTORY

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

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

As of October 1, 2007, over 176,600 XIENCE V Everolimus Eluting Coronary 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. SUMMARY OF NONCLINICAL 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 Everolimus Eluting Coronary Stent), the polymer-only coated stent alone (the MULTI-LINK VISION or MULTI-LINK MINI VISION with the primer layer and PVDF-HFP polymer layer), or the finished combination product (XIENCE V Everolimus Eluting Coronary Stent System).

A. Biocompatibility Studies

A series of Good Laboratory Practices (GLP) biocompatibility tests were conducted to demonstrate the components of the XIENCE V Everolimus Eluting Coronary Stent System are non-toxic. Tests were conducted on ethylene oxide-sterilized XIENCE V RX Everolimus Eluting Coronary Stent System (EECSS), 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.
- 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • Polymer-only coated stent: Pass (non-toxic)
Pyrogenicity	Bacterial Endotoxin (LAL)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 2.6X Stent and RX delivery system: Pass (non-hemolytic) • XIENCE V stent: Pass (non-hemolytic)
	Thrombosis (fulfilled through Hemolysis and <i>in vivo</i> animal testing)	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • XIENCE V Stent and OTW delivery system: Pass (non-hemolytic) • XIENCE V stent: Pass (non-hemolytic)
	ISO 10993-4: Clotting, PT (Human Plasma)	<ul style="list-style-type: none"> • 2.6X Stent and RX delivery system: Pass (non-hemolytic)
	ISO 10993-4: Partial Thromboplastin Time, PTT (Human Plasma)	<ul style="list-style-type: none"> • 2.6X Stent and RX delivery system: Pass (non-hemolytic)

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: <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)

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

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 EECSS to

Abbott Vascular completed a series of *in vivo* pharmacokinetic studies of the drug product. The animal PK studies are summarized in Section III. B: *In Vivo* Pharmacokinetics below. In addition, clinical pharmacokinetic studies have been performed on the XIENCE V EECSS. The human PK studies are described in Section XI. A: Global Pharmacokinetics.

There is no evidence to suggest that any chemical interactions, which would form 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.

B. *In Vivo* Animal Pharmacokinetics

B1. XIENCE V Everolimus Eluting Coronary Stent System (EECSS)

In vivo preclinical pharmacokinetic studies were performed in the porcine coronary artery model to determine: the percent drug release (%DR) 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 with preferential local delivery of everolimus. 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 Everolimus Eluting Coronary Stent System. 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 carbamazepin, 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 Everolimus Eluting Coronary Stent System labeling.

C. *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, 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 VIII. D: 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. 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.	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).	PASS
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
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

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

Test	Test Description	Results
Stent Dimensional and Functional Attributes (cont'd)		
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 is recorded. All stents met product specifications.	PASS
Finite Element Analysis (FEA)	Determines the state of stress and strain due to loading imposed by manufacturing, deployment, and expected loading conditions under cardiac motion. The analyses were divided into: <ul style="list-style-type: none"> • radial fatigue FEA which assumes the stent is deployed in a straight vessel and the stent contracts radially • bending fatigue FEA which assumes that the fatigue loads act on two derived bending configurations at the expanded state for overlapping stents. The XIENCE V will survive the simulated 10-year radial and bending fatigue loading as determined by the Goodman stress-life solution.	PASS
Accelerated Fatigue Testing	Determines that the system can adequately withstand expected <i>in vivo</i> cyclic loading conditions. Accelerated fatigue testing was conducted on the following configurations: <ul style="list-style-type: none"> • Radial Fatigue Testing: Single Configuration • Radial Fatigue Testing: Overlapped Configuration 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
Magnetic Resonance Imaging (MRI)	Demonstrates that the XIENCE V EECS, in single and in overlapped configurations up to 69 mm in length, is MR Conditional (poses no known hazards) when scanned under the following conditions: <ul style="list-style-type: none"> • Static magnetic field of 3 Tesla or less • Spatial gradient of 720 gauss/cm or less • Maximum whole body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of imaging The response of stents with fractured struts is unknown. The response of overlapped configurations greater than 69 mm in length is unknown. 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 EECS.	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

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

Test	Test Description	Results
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
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 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

D. Coating Characterization Testing

The following methods were developed to characterize and set initial specifications for the XIENCE V Everolimus Eluting Coronary 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: <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 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 (radial, single)	Demonstrates the coating durability of the XIENCE V stent under expected <i>in vivo</i> cyclic loading conditions for an equivalence of 10 years (~400 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
Embolitic Fatigue (Overlap Configuration)	Investigates the embolic particle size and count from the XIENCE V stent during an accelerated radial fatigue test equivalent to 90 days (9.3 million cycles). 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. This testing was performed for information only.	Met USP <788>

E. Chemistry, Manufacturing & Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on the XIENCE V Everolimus Eluting Coronary Stent System as part of CMC. This testing is summarized in Table 6. Information to support the stability of the XIENCE V EECSS is summarized separately in Section VIII. G: Stability.

Table 6 XIENCE V EECSS 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 <i>in vitro</i> 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

F. Animal 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 major supportive studies were carried out in a porcine non-atherosclerotic coronary artery model and rabbit iliac model at time points out to 2 years to determine the clinical dose of everolimus to incorporate into XIENCE V, to determine the pharmacokinetics of XIENCE V and to evaluate the safety and vascular response of XIENCE V. 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 and a bulk polymer system. Supportive safety data and overlapping stent safety data have also been generated in a rabbit non-atherosclerotic iliac model.

The intravascular safety of everolimus eluting stents was evaluated in a series of animal studies in a porcine model of stent-mediated vascular injury and non-atherosclerotic rabbit iliac 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 the appropriate animal care procedures were followed, and data integrity were maintained. The results of these tests support the safety of the XIENCE V Everolimus Eluting Coronary Stent. 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: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) • XIENCE (3.0 x 12 mm, 200 µg/cm²) • XIENCE (3.0 x 12 mm, 260 µg/cm²) 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. <ul style="list-style-type: none"> •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: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) • XIENCE (3.0 x 12 mm, 200 µg/cm²) • XIENCE (3.0 x 12 mm, 260 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R081704-KHB	Test Article: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R100704-KHB	Test Article: <ul style="list-style-type: none"> • XIENCE (2.5 x 8 mm, 100 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •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: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) • XIENCE (3.0 x 12 mm, 200 µg/cm²) • XIENCE (3.0 x 12 mm, 260 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R042204-PDD	Test Article: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R081103-PDD	Test Article: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) • XIENCE (3.0 x 12 mm, 200 µg/cm²) • XIENCE (3.0 x 12 mm, 260 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R041504-PDD	Test Article: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •Angiography •Histological & histomorphometric evaluations •Evaluation of degree of endothelialization by SEM •Acute delivery •Chronic vascular response
R042904-KHB	Test Article: <ul style="list-style-type: none"> • XIENCE (3.0 x 12 mm, 100 µg/cm²) Controls: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> •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	<ul style="list-style-type: none"> •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	<ul style="list-style-type: none"> •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	<ul style="list-style-type: none"> •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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> •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. <ul style="list-style-type: none"> •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.

G. Stability/Shelf Life

Stability studies were conducted to establish a shelf life/expiration date for the XIENCE V Everolimus Eluting Coronary Stent System. Testing included appearance, total content, drug release, degradation products, and butylated hydroxytoluene (BHT). 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; additional data will be provided to extend the shelf life.

H. Sterilization

The XIENCE V Everolimus Eluting Coronary 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.

IX. OVERVIEW OF CLINICAL STUDIES

Principal XIENCE V safety and efficacy evidence 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 performance in patients with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and in Table 8. In addition, SPIRIT IV is currently on-going to further evaluate the safety and efficacy of the XIENCE V EECSS in a more complex patient population.

The SPIRIT III Clinical Trial is composed of three parts; a US randomized clinical trial (RCT) and two non-randomized arms. The non-randomized arms consist of a 4.0 mm diameter stent, and a Japanese non-randomized arm. In addition, a pharmacokinetic (PK) substudy was conducted in a subset of subjects in the RCT, 4.0 non-randomized arm, and 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 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 primary endpoint in the RCT was in-segment late loss at 240 days (N = 668) and the major secondary endpoint was ischemia-driven target vessel failure (TVF) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and 1 to 5 years), as well as angiographic results and intravascular ultrasound (IVUS) results at 240 days (N = 240). Follow-up through 270 days is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT 4.0 mm arm is a prospective, multi-center, single arm registry designed to evaluate XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V EECSS) 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 at 1, 2, 3, 4, and 5 years, and QCA at 240 days. The primary endpoint was in-segment late loss (LL) at 240 days. Follow-up through 270 days 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 subject subset derived from the RCT, 4.0 mm and Japan arms. Eleven sites in the U.S. and 9 sites in Japan participated in this sub-study and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan).

The SPIRIT II trial was a randomized, single blind, active-control, multi-center clinical evaluation. Subject eligibility criteria were similar to SPIRIT III and enrollment duration overlapped between studies. In this study, 300 subjects (3:1 randomization XIENCE V EECSS:TAXUS PECSS) were enrolled at 31 sites outside the United States. The primary endpoint was in-stent late loss at 6 months. Secondary endpoints included clinical outcomes at months 1, 6, and 9 months, and 1, 2, 3, 4 and 5 years; angiographic results at 6 months and 2 years; and IVUS results at 6 months and 2 years. Follow-up through 1 year is

currently available.

SPIRIT FIRST was a randomized, single blind, control, multi-center first-in-man study. This trial was the first human study to evaluate XIENCE V EECSS safety and performance. Sixty subjects (XIENCE V Stent (n=28) and MULTI-LINK VISION bare metal control stent (n =32)) were enrolled at 9 sites in Europe. The primary endpoint was in-stent late loss at 6 months on the per-treatment evaluable population and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 6 months based on IVUS analysis on the per-treatment evaluable population. Follow-up through 24 months is currently available and follow-up for clinical parameters through 5 years is ongoing.

Table 8 Clinical Trial Design Comparison

	SPIRIT III (Pivotal US/Japan)		SPIRIT II (Supportive OUS)	SPIRIT FIRST (First in Man OUS)
	RCT	Registries		
Study Type/Design	<ul style="list-style-type: none"> • Multi-center • Randomized • Single-blinded • Active Control 	<ul style="list-style-type: none"> • Multi-center • Single-arm • Open-label 	<ul style="list-style-type: none"> • Multi-center • Randomized • Single-blinded • Active Control 	<ul style="list-style-type: none"> • Multi-center • Randomized • Single-blinded • Control
Planned Number of Subjects	Total: 1,002 XIENCE V: 668 Control: 334	Total: 168 4.0 mm: 80 Japan: 88	Total: 300 XIENCE V: 225 Control: 75	Total: 60 XIENCE V: 30 Control: 30
Treatment	Up to two <i>de novo</i> lesions in different epicardial vessels	Up to two <i>de novo</i> lesions in different epicardial vessels	Up to two <i>de novo</i> lesions in different epicardial vessels	Single <i>de novo</i> lesion
Lesion Size	RVD: $\geq 2.5 \leq 3.75$ mm Length: ≤ 28 mm	4.0 mm RVD: $> 3.75 \leq 4.25$ mm Length: ≤ 28 mm Japan RVD: $\geq 2.5 \leq 4.25$ mm Length: ≤ 28 mm	RVD: $\geq 2.5 \leq 4.25$ mm Length: ≤ 28 mm	RVD: 3 mm, on-line QCA Length: ≤ 12 mm
Stent Sizes (XIENCE V)	D: 2.5, 3.0, 3.5 mm L: 8, 18, 28 mm Planned overlapping allowed to cover long lesion throughout SPIRIT III trial	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 Planned overlapping allowed to cover long lesion throughout SPIRIT III trial	D: 2.5, 3.0, 3.5, 4.0 mm L: 8, 18, 28 mm Planned overlapping allowed to cover long lesion	D: 3.0 mm L: 18 mm Planned overlapping was not allowed
Post-procedure Antiplatelet Therapy	Clopidogrel 6 months (or ticlopidine per site standard), Aspirin 5 years	4.0 mm: same as RCT Japan: Ticlopidine 3 months, Aspirin 5 years	Clopidogrel 6 months (or ticlopidine per site standard), Aspirin 1 year	Clopidogrel 3months (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
Major Secondary Endpoint	TVF at 270-days	None	None	%VO at 180-days
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-days (all), 2-years (N=152)	180-days, 1-year (all)
IVUS Follow-up	240 days (N=240)	240 days (Japan only)	180-days, 2-years (N=152)	180-days, 1-year (all)
PK Study	US: Min 15 subjects with single lesion, max 20 with dual lesions Japan: Min 10 subjects with single lesion, max 20 with dual lesions		Min 15 subjects with single lesion, max 20 with dual lesions	None

X. POTENTIAL ADVERSE EFFECTS OF THE PRODUCT ON HEALTH

A. Observed Adverse Events

Observed adverse event information comes from three clinical studies, SPIRIT FIRST SPIRIT II, and SPIRIT III. Principal adverse events seen for these trials are shown in

Table 9. Stent apposition was recorded within the trials and is presented in Table 10. Within these tables, the Intent-to-Treat population includes all subjects randomized while the Per-Treatment Evaluable population includes only those subjects who received a study device at the target lesion with no major procedure protocol deviations except deviations relating to the treatment arm, for whom follow up data are available. See also Section X. B: Potential Adverse Events. See Section XI for more complete study design descriptions and results.

Table 9 Principal Adverse Events

	SPIRIT III XIENCE V to 9 months (N=669)	SPIRIT III Control to 9 months (N=333)	SPIRIT III XIENCE V 4.0 mm Arm to 9 months (N=69)	SPIRIT II XIENCE V to 1 year (N=223)	SPIRIT II Control to 1 year (N=77)	SPIRIT FIRST XIENCE V to 2 years (N=27)	SPIRIT FIRST Control to 2 years (N=29)
In-Hospital							
All Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
TVF ¹	0.9% (6/669)	1.8% (6/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/29)
MACE ²	0.9% (6/669)	1.8% (6/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/29)
MI	0.7% (5/669)	1.8% (6/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/29)
QMI	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
NQMI	0.7% (5/669)	1.8% (6/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)	0.0% (0/29)
Ischemia-Driven TLR	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
TLR, CABG	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
TLR, PCI	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
Ischemia-Driven TVR	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
TVR, CABG	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
TVR, PCI	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
CVA	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.4% (1/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
Out-of-Hospital							
All Death	0.9% (6/658)	0.9% (3/322)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.5% (3/657)	0.6% (2/321)	1.5% (1/68)	0.0% (0/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
TVF ¹	6.5% (43/657)	7.5% (24/321)	2.9% (2/68)	3.6% (8/220)	6.5% (5/77)	15.4% (4/26)	25.0% (7/28)
MACE ²	4.0% (26/657)	6.2% (20/321)	2.9% (2/68)	1.8% (4/220)	6.5% (5/77)	15.4% (4/26)	21.4% (6/28)
MI	1.2% (8/657)	0.6% (2/321)	0.0% (0/68)	0.0% (0/220)	1.3% (1/77)	7.7% (2/26)	0.0% (0/28)

Table 9 Principal Adverse Events (cont'd)

	SPIRIT III XIENCE V to 9 months (N=669)	SPIRIT III Control to 9 months (N=333)	SPIRIT III XIENCE V 4.0 mm Arm to 9 months (N=69)	SPIRIT II XIENCE V to 1 year (N=223)	SPIRIT II Control to 1 year (N=77)	SPIRIT FIRST XIENCE V to 2 years (N=27)	SPIRIT FIRST Control to 2 years (N=29)
Out-of-Hospital (cont'd) QMI	0.2% (1/657)	0.0% (0/321)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	1.1% (7/657)	0.6% (2/321)	0.0% (0/68)	0.0% (0/220)	1.3% (1/77)	3.8% (1/26)	0.0% (0/28)
Ischemia-Driven TLR	2.6% (17/657)	5.0% (16/321)	1.5% (1/68)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
TLR, CABG	0.2% (1/657)	0.0% (0/321)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	0.0% (0/26)	3.6% (1/28)
TLR, PCI	2.4% (16/657)	5.0% (16/321)	1.5% (1/68)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	17.9% (5/28)
Ischemia-Driven TVR	3.0% (20/657)	4.0% (13/321)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	3.6% (1/28)
TVR, CABG	0.5% (3/657)	0.6% (2/321)	0.0% (0/68)	0.5% (1/220)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
TVR, PCI	2.6% (17/657)	3.4% (11/321)	0.0% (0/68)	1.4% (3/220)	1.3% (1/77)	0.0% (0/26)	3.6% (1/28)
CVA	0.8% (5/653)	0.6% (2/320)	0.0% (0/67)	0.9% (2/220)	1.3% (1/76)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis Acute (< 1 day)	0.0% (0/669)	0.0% (0/330)	1.4% (1/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
Subacute (1 to 30 days)	0.3% (2/667)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)	0.0% (0/29)
Late (> 30 days)	0.2% (1/653)	0.0% (0/320)	0.0% (0/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

Intent to Treat Population = All subjects randomized, regardless of the treatment they actually received

Per-Treatment Evaluable Population = A subset of subjects in the full analysis set, who are characterized as those subjects who received a study device at the target lesion (subjects to be analyzed based on the treatment stent that they actually received), with no 'major procedural protocol deviations' except deviations relating to treatment arm, for whom follow up data is available.

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

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

Note: In-hospital is defined as hospitalization less than or equal to 7 days post index procedure.

Note: All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.

Note: Out-of-hospital counts only include those subjects participating in the study after in-hospitalization.

Note: This table includes revascularizations on any target vessel(s) / lesion(s) for subjects with two target vessels / lesions treated.

Note: The analysis for SPIRIT FIRST is based on per-treatment evaluable population.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

In the SPIRIT III trial, a pre-specified subgroup of subjects underwent IVUS evaluation of the treated lesion immediately following the procedure and as part of a scheduled angiographic evaluation at 8 months. In the SPIRIT II trial, all subjects underwent IVUS evaluation immediately following the procedure and as part of the follow-up angiographic evaluation at 6 months. In the SPIRIT FIRST trial, all subjects underwent IVUS evaluation immediately following the procedure and as part of the follow-up angiographic evaluation at 6 months and 1 year. In all three studies there was no correlation between clinical adverse events or major adverse cardiovascular events (MACE) (ie, cardiac death, MI and target lesion revascularization) and incomplete stent apposition. Incomplete stent apposition frequencies are shown in Table 10 for SPIRIT III, SPIRIT II and SPIRIT FIRST.

Table 10 Frequency of Incomplete Stent Apposition

	SPIRIT III		SPIRIT II		SPIRIT FIRST	
	All Lesion Analysis (Intent to Treat Population) (Matched Pairs Analysis)		All Lesion Analysis (Intent to Treat Population)		(Per-treatment Evaluable Population)	
	XIENCE V	Control	XIENCE V	Control	XIENCE V	Control
	n = 181	n = 93	n = 132	n = 45	n = 27	n = 28
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
Post-Procedure						
Incomplete Stent Apposition Rate	35.2% (32/91)	25.6% (11/43)	6.5% (7/108)	5.6% (2/39)	0% (0/27)	10.7% (3/28)
Follow-up						
	8-month follow-up		6-month follow-up		6-month follow-up	
Incomplete Stent Apposition Rate	26.4% (24/91)	16.3% (7/43)	2.9% (3/103)	0.0% (0/39)	0.0% (0/21)	0.0% (0/21)
Persisting Incomplete Stent Apposition	25.3% (23/91)	14.0% (6/43)	2.5% (3/120)	0.0% (0/42)	0.0% (0/27)	0.0% (0/28)
Late Acquired Stent Apposition	1.1% (1/91)	2.3% (1/43)	0.0% (0/104)	0.0% (0/39)	0.0% (0/21)	0.0% (0/22)

Intent to Treat Population = All subjects randomized, regardless of the treatment they actually received

Per-Treatment Evaluable Population = A subset of subjects in the full analysis set, who are characterized by those subjects who received a study device at the target lesion (subjects to be analyzed based on the treatment stent that they actually received), with no 'major procedural protocol deviations' except deviations relating to treatment arm, for whom follow up data is available.

IA = Incomplete Apposition, BL = Baseline, FU = Follow-up.

Persisting = # patients with BL IA and with FU IA , # patients evaluable at baseline and follow-up.

Late Acquired = # patients without BL IA and with FU IA , # patients evaluable at baseline and follow-up.

Incomplete Apposition variables are from assessment by IVUS core laboratory.

B. Potential Adverse Events

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

- Abrupt closure
- Acute myocardial infarction
- Allergic reaction or hypersensitivity to contrast agent and drug reactions to anti-platelet 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
- 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)

- Myelosuppression
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Restenosis of the stented segment of the artery
- 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 include but are not limited to:

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

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

XI. SUMMARY OF CLINICAL STUDIES

A. SPIRIT III Pivotal Clinical Trial (US/Japan)

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V EECSS to the TAXUS EXPRESS² Paclitaxel Eluting Coronary Stent System (TAXUS PECSS) 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. Enrollment is complete in the RCT, the US 4.0 mm arm and the Japan arm.

SPIRIT III Randomized Clinical Trial (RCT)

Objective: The objective of the SPIRIT III RCT was to evaluate the XIENCE V EECSS compared to TAXUS PECSS 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.

Conclusion: In the SPIRIT III RCT, the XIENCE V EECSS has shown non-inferiority to the TAXUS PECSS in terms of the primary endpoint of in-segment late loss (LL) at 240 days ($p < 0.0001$). Specifically, XIENCE V EECSS resulted in a highly significant 50% reduction in LL over TAXUS PECSS (0.14 mm – 0.28 mm = -0.14 mm).

Statistical analyses also demonstrated XIENCE V EECSS superiority to TAXUS PECSS in terms of the primary endpoint ($p = 0.0037$). Furthermore, XIENCE V EECSS also showed non-inferiority to TAXUS PECSS with respect to the major secondary endpoint of target vessel failure (TVF) rates (7.2% versus 9.0%, p value < 0.0001) and a clear trend towards lower MACE rate (4.6% versus 8.1%) through 284 days.

IVUS follow-up data also supported the angiographic endpoint results. There was a 38.4% reduction in % volume obstruction (VO) at 240 days in the XIENCE V EECSS arm (6.91%) as compared to the TAXUS PECSS arm (11.21%) and a 51.5% reduction in neointimal hyperplasia (NIH) volume in the XIENCE V EECSS arm as compared to the TAXUS PECSS arm. For key clinical endpoints through 284 days the XIENCE V EECSS arm consistently had lower observed event rates than the TAXUS PECSS arm: ischemia driven target lesion revascularization (ID-TLR) (2.6% vs. 5.0%); ischemia driven target vessel revascularization (ID-TVR) (3.0% vs. 4.0%); and ID-MACE (4.6% vs. 8.1%). Therefore, 240-day angiographic, IVUS, and clinical endpoints through 284 days have demonstrated XIENCE V EECSS safety and efficacy.

Design: The SPIRIT III RCT is a prospective, 2:1 randomized, active-controlled, single blinded, parallel, multi-center clinical evaluation of the XIENCE V EECSS compared to TAXUS PECSS in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

Pre-dilatation was performed prior to stent deployment with an angioplasty balloon. Post-dilatation was left to the discretion of the investigator. However if post-dilatation

was performed, the balloon was sized to fit within the boundaries of the stent.

The clinical trial protocol required that IVUS be performed after optimal stent placement was obtained. IVUS was performed at follow-up in a pre-specified group of subjects and for subjects who received a bailout stent.

During the index procedure, medications administered included a loading dose of clopidogrel bisulfate (≥ 300 mg) and aspirin (≥ 300 mg). Loading doses of antiplatelet medications were to be given at least six hours prior to the implant procedure if possible, but no later than one hour after the procedure in any case. All subjects in the US who received XIENCE V were to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of 6 months following the procedure. All subjects who received the TAXUS PECSS were to be maintained on clopidogrel bisulfate for 6 months as instructed in the Instructions For Use (IFU) for TAXUS PECSS. For subjects allergic to clopidogrel bisulfate, ticlopidine hydrochloride was allowed at a dose according to standard hospital practice. All subjects were also required to receive ≥ 80 mg of aspirin daily to be taken throughout the length of the trial (5 years).

Clinical and angiographic follow-up through 9 months are currently available and follow-up for clinical parameters through 5-years is ongoing.

Demographics: Key baseline demographics and risk factors were similar between treatment arms in the RCT as shown in Table 11.

Methods: One thousand and two subjects were enrolled in the SPIRIT III trial, a prospective, controlled, randomized, single blind, parallel two-arm, multi-center, clinical study evaluating the XIENCE V EECSS safety and effectiveness at 65 clinical sites in the United States. Subject randomization was 2:1 with 668 subjects enrolled to receive the XIENCE V EECSS and 334 subjects enrolled to receive the TAXUS PECSS. Subjects in the RCT were enrolled into three groups depending on their angiographic and intravascular ultrasound (IVUS) follow-up regimen. In addition, pharmacokinetic data was also collected from a subset of the subjects in this RCT at pre-determined clinical sites.

Results: The XIENCE V EECSS when placed in single or dual *de novo* native coronary artery lesions was found to be statistically non-inferior to the TAXUS PECSS. The primary endpoint was met with an in-segment LL of 0.14 ± 0.41 mm for the XIENCE V arm and 0.28 ± 0.48 mm for the TAXUS arm. The null hypothesis was rejected proving that XIENCE V EECSS was non-inferior to TAXUS PECSS for in-segment LL at 240 days (non-inferiority $p < 0.0001$, $\delta = 0.195$ mm). Additionally, since non-inferiority was demonstrated, a superiority analysis of the primary endpoint was performed using a two-sided t-test with $\alpha = 0.05$ as pre-specified in the statistical analysis plan. The analysis showed the superiority of XIENCE V EECSS to TAXUS PECSS in terms of the primary endpoint of in-segment LL at 240 days ($p = 0.0037$). The major secondary endpoint was also met with ischemia-driven TVF rate of 7.2% (47/657) for the XIENCE V arm and 9.0% (29/321) for the TAXUS arm (non-inferiority $p < 0.0001$).

**Table 11 Key Demographics and Risk Factors – Per Subject Analysis
(SPIRIT III RCT)
(Intent-To-Treat Population)**

	XIENCE V (N=669)	TAXUS (N=333)	Total (N=1002)	Difference [Precision]¹
Age (year) Mean ± SD (n)	63.23 ± 10.53 (669)	62.80 ± 10.24 (332)	63.08 ± 10.43 (1001)	0.43 [-0.94, 1.79]
Male Subjects	70.1% (469/669)	65.7% (218/332)	68.6% (687/1001)	4.44% [-1.73%, 10.62%]
Current Tobacco Use	23.4% (154/659)	22.5% (73/324)	23.1% (227/983)	0.84% [-4.74%, 6.42%]
All Diabetes Mellitus	29.6% (198/669)	27.9% (92/330)	29.0% (290/999)	1.72% [-4.23%, 7.67%]
Diabetes Mellitus Requiring Medication	25.6% (171/669)	25.2% (83/330)	25.4% (254/999)	0.41% [-5.32%, 6.14%]
Hypertension Requiring Medication	76.2% (510/669)	74.0% (245/331)	75.5% (755/1000)	2.22% [-3.51%, 7.94%]
Hypercholesterolemia Requiring Medication	74.2% (489/659)	71.5% (233/326)	73.3% (722/985)	2.73% [-3.20%, 8.66%]
All Prior Cardiac Interventions	32.3% (215/666)	29.5% (98/332)	31.4% (313/998)	2.76% [-3.29%, 8.82%]
Prior Cardiac Intervention on Target Vessel(s)	11.0% (72/655)	10.4% (34/326)	10.8% (106/981)	0.56% [-3.53%, 4.66%]
MI within 2 Months	2.8% (18/652)	2.4% (8/327)	2.7% (26/979)	0.31% [-1.78%, 2.41%]

¹ By normal approximation.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only.

**Table 12 Principal Effectiveness and Safety Results - All Lesions
(SPIRIT III RCT)
(Intent-To-Treat Population)**

Measurements	XIENCE V (N=669) (M=772)	TAXUS (N=333) (M=383)	Difference [Precision]
Effectiveness Measures			
Clinical Device Success	98.3% (750/763)	98.7% (374/379)	-0.38% [-1.86%, 1.09%]
Clinical Procedure Success	98.5% (651/661)	97.3% (322/331)	1.21% [-0.78%, 3.19%]
240-Day Results - All-Lesion Analysis			
In-Segment Late Loss Mean ± SD (m)	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04]
In-Stent Late Loss Mean ± SD (m)	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
Proximal Late Loss Mean ± SD (m)	0.12 ± 0.40 (293)	0.20 ± 0.41 (134)	-0.07 [-0.16, 0.01]
Distal Late Loss Mean ± SD (m)	0.09 ± 0.36 (327)	0.10 ± 0.37 (154)	-0.01 [-0.08, 0.06]
In-Stent %DS Mean ± SD (m)	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment %DS Mean ± SD (m)	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Proximal %DS Mean ± SD (m)	10.17 ± 13.11 (315)	11.04 ± 13.21 (143)	-0.87 [-3.49, 1.75]
Distal %DS Mean ± SD (m)	10.44 ± 11.45 (334)	10.24 ± 11.37 (155)	0.20 [-1.98, 2.38]

Summary of Safety and Effectiveness Data

XIENCE™ V Everolimus Eluting Coronary Stent System (P070015)

**Table 12 (cont'd) Principal Effectiveness and Safety Results - All Lesions
(SPIRIT III RCT)
(Intent-To-Treat Population)**

Measurements	XIENCE V (N=669) (M=772)	TAXUS (N=333) (M=383)	Difference [Precision]
240-Day Results - All-Lesion Analysis (cont'd)			
In-Stent ABR	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment ABR	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]
Proximal ABR	2.9% (9/315)	2.8% (4/143)	0.06% [Assump. not met]
Distal ABR	0.9% (3/334)	1.3% (2/155)	-0.39% [Assump. not met]
In-Stent MLD Mean ± SD (m)	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD Mean ± SD (m)	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
Proximal MLD Mean ± SD (m)	2.69 ± 0.58 (316)	2.70 ± 0.57 (143)	-0.00 [-0.12, 0.11]
Distal MLD Mean ± SD (m)	2.37 ± 0.52 (334)	2.39 ± 0.54 (155)	-0.02 [-0.12, 0.08]
Aneurysm	0.0% (0/343)	0.0% (0/158)	0.00% [Assump. not met]
Persisting Dissection	0.0% (0/343)	0.0% (0/157)	0.00% [Assump. not met]
% volume obstruction Mean ± SD (m)	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)	-4.30 [-7.72, -0.88]
Persisting Incomplete Apposition	24.4% (22/90)	14.0% (6/43)	10.49% [-3.15%, 24.13%]
Late-acquired Incomplete Apposition	1.1% (1/90)	2.3% (1/43)	-1.21% [Assump. not met]
Clinical Endpoints to 284 Days¹ - Per-Subject Analysis			
TVF-free	92.9%	91.1%	1.81% [-1.86%, 5.48%]
TLR-free	97.4%	95.0%	2.38% [-0.28%, 5.04%]
Revascularization ² -free	94.7%	93.5%	1.20% [-1.99%, 4.39%]
Cardiac Death-free	99.5%	99.4%	0.16% [-0.84%, 1.16%]
MACE-free	95.5%	92.0%	3.46% [0.11%, 6.81%]
Safety Measures - Per-Subject Analysis			
TVF in-hospital ³	0.9% (6/669)	1.8% (6/330)	-0.92% [-2.53%, 0.69%]
TVF through 37 days	1.5% (10/667)	2.7% (9/330)	-1.23% [-3.21%, 0.76%]
TVF through 194 days	3.8% (25/663)	4.9% (16/326)	-1.14% [-3.89%, 1.62%]
TVF through 284 days	7.2% (47/657)	9.0% (29/321)	-1.88% [-5.58%, 1.82%]
MACE in-hospital ³	0.9% (6/669)	1.8% (6/330)	-0.92% [-2.53%, 0.69%]
MACE through 37 days	1.2% (8/667)	2.4% (8/330)	-1.22% [-3.08%, 0.63%]
MACE through 194 days	2.6% (17/663)	4.6% (15/326)	-2.04% [-4.61%, 0.54%]
MACE through 284 days	4.6% (30/657)	8.1% (26/321)	-3.53% [-6.92%, -0.15%]
Stent Thrombosis (per protocol) 0 to 30 days	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Stent Thrombosis (per protocol) 31 to 284 days	0.2% (1/653)	0.0% (0/320)	0.15% [Assump. not met]
Bleeding Complication to 284 days	3.1% (20/653)	4.7% (15/320)	-1.62% [-4.29%, 1.04%]
Vascular Complication to 284 days	0.9% (6/654)	0.9% (3/320)	-0.02% [Assump. not met]
CVA to 284 days	0.8% (5/653)	0.6% (2/320)	0.14% [Assump. not met]

Summary of Safety and Effectiveness Data
XIENCE™ V Everolimus Eluting Coronary Stent System (P070015)

¹ Kaplan-Meier estimates.

² Revascularization includes both TLR and TVR, non-target lesion.

³ In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.

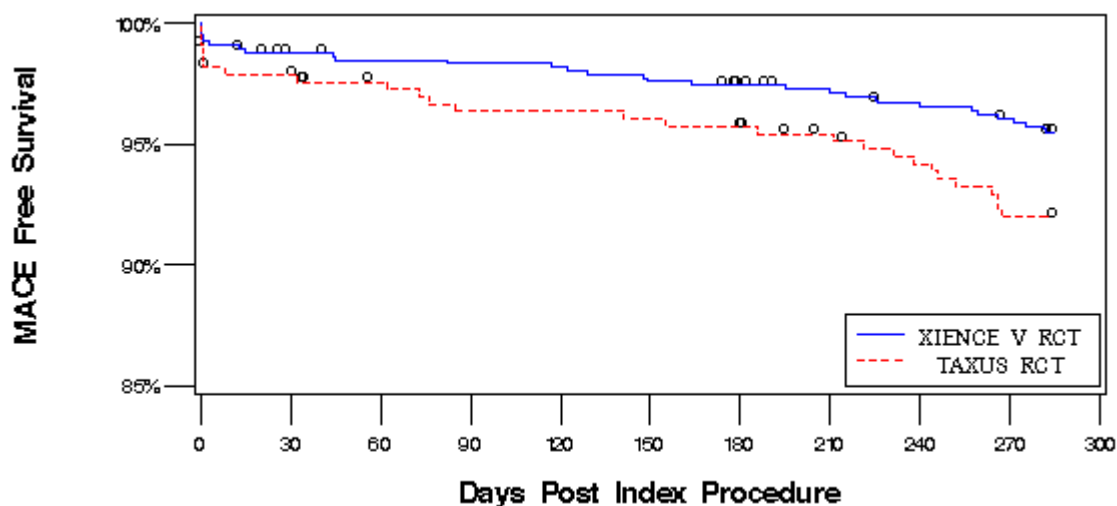
Notes:

- N = number of patients; M = number of lesions treated
- Numbers are % (counts/sample size) and Mean ± SD; CI=Confidence Interval
- Relative risk = XIENCE V/TAXUS; $SE = \sqrt{(1-p_1)/n_1 + (1-p_2)/n_2}$; $CI = \exp(\ln(RR) \pm 1.96 * SE)$
- Difference = XIENCE V- TAXUS; Binomial: $SE = \sqrt{p_1 * q_1/n_1 + p_2 * q_2/n_2}$; Normal: $SE = \sqrt{Sp^2(1/n_1 + 1/n_2)}$; Survival: $SE = \sqrt{SE_1^2 + SE_2^2}$; Binomial/Survival: $CI = Diff \pm 1.96 * SE$; Normal: $CI = Diff \pm t_{0.025} * SE$
- ABR (angiographic binary restenosis): A follow-up percent diameter stenosis of $\geq 50\%$.
- TVF (target vessel failure): Death, Q-Wave and Non-Q-Wave MI, Target Lesion Revascularization, or Target Vessel Revascularization.
- TLR (target lesion revascularization): Revascularization at the target lesion associated with either a positive functional ischemia test or ischemic symptoms, and having an angiographic minimal lumen diameter stenosis $\geq 50\%$ by QCA, or having a revascularization of target lesion with diameter stenosis $> 70\%$ by QCA without either angina or positive functional test.
- TVR (target vessel revascularization): Revascularization at the target vessel associated with either: (1) positive functional ischemia test, (2) ischemic symptoms, and having an angiographic minimum lumen diameter stenosis $\geq 50\%$ by QCA, or having a revascularization of target lesion with diameter stenosis $> 70\%$ by QCA without either angina or positive functional test.
- MACE: Cardiac Death, Q-Wave and Non-Q-Wave MI, or Target Lesion Revascularization.
- Bleeding (Hemorrhagic) Complications: Any peri or post-procedural vascular injury or event (ie, hematoma requiring transfusion or surgical repair, retroperitoneal bleed, GI bleed).
- Vascular Complications: Any peri or post-procedural vascular injury or event (ie, arteriovenous fistula, pseudoaneurysm).
- CVA (Cerebrovascular Accident): The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke).
- Clinical device success is computed per lesion and clinical procedure success is computed per subject.
- Angiographic results at 240 days only include subjects who were assigned to Group A and Group B at randomization with follow-up angiogram.
- This table includes revascularizations on any target vessel(s) / lesions for subjects with two target vessels / lesions treated.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study; Data from this subject is excluded from all data analyses.

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only.

**Figure 3 Kaplan-Meier Survival Curve: MACE Free Survival through 284 Days
(SPIRIT III RCT)
(Intent-To-Treat Population)**



Time After Index Procedure (days)				
	0	37	194	284
XIENCE V: # At Risk	669	656	640	624
# Events	3	8	17	30
% Survived	99.6%	98.8%	97.4%	95.5%
% SEM	0.3%	0.4%	0.6%	0.8%
TAXUS: # At Risk	332	319	309	295
# Events	3	8	15	26
% Survived	99.1%	97.6%	95.4%	92.0%
% SEM	0.5%	0.8%	1.2%	1.5%
Test Between Groups	Test	Chi-Square	DF	p-value
	Log-Rank	4.917	1	0.0266

Note: Includes only each subject's first occurrence of MACE.

Note: One subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

Note: There are 2 NQMI in the TAXUS arm not included in this table. They were adjudicated by CEC after unblinding.

SPIRIT III 4.0 mm Arm

Objective: The objective of the SPIRIT III 4.0 mm arm was to evaluate the XIENCE V EECSS compared to TAXUS PECSS 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.

Conclusion: In the SPIRIT III 4.0 mm clinical non-randomized arm, the XIENCE V EECSS has shown non-inferiority to TAXUS PECSS in terms of the primary endpoint, in-segment LL at 240 days ($p < 0.0001$). In the interim analysis of 69 subjects, 49 subjects (71%) had angiographic follow up. In-segment LL at 240 days was 0.17 ± 0.38 mm for the XIENCE V Stent, 4.0 mm arm and 0.28 ± 0.48 mm for the TAXUS Stent, RCT arm ($p < 0.0001$). The difference between the two arms (0.17 mm – 0.28 mm = -0.11 mm) represents a 39% reduction in in-segment LL in the XIENCE V Stent, 4.0 mm arm compared to the TAXUS Stent, RCT arm.

The XIENCE V Stent, 4.0 mm arm consistently had lower observed event rates than the TAXUS Stent, RCT arm through 284 days: TLR (1.5% vs. 5.0%); TVR (1.0% vs. 4.0%); MACE (5.9% vs. 8.1%). For stent thrombosis rates, the small sample size and occurrence rate made this difference clinically insignificant.

Therefore, 240 day angiographic endpoint results and clinical endpoint results through 284 days have demonstrated the safety and efficacy of the 4.0 mm diameter XIENCE V EECSS.

Design: Prospective, single arm, multi-center, five-year clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V EECSS: Non-Inferiority to TAXUS PECSS arm in the SPIRIT III Randomized Control Trial (RCT)

The XIENCE V Stent, 4.0 mm arm included a stent diameter of 4.0 mm and lengths of 8, 18 and 28 mm. The XIENCE V Stent had to adequately cover the lesion such that a minimum of 3 mm of healthy vessel on either side of the lesion was covered by the stent. Therefore, in the XIENCE V arm, treatment of target lesion > 22 mm and ≤ 28 mm in length was accomplished by overlapping either two 18 mm stents or a 28 mm and an 8 mm stent.

Pre-dilatation was performed prior to stent deployment with an angioplasty balloon. Post-dilatation was left to the discretion of the investigator. However if post-dilatation was performed, then the balloon was sized to fit within the boundaries of the stent.

IVUS was performed at follow-up in a pre-specified group of subjects and for subjects who received a bailout stent.

During the index procedure, medications administered included loading dose of clopidogrel bisulfate (≥ 300 mg) and aspirin (≥ 300 mg). Loading doses of antiplatelet medications were to be given at least six hours prior to the implant procedure if possible, but no later than one hour after the procedure in any case. All subjects in the

US who received XIENCE V were to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of 6 months following the procedure. All subjects who received the TAXUS PECSS were to be maintained on clopidogrel bisulfate for 6 months as instructed in the Instructions For Use (IFU) for TAXUS PECSS. For subjects allergic to clopidogrel bisulfate, ticlopidine hydrochloride was allowed at a dose according to standard hospital practice. All subjects were also required to receive ≥ 80 mg of aspirin daily to be taken throughout the length of the trial (5 years).

Clinical and angiographic follow-up through 9 months are currently available and follow-up for clinical parameters through 5-years is ongoing.

Demographics: Key baseline demographics and risk factors in the SPIRIT III 4.0 mm arm as shown in Table 13.

Method: The SPIRIT III 4.0 mm arm was a prospective, multi-center, single arm registry designed to enroll up to 80 subjects in the US. Subject eligibility was confirmed based on pre-procedure angiography prior to the index procedure.

Results: The SPIRIT III 4.0 mm arm was a study conducted to determine the safety and efficacy of the XIENCE V EECSS in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. In this prospective, multi-center, single arm registry, XIENCE V EECSS 4.0 mm diameter showed statistically significant non-inferiority to TAXUS PECSS in terms of the primary endpoint, in-segment LL at 240 days. In-segment LL at 240 days was 0.17 ± 0.38 mm for the XIENCE V Stent, 4.0 mm arm and 0.28 ± 0.48 mm for the TAXUS Stent, RCT arm. These results are similar to what was observed in the RCT. In-segment LL at 240 days was 0.14 ± 0.41 mm in the XIENCE V Stent arm as compared to 0.28 ± 0.48 mm in the TAXUS Stent arm. In-segment LL at 240 days was 0.17 ± 0.38 mm for the XIENCE V Stent, 4.0 mm arm which is comparable to the 0.14 ± 0.41 mm observed in the XIENCE V Stent arm of the RCT.

For secondary endpoints, the XIENCE V Stent, 4.0 mm arm showed non-inferiority to the TAXUS Stent arm in terms of ischemia-driven TVF rates (5.9% vs. 9.0%) through 284 days. MACE rates in the XIENCE V Stent, 4.0 mm arm were lower than in the TAXUS Stent, RCT arm. Stent thrombosis rates were comparable in the 2 treatment arms.

Secondary angiographic endpoint results were comparable between the treatment groups except for in-stent LL, in-stent MLD, in-segment MLD, proximal MLD, distal MLD, in-stent %DS, in-segment %DS, in-stent ABR and in-segment ABR. Neither aneurysm nor persisting dissection were observed in either arm. In-stent LL in the XIENCE V Stent, 4.0 mm arm was lower than that in the TAXUS Stent, RCT arm. In-stent MLD, in-segment MLD, and proximal MLD, in XIENCE V Stent, 4.0 mm arm were greater than in the TAXUS Stent, RCT arm, as would be expected because of the difference in vessel size. In-stent %DS and in-segment %DS in the XIENCE V Stent, 4.0 mm arm were lower than those in the TAXUS Stent, RCT arm. In addition, in-stent ABR and in-

segment ABR in the XIENCE V Stent, 4.0 mm arm were lower than those in the TAXUS Stent, RCT arm.

Clinical Pharmacology: A subgroup of 17 subjects in the SPIRIT III trial (RCT and 4.0 mm arm) was enrolled in a PK substudy. Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level at a minimum of 5 pre-determined sites.

**Table 13 Key Demographics and Risk Factors – Per Subject Analysis
(SPIRIT III 4.0 mm Arm)
(Intent-To-Treat Population)**

	XIENCE V 4.0 mm Arm (N=69)
Age (year) Mean ± SD (n)	61.93 ± 11.20 (69)
Male Subjects	72.5% (50/69)
Current Tobacco Use	27.9% (19/68)
All Diabetes Mellitus	30.4% (21/69)
Diabetes Mellitus Requiring Medication	23.2% (16/69)
Hypertension Requiring Medication	65.2% (45/69)
Hypercholesterolemia Requiring Medication	77.9% (53/68)
All Prior Cardiac Interventions	21.7% (15/69)
Prior Cardiac Intervention on Target Vessel(s)	8.7% (6/69)
MI within 2 Months	5.8% (4/69)

**Table 14 Principal Effectiveness and Safety Results
(XIENCE V 4.0 mm Arm)
(Intent-To-Treat Population)**

Measurements	XIENCE V 4.0 mm Arm (N=69) (M=69)
Effectiveness Measures	
Clinical Device Success	98.5% (67/68)
Clinical Procedure Success	94.2% (65/69)
240-Day Results - All-Lesion Analysis	
In-Segment Late Loss Mean ± SD (m)	0.17 ± 0.38 (49)
In-Stent Late Loss Mean ± SD (m)	0.12 ± 0.34 (49)
Proximal Late Loss Mean ± SD (m)	0.19 ± 0.38 (46)
Distal Late Loss Mean ± SD (m)	0.10 ± 0.32 (46)
In-Stent %DS Mean ± SD (m)	4.78 ± 13.20 (49)
In-Segment %DS Mean ± SD (m)	17.92 ± 10.83 (49)
Proximal %DS Mean ± SD (m)	10.22 ± 10.98 (49)
Distal %DS Mean ± SD (m)	9.18 ± 6.99 (48)
In-Stent ABR	0.0% (0/49)
In-Segment ABR	2.0% (1/49)
Proximal ABR	2.0% (1/49)
Distal ABR	0.0% (0/48)
In-Stent MLD Mean ± SD (m)	3.36 ± 0.46 (49)
In-Segment MLD Mean ± SD (m)	2.91 ± 0.51 (49)
Proximal MLD Mean ± SD (m)	3.42 ± 0.59 (49)
Distal MLD Mean ± SD (m)	3.20 ± 0.48 (48)
Aneurysm	0.0% (0/49)
Persisting Dissection	0.0% (0/49)
Clinical Endpoints to 284 Days¹ - Per-Subject Analysis	
TVF-free	94.2%
TLR-free	98.5%
Revascularization ² -free	98.5%
Cardiac Death-free	98.5%
MACE-free	94.2%
Safety Measures - Per-Subject Analysis	
TVF in-hospital ³	4.3% (3/69)
TVF through 37 days	4.3% (3/69)
TVF through 194 days	5.9% (4/68)

**Table 14 (cont'd) Principal Effectiveness and Safety Results
(XIENCE V 4.0 mm Arm)
(Intent-To-Treat Population)**

Safety Measures - Per-Subject Analysis (cont'd)	
TVF through 284 days	5.9% (4/68)
MACE in-hospital ³	4.3% (3/69)
MACE through 37 days	4.3% (3/69)
MACE through 194 days	5.9% (4/68)
MACE through 284 days	5.9% (4/68)
Stent Thrombosis 0 to 30 days	1.4% (1/69)
Stent Thrombosis 31 to 284 days	0.0% (0/67)
Bleeding Complication to 284 days	6.0% (4/67)
Vascular Complication to 284 days	0.0% (0/67)
CVA to 284 days	0.0% (0/67)

¹ Kaplan-Meier estimates.

² Revascularization includes both TLR and TVR, non-target lesion.

³ In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.

Notes:

· Numbers are % (counts/sample size) and Mean ± SD.

· ABR (angiographic binary restenosis): A follow-up percent diameter stenosis of $\geq 50\%$.

· TVF (target vessel failure): Death, Q-Wave and Non-Q-Wave MI, Target Lesion Revascularization, or Target Vessel Revascularization.

· TLR (target lesion revascularization): Revascularization at the target lesion associated with either a positive functional ischemia test or ischemic symptoms, and having an angiographic minimal lumen diameter stenosis $\geq 50\%$ by QCA, or having a revascularization of target lesion with diameter stenosis $> 70\%$ by QCA without either angina or positive functional test.

· TVR (target vessel revascularization): Revascularization at the target vessel associated with either: (1) positive functional ischemia test, (2) ischemic symptoms, and having an angiographic minimum lumen diameter stenosis $\geq 50\%$ by QCA, or having a revascularization of target lesion with diameter stenosis $> 70\%$ by QCA without either angina or positive functional test.

· MACE: Cardiac Death, Q-Wave and Non-Q-Wave MI, or Target Lesion Revascularization.

· Bleeding (Hemorrhagic) Complications: Any peri or post-procedural vascular injury or event (ie, hematoma requiring transfusion or surgical repair, retroperitoneal bleed, GI bleed).

· Vascular Complications: Any peri or post-procedural vascular injury or event (ie, arteriovenous fistula, pseudoaneurysm).

· CVA (Cerebrovascular Accident): The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke).

· Clinical device success is computed per lesion and clinical procedure success is computed per subject.

B. SPIRIT II Supportive Clinical Trial (OUS)

Objective: The objective of the SPIRIT II clinical study was to continue the assessment of safety and performance of the XIENCE V EECSS in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. The SPIRIT II clinical study arm allowed the treatment of *de novo* lesions ≤ 28 mm in length in coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 4.0 mm.

Conclusion: The SPIRIT II study one year follow-up demonstrated that the treatment effect that was observed at 6 month follow-up was sustained at 270 days and at 1 year for the XIENCE V Stent group.

At 180-day follow-up for the SPIRIT II clinical study, the XIENCE V EECSS demonstrated non-inferiority to the TAXUS PECSS in terms of primary endpoint of in-stent late loss ($p < 0.0001$). As pre-specified in the protocol, a superiority test of the primary endpoint was performed. The difference between the two stents (0.11 mm – 0.36 mm = -0.25 mm) represents a 72% reduction in late loss and is highly significant ($p < 0.0001$). Therefore, XIENCE V Stent was superior to TAXUS Stent for the primary endpoint. The IVUS results support the angiographic endpoint results. There was a 66% reduction in %VO in the

XIENCE V Stent group compared to the TAXUS Stent group (2.5% vs. 7.4%) and a 73% reduction in NIH volume (3.8 vs. 14.4) in XIENCE V Stent group compared to TAXUS Stent group. In addition, for other key clinical endpoints the XIENCE V Stent group also had lower observed event rates than the TAXUS Stent group, eg, ischemia driven (ID)-TLR (1.8% vs. 3.9%), ID-TVR (2.7% vs. 5.2%), ID-MACE (2.7% vs. 6.5%), and stent thrombosis (0.5% vs. 1.3%). Therefore, 180-day angiographic, IVUS, and clinical endpoint results have demonstrated the safety and efficacy of the XIENCE V EECSS.

The clinical safety observed at 6 months was sustained at 1 year. This was demonstrated by no new observations of late stent thrombotic events or MACE in the XIENCE V Stent group.

Design: The SPIRIT II clinical study is a prospective, active-control, randomized, single blind, parallel two-group, multicenter study. Three hundred subjects were enrolled in the study at 28 international sites in Europe, India and New Zealand. All subjects were enrolled in a 3:1 ratio (XIENCE V Stent group: TAXUS Stent group). Subjects were stratified by diabetes mellitus (diabetic vs. non-diabetic), dual vessel treatment (single vessel vs. dual vessel), and IVUS pre-selected sites (IVUS site vs. non-IVUS site). Pre-dilatation was required prior to stent deployment with balloon angioplasty.

All subjects enrolled into this clinical study were required to receive a loading dose of antiplatelet medications (clopidogrel bisulfate \geq 300 mg and aspirin \geq 75 mg) at least 6 hours prior to the index procedure, but no later than 1 hour after the procedure. Loading dose could be adjusted in patients on chronic antiplatelet medication. All patients were also required to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of 6 months following the procedure and \geq 75 mg of aspirin daily for a minimum of one year following the procedure. During the procedure, patients were to receive appropriate anticoagulation and other therapy according to standard hospital practice.

All subjects were to have clinical follow-up at 1 month, 6 months, 9 months and 1, 2, 3, 4, and 5 years, and angiographic follow-up at baseline and 6 months. A pre-specified subgroup of 152 consecutively enrolled subjects at selected sites was to have IVUS follow-up at baseline, 6 months and 2 years and angiographic follow-up at 2 years. Follow-up through 1 year is currently available and follow-up for clinical and angiographic parameters through 2 years is ongoing.

A subgroup of 35 subjects was enrolled in a PK substudy. Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level at a minimum of 5 pre-determined sites.

Demographics: Key baseline demographics and risk factors in the SPIRIT II clinical study are shown in Table 15.

Methods: The SPIRIT II clinical study is a prospective, active control, randomized, single blind, parallel two-group, multicenter study. Three hundred subjects were enrolled in the study at 28 international sites in Europe, India and New Zealand.

The SPIRIT II clinical study was designed to enroll subjects with a maximum of two *de novo* target lesions, each in a different epicardial vessel, reference vessel diameter (RVD) of ≥ 2.5 mm and ≤ 4.25 mm¹, lesion length ≤ 28 mm by visual estimation, percent diameter stenosis (%DS) of $\geq 50\%$ and $< 100\%$, TIMI flow of ≥ 1 , non-target vessel percutaneous intervention in non-target vessel planned ≥ 90 days prior to or > 9 months after the index procedure.

Results: At one year clinical follow-up data was available in 99% and 97% of subjects in the everolimus and paclitaxel arms respectively. Key baseline demographics and risk factors were comparable between both arms and had similar angiographic, and procedural characteristics.

Hierarchical analysis of 270-day clinical results showed that MACE or TVF events occurring since the 180-day time point were limited to 2 additional ID-TVF: one ID non-target lesion TVR by CABG and one ID non-target lesion TVR by PCI both in the XIENCE V Stent group. The total MACE rates for the procedure through the 270-day interval remained at 2.7% in the XIENCE V Stent group and 6.6% in the TAXUS Stent group. The TVF rates for the procedure through the 270 day interval were 4.5% in the XIENCE V Stent group and 6.6% in the TAXUS Stent group.

Hierarchical analysis of 1 year clinical results showed that MACE or TVF events occurring since the 270 days time point were limited to two ID-TLRs by PCI in the TAXUS Stent group. The total MACE rates for the procedure through the 1 year interval were 2.7% in the XIENCE V Stent group and 9.2% in the TAXUS Stent group. Although not the primary endpoint, there was a statistically significant benefit in MACE ($p = 0.017$) favoring XIENCE V compared to TAXUS. The TVF rates for the procedure through the 365-day interval were 4.5% in the XIENCE V group and 9.2% in the TAXUS group. One additional ID-TLR occurred in a XIENCE V subject who had already an ID-TLR before 6 months

A total of 2 cases of late stent thrombosis were reported in the subjects in the SPIRIT II clinical study through 180 days post-procedure, of which one stent thrombosis was reported in a subject in the XIENCE V group and one in a subject in the TAXUS group. No new instances of late stent thrombosis were observed in either group between the 180 days time point up to the 1 year follow-up time point.

¹ Stent sizes used were 2.5 to 3.5 mm until the 4.0 mm TAXUS PECSS was commercially available.

**Table 15 Key Demographic and Risk Factors
(SPIRIT II)
(Intent-To-Treat Population)**

	XIENCE V (N=223)	TAXUS (N=77)	Total (N=300)	Difference [Precision]
Age (yrs) Mean ± SD (n)	61.95 ± 10.29 (223)	61.92 ± 9.44 (77)	61.94 ± 10.06 (300)	0.03 [-2.49, 2.56]
Number of Men	70.9% (158/223)	79.2% (61/77)	73.0% (219/300)	-8.37% [-19.22%, 2.48%]
Current Tobacco Use	31.6% (66/209)	29.9% (20/67)	31.2% (86/276)	1.73% [-10.91%, 14.37%]
Diabetes Treated with Medication	20.2% (45/223)	21.1% (16/76)	20.4% (61/299)	-0.87% [-11.44%, 9.70%]
Hypertension Requiring Medication	67.3% (150/223)	64.9% (50/77)	66.7% (200/300)	2.33% [-9.98%, 14.64%]
Hypercholesterolemia Requiring Medication	68.7% (149/217)	75.0% (57/76)	70.3% (206/293)	-6.34% [-17.86%, 5.19%]
Prior Cardiac Intervention on Target Vessel(s)	3.6% (8/221)	4.0% (3/75)	3.7% (11/296)	-0.38% [Assump. not fulfilled]
MI within 2 months	18.4% (40/217)	7.8% (6/77)	15.6% (46/294)	10.64% [2.74%, 18.54%]

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only.

**Table 16 Principal Effectiveness and Safety Results
(SPIRIT II)
(Per-treatment Evaluable Population)**

Measurements	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Difference [Precision]
Effectiveness Measures			
Clinical Device Success	98.8% (256/259)	98.9% (89/90)	-0.05% [Assump. not met]
Clinical Procedure Success	99.1% (221/223)	97.4% (75/77)	1.70% [Assump. not met]
180-Day Results - All Lesion Analysis			
In-Stent Late Loss Mean ± SD (n)	0.12 ± 0.29 (237)	0.37 ± 0.38 (86)	-0.25 [-0.34, -0.16]
In-Segment Late-Loss Mean ± SD (n)	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
Proximal Late-Loss Mean ± SD (n)	0.12 ± 0.39 (237)	0.16 ± 0.40 (86)	-0.04 [-0.14, 0.06]
Distal Late-Loss Mean ± SD (n)	0.02 ± 0.35 (237)	-0.01 ± 0.37 (86)	0.04 [-0.05, 0.13]
n-Stent %DS Mean ± SD (n)	15.70 ± 9.88 (237)	20.89 ± 11.59 (86)	-5.18 [-7.96, -2.41]
In-Segment %DS Mean ± SD (n)	23.61 ± 11.65 (237)	27.05 ± 12.68 (86)	-3.44 [-6.53, -0.35]
Proximal %DS Mean ± SD (n)	10.73 ± 8.50 (237)	10.09 ± 6.85 (86)	0.64 [-1.18, 2.46]
Distal %DS Mean ± SD (n)	11.52 ± 8.21 (237)	12.09 ± 7.31 (86)	-0.58 [-2.45, 1.30]
In-Stent ABR	1.3% (3/237)	3.5% (3/86)	-2.22% [Assump. not met]
In-Segment ABR	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]

**Table 16 (cont'd) Principal Effectiveness and Safety Results
(SPIRIT II)
(Per-treatment Evaluable Population)**

Measurements	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Difference [Precision]
180-Day Results - All Lesion Analysis (cont'd)			
Proximal ABR	0.4% (1/237)	0.0% (0/86)	0.42% [Assump. not met]
Distal ABR	0.4% (1/237)	0.0% (0/86)	0.42% [Assump. not met]
In-Stent MLD Mean ± SD (n)	2.38 ± 0.50 (237)	2.27 ± 0.54 (86)	0.10 [-0.03, 0.23]
In-Segment MLD Mean ± SD (n)	2.10 ± 0.51 (237)	2.08 ± 0.54 (86)	0.02 [-0.11, 0.15]
Proximal MLD Mean ± SD (n)	2.50 ± 0.60 (237)	2.59 ± 0.65 (86)	-0.09 [-0.25, 0.07]
Distal MLD Mean ± SD (n)	2.26 ± 0.59 (237)	2.33 ± 0.58 (86)	-0.07 [-0.21, 0.07]
Aneurysm	0.0% (0/237)	0.0% (0/86)	0.00% [Assump. not me]
Persisting Dissection	0.0% (0/260)	1.1% (1/90)	-1.11% [Assump. not met]
%Volume Obstruction	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
Persisting Incomplete Apposition	2.5% (3/120)	0.0% (0/42)	2.50% [Assump. not met]
Clinical Endpoints to 365 Days¹ Per-Subject Analysis			
TVF-free	95.50%	90.84%	4.66% [-2.36%, 11.68%]
ID-TLR-free	98.20%	93.44%	4.76% [-1.07%, 10.59%]
ID-Revascularization ² -free	96.39%	93.44%	2.96% [-3.12%, 9.04%]
Cardiac Death-free	100.00%	98.70%	1.30% [-1.23%, 3.83%]
MACE-free	97.30%	90.84%	6.46% [-0.35%, 13.28%]
TVF through 30 days	0.9% (2/223)	3.9% (3/77)	-3.00% [Assump. not met]
TVF through 194 days	3.6% (8/222)	6.5% (5/77)	-2.89% [-8.92%, 3.14%]
TVF through 270 days	4.5% (10/220)	6.6% (5/76)	-2.03% [-8.25%, 4.18%]
TVF through 365 days	4.5% (10/220)	9.2% (7/76)	-4.67% [-11.73%, 2.40%]
MACE in-hospital ³	0.9% (2/223)	2.6% (2/77)	-1.70% [Assump. not met]
MACE through 30 days	0.9% (2/223)	3.9% (3/77)	-3.00% [Assump. not met]
MACE through 194 days	2.7% (6/222)	6.5% (5/77)	-3.79% [-9.69%, 2.11%]
MACE through 270 days	2.7% (6/220)	6.6% (5/76)	-3.85% [-9.83%, 2.12%]
MACE through 365 days	2.7% (6/220)	9.2% (7/76)	-6.48% [-13.33%, 0.37%]
Stent Thrombosis 0 to 30 days	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Stent Thrombosis 31 to 365 days	0.5% (1/220)	1.3% (1/76)	-0.86% [Assump. not met]
Bleeding Complication to 365 days	2.7% (6/220)	0.0% (0/75)	2.73% [Assump. not met]
Vascular Complication to 365 days	8.6% (19/220)	14.5% (11/76)	-5.84% [-14.58%, 2.90%]
CVA/TIA to 365 days	0.9% (2/220)	1.3% (1/75)	-0.42% [Assump. not met]

¹ Kaplan-Meier estimates

² ID-Revascularization includes both ID-TLR and ID-TVR, non-target lesion

³ In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure

Notes:

· Numbers are % (counts/sample size) and Mean ± SD; CI=Confidence Interval

· Relative risk = XIENCE V/TAXUS SE=sqrt[(1-p1)/n1+1+(1-p2)/n2]; CI=exp(ln(RR)±1.96*SE)

· Difference = XIENCE V- TAXUS; Binomial: SE=sqrt(p1*q1/n1+p2*q2/n2); Normal: SE=sqrt(s1²/n1+ s2²/n2); Survival: SE=sqrt(SE1²+SE2²) Binomial/Survival: CI=Diff±1.96*SE; Normal: CI=Diff±t0.025*SE

· ABR (angiographic binary restenosis): A follow-up percent diameter stenosis of ≥ 50 %

· TVF (target vessel failure): Cardiac Death, Q-Wave and Non-Q-Wave MI, Ischemia Driven Target Lesion

Revascularization, or Ischemia Driven Target Vessel Revascularization

· MACE: Cardiac Death, Q-Wave and Non-Q-Wave MI, or ischemia Driven Target Lesion Revascularization

· ID-TLR (ischemia driven target lesion revascularization): Revascularization at the target lesion associated with any of the following: non-invasive positive functional ischemia study (eg, exercise testing or equivalent tests) or invasive positive

Summary of Safety and Effectiveness Data

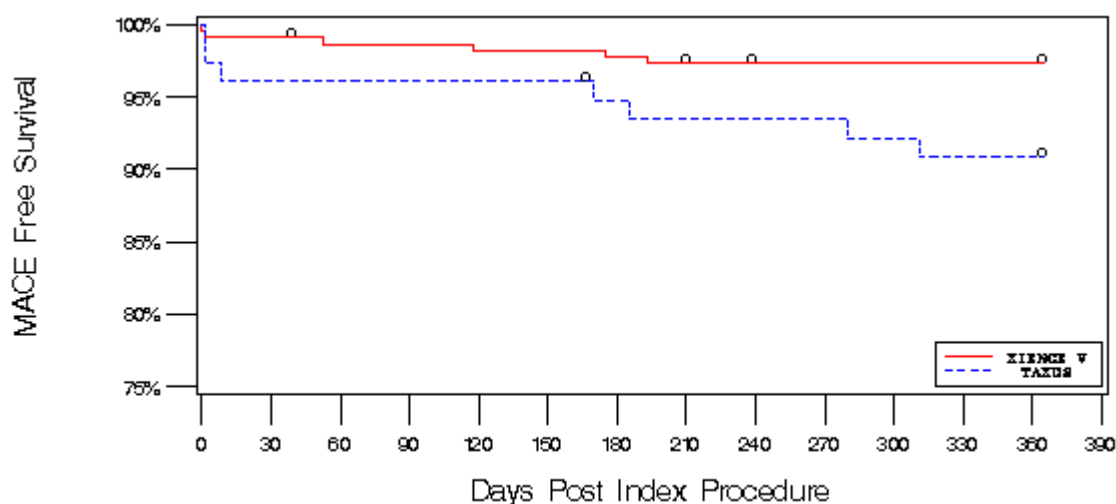
XIENCE™ V Everolimus Eluting Coronary Stent System (P070015)

functional ischemia study (eg, Fractional Flow Reserve (FFR) or Coronary Flow Reserve (CFR)), ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by on-line quantitative coronary angiography (QCA), diameter stenosis $\geq 70\%$ by on-line QCA without either ischemic symptoms or a positive functional study

- ID-IVR (ischemia driven target vessel revascularization): Revascularization in the target vessel associated with any of the following: non-invasive positive functional ischemia study (eg, exercise testing or equivalent tests) or invasive positive functional ischemia study (eg, Fractional Flow Reserve (FFR) or Coronary Flow Reserve (CFR)), ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by on-line quantitative coronary angiography (QCA), diameter stenosis $\geq 70\%$ by on-line QCA without either ischemic symptoms or a positive functional study
- Bleeding (Hemorrhagic) Complications: These may include hematoma requiring transfusion or surgical repair, and any bleeding event associated with hemoglobin drop > 5 g/dl or requiring transfusion or surgical repair (eg, retroperitoneal bleed, GI bleed, access site bleed)
- Vascular Complications: These may include hematoma, pseudoaneurysm, arteriovenous fistula, CVA or TIA, and peripheral ischemia or nerve injury. In this table Vascular complications excludes CVA/TIA as presented as a separate item
- CVA (Cerebrovascular Accident): The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke)
- Clinical device success is computed per lesion and clinical procedure success is computed per subject
- This table includes revascularizations on any target vessel(s) / lesion(s) for subjects with two target vessels / lesions treated

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only.

Figure 4 Kaplan-Meier Survival Curve: Ischemia Driven MACE Free Survival to 365 Days (SPIRIT II) (Intent-To-Treat Population)



	Time After Index Procedure (days)				
	0	30	194	270	365
XIENCE V: # At Risk	223	222	220	214	214
# Events	1	2	6	6	6
% Survived	99.6%	99.1%	97.3%	97.3%	97.3%
% SEM	0.4%	0.6%	1.1%	1.1%	1.1%
TAXUS: # At Risk	77	77	73	71	71
# Events	0	3	5	5	7
% Survived	100.0%	96.1%	93.5%	93.5%	90.8%
% SEM	0.0%	2.2%	2.8%	2.8%	3.3%
Tests Between Groups	Test	Chi-Square	DF	p-value	
	Log-Rank	5.663	1	0.0173	

Note: Includes only each patient's first occurrence of Ischemia Driven MACE.

C. SPIRIT FIRST First-in-Man Study (OUS)

Objective: The objective of the SPIRIT FIRST clinical study was to assess the feasibility and performance of the XIENCE V Everolimus Eluting Coronary Stent System in the treatment of patients with *de novo* native coronary artery lesions. This study compared XIENCE V EECSS to a matched uncoated metallic stent control (MULTI-LINK VISION).

Conclusions: In the SPIRIT FIRST clinical trial, the XIENCE V EECSS demonstrated superiority to the MULTI-LINK VISION stent in in-stent late loss and % volume obstruction at 180 days and 1 year follow-up. Additionally, the XIENCE V EECSS has demonstrated favorable clinical outcomes up to the 2-year time-point. No stent thromboses have been reported during the 2 years following the index procedure and no additional TVF events between 1 year and 2 years in the XIENCE V Stent arm have been reported.

Design: First-in-man 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 patients with *de novo* native coronary artery lesions.

Pre-dilatation was required prior to stent deployment with balloon angioplasty.

Subjects were maintained on 75 mg of clopidogrel bisulfate daily for a minimum of three months following the procedure. All subjects receive ≥ 80 mg of aspirin daily for one year following the procedure.

Clinical evaluation was scheduled at 1, 6, 12 and 24 months with annual evaluation up to 5 years. Follow-up was obtained by office visit or a telephone interview and included a series of questions for the determination of the occurrence of death, recurrent angina, repeat angiography, functional testing performed, myocardial infarction, repeat revascularization procedure, and any hospitalization. In case a major adverse cardiac event was reported, review of hospital records, chart review, telephone contact with the referring cardiologists or the patient's general practitioner were used to complete information. Angiographic and IVUS was required at 180 days and 1 year.

Follow-up through 2 years is currently available and follow-up for clinical and angiographic parameters through 5 years is ongoing.

Demographics: Key baseline demographics and risk factors in the SPIRIT FIRST Supportive Study as shown in Table 17.

Methods: SPIRIT FIRST Supportive Study is a prospective, controlled, randomized, single-blinded, parallel 2-arm, multi-center clinical trial. Subjects enrolled in the study had a single *de novo* coronary artery stenosis of between 50 – 99% and a vessel diameter of 3.0 mm as assessed by on-line quantitative coronary angiography (QCA) that could

be covered by a single 18 mm stent. Sixty subjects were randomized to either an everolimus eluting (XIENCE V Stent) or a bare metal control stent (MULTI-LINK VISION Stent).

Results: At two years, clinical follow-up data were available in 96% and 97% of patients in the everolimus and control arm respectively.

There were no additional MACE or TVF events in the XIENCE V Stent arm from the 1 year to the 2 year follow-up. In the VISION Stent arm, TVF events occurring during same duration were limited to one CD-TLR by PCI (MACE and TVF event) and one CD-TVR by PCI (TVF event).

The TVF rate at 2 years was 15.4% for the XIENCE V Stent arm and 28.6% for the VISION Stent arm. The MACE rates were 15.4% and 25.0% in the XIENCE V Stent and VISION Stent arms, respectively.

In the VISION Stent arm in the period from index procedure through 2 years, hierarchical Q-wave MI was 3.8% and non Q-wave MI was 3.8%. Both MIs were not device-related; one Q-wave MI was in a non-target vessel and one non-Q-wave MI occurred during the 1-year follow-up IVUS procedure. The CD-TLR rate was 7.7% (2 by PCI) and the CD-TVR rate (excluding TLR) was 0.0%

In the VISION Stent arm, no MIs were reported through 2-year follow-up. The hierarchical CD-TLR rate was 25.0% (1 of 7 by CABG and 6 of 7 by PCI), and the CD-TVR rate (excluding TLR) was 3.6% (1 of 1 by PCI).

No late stent thrombosis events were reported in either arm through the 2-year follow-up time point.

In the everolimus arm no additional death, myocardial infarction, clinically driven TLR, or TVR events were observed between one and two-year follow-up. The 2-year hierarchical MACE rate for the everolimus arm remained 15.4% (4/26). In the control group, one subject developed recurrent angina pectoris and was found to have a proximal edge restenosis of the target lesion.

Table 18 summarizes the principal safety and effectiveness results of the SPIRIT FIRST Trial through 758 days. Figure 5 shows the MACE-free survival through 2 years.

**Table 17 Key Demographic and Risk Factors
(SPIRIT FIRST)
(Per-treatment Evaluable Population)**

	XIENCE V (n = 27)	VISION (n = 29)	Total (n = 56)	Difference [Precision]
Age(yrs)	64.21 ± 9.56 (27)	61.36 ± 9.31 (29)	62.74 ± 9.45 (56)	[-7.91, 2.21]
Number of Men	70.4% (19/27)	75.9% (22/29)	73.2% (41/56)	[-28.71%, 17.73%]
Current Cigarette Use	28.0% (7/25)	31.0% (9/29)	29.6% (16/54)	[-27.39%, 21.32%]
Diabetes Requiring Medication	3.7% (1/27)	3.4% (1/29)	3.6% (2/56)	[Assump. not fulfilled]
Any Diabetes	11.1% (3/27)	10.3% (3/29)	10.7% (6/56)	[Assump. not fulfilled]
Hypertension Requiring Medication	70.4% (19/27)	41.4% (12/29)	55.4% (31/56)	[4.13%, 53.85%]
Hyperlipidemia Requiring Medication	70.4% (19/27)	75.9% (22/29)	73.2% (41/56)	[-28.71%, 17.73%]
Prior CABG on Target Vessel	0.0% (0/27)	0.0% (0/29)	0.0% (0/56)	[Assump. not fulfilled]
Angina	96.3% (26/27)	93.1% (27/29)	94.6% (53/56)	[Assump. not fulfilled]
Stable CCS III or IV	37.0% (10/27)	51.7% (15/29)	44.6% (25/56)	[-40.43%, 11.05%]
Unstable Braunwald III	0.0% (0/27)	3.4% (1/29)	1.8% (1/56)	[Assump. not fulfilled]
Prior MI	24.0% (6/25)	13.8% (4/29)	18.5% (10/54)	[Assump. not fulfilled]
MI within 2 Months	8.3% (2/24)	6.9% (2/29)	7.5% (4/53)	[Assump. not fulfilled]

Note: the normality assumption may not be valid given the small sample size

Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only.

**Table 18 Principal Effectiveness and Safety Results
(SPIRIT FIRST)
(Per-treatment Evaluable Population)**

Measurements	XIENCE V (n = 27)	VISION (n = 29)	Difference [Precision]
Effectiveness Measures			
Device Success	100.0% (27/27)	100.0% (29/29)	0.00% [Assump. not fulfilled]
Procedure Success	100.0% (27/27)	100.0% (29/29)	0.00% [Assump. not fulfilled]
Clinical Success	96.3% (26/27)	100.0% (29/29)	-3.70% [Assump. not fulfilled]
180-Day Results			
In-Stent Late Loss Mean ± SD (n)	0.10 ± 0.23 (23)	0.85 ± 0.36 (27)	-0.76 [-0.93, -0.59]
In-Segment Late Loss Mean ± SD (n)	0.09 ± 0.20 (23)	0.61 ± 0.37 (27)	-0.53 [-0.69, -0.36]
Proximal Late Loss Mean ± SD (n)	0.10 ± 0.17 (23)	0.40 ± 0.38 (27)	-0.30 [-0.46, -0.13]
Distal Late Loss Mean ± SD (n)	0.07 ± 0.20 (23)	0.25 ± 0.40 (27)	-0.18 [-0.36, -0.00]
In-Stent %DS Mean ± SD (n)	15.57 ± 7.64 (23)	38.61 ± 14.25 (27)	-23.05 [-29.45, -16.64]
In-Segment %DS Mean ± SD (n)	21.89 ± 11.15 (23)	40.78 ± 13.67 (27)	-18.89 [-25.95, -11.83]
Proximal %DS Mean ± SD (n)	11.94 ± 12.11 (23)	17.44 ± 17.00 (27)	-5.50 [-13.81, 2.82]
Distal %DS Mean ± SD (n)	16.40 ± 9.63 (23)	19.02 ± 14.36 (27)	-2.63 [-9.50, 4.25]
In-Stent ABR	0.0% (0/23)	25.9% (7/27)	-25.93% [Assump. not fulfilled]
In-Segment ABR	4.3% (1/23)	33.3% (9/27)	-28.99% [Assump. not fulfilled]
Proximal ABR	4.3% (1/23)	3.7% (1/27)	0.64% [Assump. not fulfilled]
Distal ABR	0.0% (0/23)	7.4% (2/27)	-7.41% [Assump. not fulfilled]
In-Stent MLD Mean ± SD (n)	2.28 ± 0.33 (23)	1.58 ± 0.41 (27)	0.70 [0.49, 0.91]
In-Segment MLD Mean ± SD (n)	2.04 ± 0.40 (23)	1.54 ± 0.41 (27)	0.50 [0.27, 0.73]
Proximal MLD Mean ± SD (n)	2.45 ± 0.46 (23)	2.19 ± 0.49 (27)	0.27 [-0.00, 0.54]
Distal MLD Mean ± SD (n)	2.18 ± 0.38 (23)	2.00 ± 0.45 (27)	0.18 [-0.06, 0.42]
Aneurysm	0.0% (0/23)	0.0% (0/27)	0.00% [Assump. not fulfilled]
Persisting Dissection	0.0% (0/26)	0.0% (0/29)	0.00% [Assump. not fulfilled]
%Volume Obstruction	7.95± 10.44 (21)	28.11± 13.98 (24)	-20.16 [-27.53, -12.79]
Persisting Incomplete Apposition	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not fulfilled]
Late-acquired Incomplete Apposition	0.0% (0/21)	0.0% (0/22)	0.00% [Assump. not fulfilled]
Clinical Endpoints to 758 Days¹ - Per-subject Analysis			
TVF-free	84.88%	71.43%	13.45% [-8.16%, 35.05%]
CD-TLR-free	92.44%	75.00%	17.44% [-1.50%, 36.38%]
CD-Revascularization ² -free	92.44%	71.43%	21.02% [1.48%, 40.55%]
Cardiac Death-free	100.00%	100.00%	0.00 [NA]

**Table 18 (cont'd) Principal Effectiveness and Safety Results
(SPIRIT FIRST)
(Per-treatment Evaluable Population)**

Measurements	XIENCE V (n = 27)	VISION (n = 29)	Difference [Precision]
Clinical Endpoints to 758 Days¹ - Per-subject Analysis (cont'd)			
MACE-free	84.88%	75.00%	9.88% [-11.2%, 30.95%]
Safety Measures - Per-subject Analysis			
TVF in-hospital ³	3.7% (1/27)	0.0% (0/29)	3.70% [Assump. not fulfilled]
TVF through 37 days	7.4% (2/27)	0.0% (0/29)	7.41% [Assump. not fulfilled]
TVF through 194 days	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not fulfilled]
TVF through 284 days	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not fulfilled]
TVF through 393 days	15.4% (4/26)	21.4% (6/28)	-6.04% [Assump. not fulfilled]
TVF through 758 days	15.4% (4/26)	28.6% (8/28)	-13.19% [Assump. not fulfilled]
MACE in-hospital ³	3.7% (1/27)	0.0% (0/29)	3.70% [Assump. not fulfilled]
MACE through 37 days	7.4% (2/27)	0.0% (0/29)	7.41% [Assump. not fulfilled]
MACE through 194 days	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not fulfilled]
MACE through 284 days	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not fulfilled]
MACE through 393 days	15.4% (4/26)	21.4% (6/28)	-6.04% [Assump. not fulfilled]
MACE through 758 days	15.4% (4/26)	25.0% (7/28)	-9.62% [Assump. not fulfilled]
Stent Thrombosis 0 to 30 days	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not fulfilled]
Stent Thrombosis 31 to 758 days	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not fulfilled]
Bleeding Complication to 758 days	3.8% (1/26)	10.7% (3/28)	-6.87% [Assump. not fulfilled]
Vascular Complication to 758 days	7.7% (2/26)	10.7% (3/28)	-3.02% [Assump. not fulfilled]
CVA to 758 days	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not fulfilled]

¹ Kaplan-Meier estimates

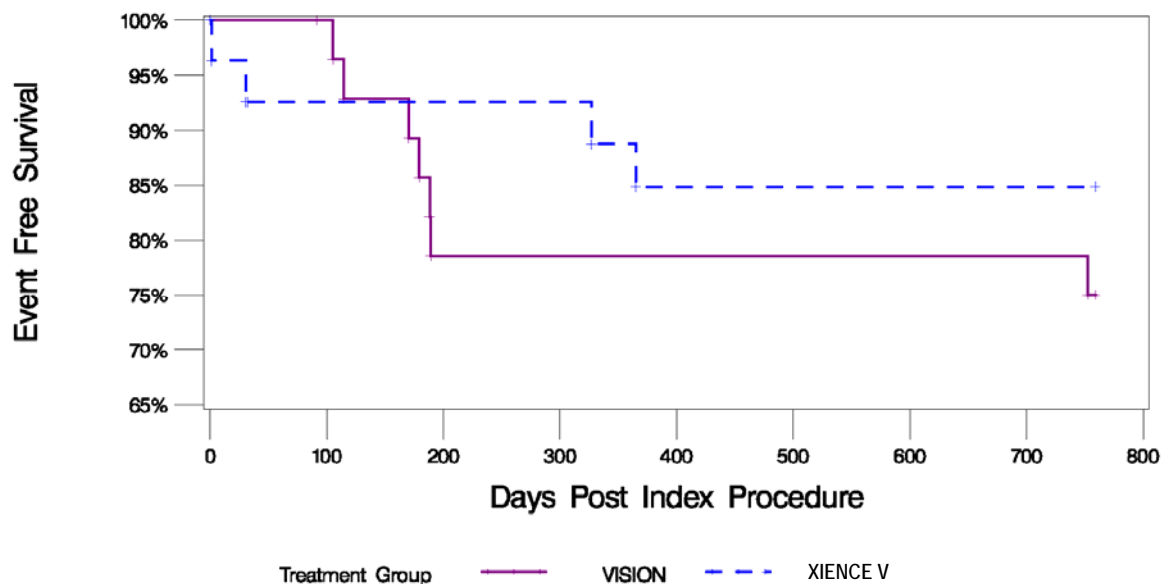
² CD-Revascularization includes both CD-TLR and CD-TVR, non-target lesion

³ In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure

Notes:

- NA indicates results could not be calculated due to data not being categorical or in case of extreme (high or low) rates
 - Numbers are % (counts/sample size) and Mean ± SD; CI=Confidence Interval
 - Relative risk = XIENCE V/VISION; SE=sqrt[(1-p1)/n1+(1-p2)/n2]; CI=exp(ln(RR)±1.96*SE)
 - Difference = XIENCE V - VISION; Binomial: SE=sqrt(p1*q1/n1+p2*q2/n2); Normal: SE=sqrt(SE1²/n1+ SE2²/n2); Survival: SE=sqrt(SE1²+SE2²) Binomial/Survival: CI=Diff±1.96*SE; Normal: CI=Diff±t0.025*SE
 - ABR (angiographic binary restenosis): A follow-up percent diameter stenosis of ≥50 %
 - TVF (target vessel failure): Cardiac Death, Q-Wave and Non-Q-Wave MI, Clinically Driven Target Lesion Revascularization, or Clinically Driven Target Vessel Revascularization
 - MACE: Cardiac Death, Q-Wave and Non-Q-Wave MI, or Clinically Driven Target Lesion Revascularization
 - CD-TLR (clinically driven target lesion revascularization): Revascularization at the target site associated with positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis ≥ 50% by quantitative coronary angiography (QCA), or revascularization of a target site with diameter stenosis ≥ 70% by QCA without either angina or a positive functional study
 - CD-TVR (clinically driven target vessel revascularization): Revascularization in the target vessel associated with positive functional ischemia study or ischemic symptoms
 - Bleeding (Hemorrhagic) Complications: These may include hematoma requiring transfusion or surgical repair, and any bleeding event associated with hemoglobin drop > 5 g/dl or requiring transfusion or surgical repair (eg, retroperitoneal bleed, GI bleed)
 - Vascular Complications: These may include pseudoaneurysm, AV fistula, stroke, peripheral ischemia
- Note: Confidence intervals are unadjusted for multiple comparisons and are for descriptive purposes only.

Figure 5 Kaplan-Meier Survival Curve: MACE (Cardiac Death, MI or Clinically-Driven TLR) Survival to 2-year follow-up (SPIRIT FIRST) (Per-Treatment Evaluable Population)



Time After Index Procedure (days)					
	0	30-day	6-month	1-year	2-year
XIENCE V:					
# At Risk	27	25	24	22	22
# Events	0	2	2	4	4
% Survived	100%	92.6%	92.6%	84.9%	84.9%
% SEM	0.0%	5.0%	5.0%	7.0%	7.0%
VISION:					
# At Risk	29	29	22	22	21
# Events	0	0	6	6	7
% Survived	100%	100%	78.6%	78.6%	75.0%
% SEM	0.0%	0.0%	7.8%	7.8%	8.2%
Tests Between Groups	Test	Chi-Square	DF		p-value
	Log-Rank	0.714	1		0.3980

D. Global Pharmacokinetics

Objective: 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.

Conclusion: The pharmacokinetic profile for everolimus eluted from the XIENCE V stent is consistent across all geographies. The pharmacokinetic profile in clinical trials of the XIENCE V EECSS is consistent with the pre-clinical profile. The local arterial delivery and limited systemic exposure provide the opportunity for successful treatment of coronary lesions with limited risk associated with systemic exposure.

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.

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.

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.

Results: 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.

E. Gender Bias

The gender selection in this series of clinical trial was completely random, and solely based upon exclusion and inclusion criteria. In the SPIRIT III pivotal trial (conducted in the US),

men represented 68.6% of the subject population and in the 4.0 mm registry, men represented 72.5% of the subject population. In the SPIRIT II supporting trial (conducted OUS), men represented 73% of the subject population. In the SPIRIT FIRST first-in-man trial (conducted OUS), men represented 73.2 % of the subject population. The ratio of men versus women in each of these trials is reflective of the underlying distribution of the disease for the given age groups, ethnic groups, and stages of disease in these populations. No selection bias on the basis of gender was identified during the review. In addition, no differences in safety or effectiveness were found with respect to gender.

XII. CONCLUSIONS DRAWN FROM THE 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 9 months.
- The clinical pharmacokinetics showed that the C_{max} never reached the minimum therapeutic value necessary for effective systemic administration to prevent organ rejection.
- In addition, the clinical testing conducted demonstrated that the product provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the Instructions for Use.

XIII. PANEL RECOMMENDATION

FDA to insert Panel Recommendations

XIV. CDRH DECISION

FDA to insert CDRH Decision

XV. APPROVAL SPECIFICATIONS

FDA to insert Approval Specifications

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