SECTION 4.0
SPONSOR EXECUTIVE SUMMARY

4.1 Background

Coronary stents were introduced in 1987 as a major advance over balloon angioplasty alone for treating atherosclerosis derived coronary artery disease. Coronary stents reduced angiographic and clinical restenosis rates in *de novo* lesions compared to percutaneous transluminal coronary angioplasty (PTCA) alone and decreased emergency coronary artery bypass graft (CABG) surgery. However, in-stent restenosis resulting in repeat revascularization remained a challenge[1,2]. In an effort to address the restenosis problem, stents coated with various drug doses and formulations have been developed to reduce neointimal proliferation at the lesion site[3,4,5,6].

Current considerations for DES development include both effectiveness and safety measures. The ideal drug eluting stent should be deliverable with a stable drug coating and should show angiographic and clinical measures of safety, namely, a low late loss, low rates of TLR and angiographic binary restenosis, and low TVF and MACE rates. Safety should be demonstrated by death, MI and stent thrombosis rates that are not inferior to currently available DES. In addition, lower TLR and MACE rates are indices of safety, as in-stent restenosis is not a benign entity, and TLRs are associated with peri-procedural morbidity and mortality. The XIENCE V EECSS studies (SPIRIT II and SPIRIT III) were conducted in single and dual vessel disease, and met their primary and major secondary endpoints on effectiveness measures, with no adverse safety signals out to 1 year follow up. The safety and effectiveness of the system will continue to be studied in continued access and post-approval studies that will include over 13,000 XIENCE V patients followed up for a period of 5 years.

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

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[1] Chan A, Moliterno DJ. Restenosis: The Clinical Issues. In: Topol EJ, ed. *Textbook of Interventional Cardiology*. 4th edition ed. Philadelphia, USA: Saunders; 2003:415-453.
[2] Narins CR, Topol EJ. In-Stent Restenosis. In: Topol EJ, ed. *Textbook of Interventional Cardiology*. 4th edition ed. Philadelphia, USA: Sauders; 2003:455-473.
[3] Gunn J, Cumberland D. Stent coatings and local drug delivery; state of the art. *Eur Heart J.* 1999;20:1693-1700.
[4] Muller DWM. Coated Stents and Local Drug Delivery for the Prevention of Restenosis. In: Topol EJ, ed. *Textbook of Interventional Cardiology*. 4th edition ed. Philadelphia, USA: Saunders; 2003:649-673.
[5] Ong AT, van der Giessen WJ. Drug-eluting stents for interventional revascularization of coronary multivessel disease. *J Interv Cardiol.* 2005;18:447-453.
[6] Salam AM, Al Suwaidi J, Holmes DR, Jr. Drug-eluting coronary stents. *Curr Probl Cardiol.* 2006;31:8-119.

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4.3 Regulatory History

Working in consultation with FDA, and in consideration of the fact that the XIENCE V is comprised of an approved stent and delivery platform and that the drug, everolimus is well-studied and not a new molecular entity, Abbott Vascular developed the clinical trial design for SPIRIT III.

In May of 2005, Abbott Vascular received conditional Investigational Device Exemption (IDE) approval for the initiation of SPIRIT III in the United States. SPIRIT III was a prospective, randomized (2:1 XIENCE V:TAXUS), active-controlled, single-blinded, multi-center, clinical trial 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 (approved under a Clinical Trial Notification in Japan). The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States. Enrollment in the RCT began on June 2005 and was completed in March 2006. This study also contained a pharmacokinetic substudy. The 4.0 mm has enrolled a total of 73 subjects (69 of which were available for interim analysis) with the first patient enrolled in September 2005.

Supportive studies were conducted outside the United States. These studies included SPIRIT FIRST with a total enrollment of 60 patients at 9 sites. This study began in December 2004 and was completed in April 2005. SPIRIT II enrolled a total of 300 subjects at 28 international sites outside the United States. Enrollment commenced on July 2005 and was completed on November 2005.

The XIENCE V EECSS is currently approved in 64 countries outside the United States. Over 176,600 XIENCE V systems have been distributed to these countries and the XIENCE V has not been withdrawn from marketing in any country for any reason.

The SPIRIT IV Continued Access Clinical Trial was initiated in August 2006 to further evaluate the safety and effectiveness of the XIENCE V Everolimus Eluting Coronary Stent System. The SPIRIT IV Clinical Trial is a single-blinded, randomized (2:1 XIENCE V: TAXUS), multi-center clinical trial and will enroll approximately 3,690 subjects at up to 70 sites in the United States. Enrollment is currently on-going.

Abbott Vascular provided a modular PMA to FDA with the final module received by FDA on June 1, 2007. Additional information has been requested by FDA over the course of their review and Abbott Vascular is working with FDA to provide the supplemental information. The following additional clinical datasets have been provided to FDA for their review: SPIRIT FIRST 3 year data, and SPIRIT III 1 year data. In addition, a post-approval study plan for a 5,000 patient trial in the United States (XIENCE V USA) has been provided to FDA for their review.

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4.4 Device Description

The XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) is a combination product comprised of a coronary stent coated with a drug in a polymer matrix mounted on one of two delivery systems - the XIENCE V RX EECSS (Rapid Exchange) or the XIENCE V OTW EECSS (Over-the-Wire). The XIENCE V EECSS was designed to meet several key performance objectives. The FDA approved and proven MUTLI-LINK VISION® and MULTI-LINK MINI VISION® Coronary Stent Systems were chosen because these systems offered a flexible stent with thin struts and excellent deliverability. A thin, biocompatibile drug coating was key to the design of the system. The drug coating components were chosen to optimize performance with minimal drug content and robust coating integrity using stable, hemocompatible, and biocompatible materials.

The XIENCE V Everolimus Eluting Coronary Stent is a balloon expandable stent fabricated from a single piece of medical grade L-605 Cobalt Chromium (CoCr) alloy. There are two stent designs for the XIENCE V stent: small and medium. The small XIENCE V stent design is available in 2.5, 2.75, and 3.0 mm diameters. The medium XIENCE V stent design is available in 3.5 mm and 4.0 mm diameters. All stent diameters will be available in lengths of 8, 12, 15, 18, 23, and 28 mm as shown in Table 4-1.

Table 4-1 The XIENCE V Stent Sizes

Stent Design	Diameter (mm)	Length (mm)					
		8	12	15	18	23	28
Small	**2.5**	x	x	x	x	x	x
	2.75	x	x	x	x	x	x
	3.0	x	x	x	x	x	x
Medium	**3.5**	x	x	x	x	x	x
	4.0	x	x	x	x	x	x

The XIENCE V stent utilizes the same stent design and L-605 alloy cobalt chromium material as the MUTLI-LINK VISION and MULTI-LINK MINI VISION stent. L-605 cobalt chromium provides both excellent strength and fatigue resistance characteristics, enabling the XIENCE V stent to have significantly thinner struts than contemporary stainless steel stents, while maintaining comparable radial strength. Thinner struts, cobalt chromium material, and the multi-link stent pattern were intended for increased flexibility and conformability.

The XIENCE V stent has a coating consisting of two layers: a primer layer and a drug matrix layer. The primer layer is composed of an acrylic polymer which has been approved for other blood contacting applications. The drug matrix layer consists of a durable copolymer of vinylidene fluoride and hexafluoropropylene (PVDF-HFP), which also is a component of an approved blood contacting product. PVDF-HFP is blended with the anti-proliferative drug everolimus (Certican®, Novartis Pharmaceuticals Corporation) and applied to the entire surface of the primer coated

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stent. No topcoat layer is used.

PVDF-HFP was chosen as the drug matrix polymer because it met the design objectives for the XIENCE V stent and worked well in a simple matrix design which offered good coating quality and integrity, versatility and reproducibility of the release profile, and ease of manufacturing. This material has a history of use in approved coronary applications and proven vascular biocompatibility, showed excellent mechanical coating integrity, was stable *in vitro* and *in vivo*, showed compatible solubility, coatability and sterilizability, was available in a high purity grade, and demonstrated drug permeability.

Everolimus is a novel semi-synthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Everolimus possesses anti-fungal, immunosuppressive and anti-proliferating properties. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation in a reversible manner. Everolimus is utilized on the XIENCE V stent at a dose of 100 $\mu g/cm^2$ of stent surface area. The nominal everolimus content on the XIENCE V stent is based on stent design and length as shown in Table 4-2.

Table 4-2 Nominal Everolimus Content on XIENCE V Stents

Stent Diameter	Stent Length (mm)	Nominal Everolimus Content (μg)
2.5, 2.75, 3.0	8	37
3.5, 4.0	8	53
2.5, 2.75, 3.0	12	56
3.5, 4.0	12	75
2.5, 2.75, 3.0	15	75
3.5, 4.0	15	98
2.5, 2.75, 3.0	18	88
3.5, 4.0	18	113
2.5, 2.75, 3.0	23	113
3.5, 4.0	23	151
2.5, 2.75, 3.0	28	132
3.5, 4.0	28	181

The XIENCE V EECSS delivery system will be available in two platforms: the XIENCE V RX EECSS (Rapid Exchange) and the XIENCE V OTW EECSS (Over-the-Wire). These delivery systems are the FDA approved MULTI-LINK VISION and MULTI-LINK MINI VISION Coronary Stent Systems. The balloon portions of the XIENCE V OTW and RX EECSS delivery systems are identical, the distal portions of these systems are identical in design and materials, and the proximal ends are specifically designed to accommodate either the RX or OTW platform.
Upon completion of the finished good manufacturing, the XIENCE V EECSS is placed into a dispenser coil and a labeled Tyvek® header bag. The product is sterilized by Ethylene Oxide (EtO). Post sterilization, each header bag is placed inside a labeled foil

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pouch and carton.

4.5 Drug Substance (Everolimus)

Everolimus is manufactured and supplied by Novartis Pharmaceuticals Corporation. Everolimus (Certican) has obtained market approval in over 65 countries outside the United States. Additionally, everolimus is under review for market approval in the United States and has received two approvable letters from FDA. Novartis continues to work with the FDA towards a final NDA decision using additional clinical data from prospective transplant trials that evaluate a regimen of everolimus with therapeutic drug monitoring and reduced dose Neoral® (cyclosporine, USP) MODIFIED to support the NDA review. Novartis supplied a letter granting permission to FDA to review relevant sections of their drug substance sections within the IND and NDAs filed with FDA.

In comparison with rapamycin (INN: sirolimus), an immunosuppressant of the same class of macrolide compounds, everolimus showed similar systemic exposure and toxicity profiles in pre-clinical studies. 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. Figure 4-1 shows a schematic of everolimus inhibition of cell proliferation.

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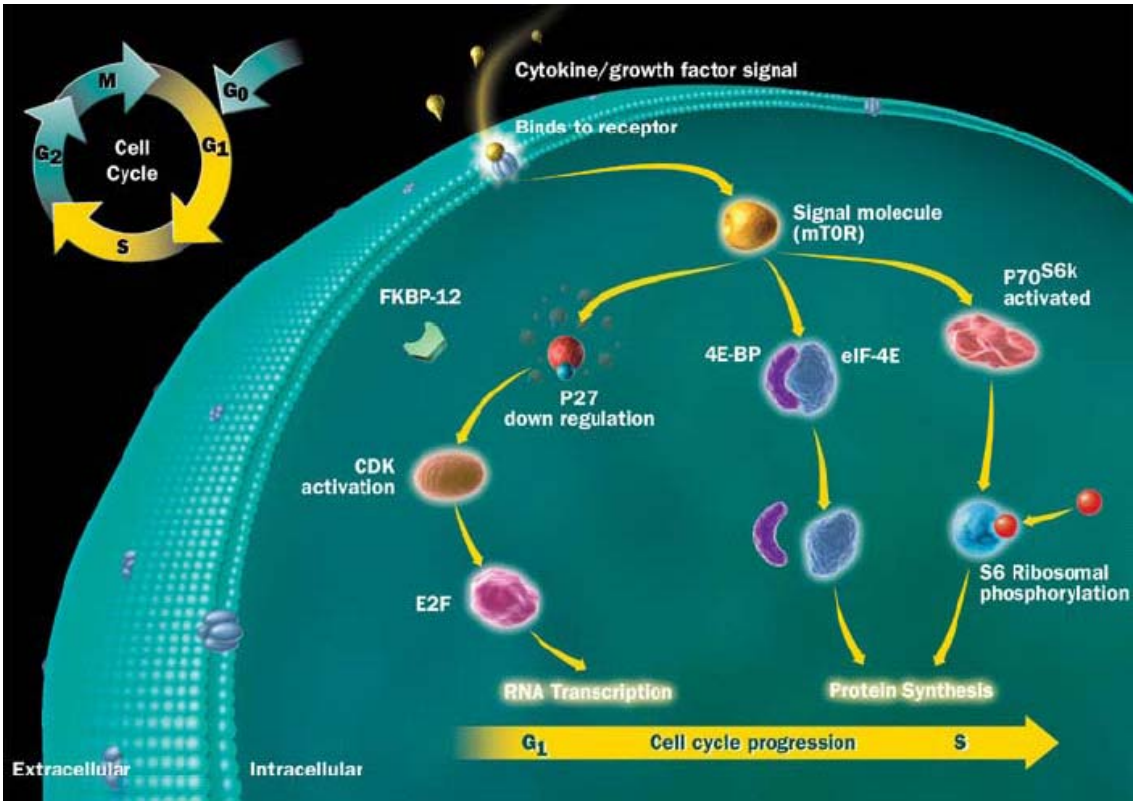

Figure 4-1 Everolimus Inhibition of Cell Proliferation

Novartis conducted a number of non-clinical studies on Certican (everolimus) including carcinogenicity, reproductive toxicology (teratology), mutagenicity, special and combination toxicity, absorption and bioavailability, distribution, metabolism, excretion/elimination, drug-drug interaction potential, and the evaluation of the prevention of vascular proliferation. These data supported the further investigation of everolimus as a potential therapeutic agent for the reduction of restenosis following PTCA and stenting.

Novartis also conducted a number of clinical studies on Certican (everolimus). Everolimus has been studied extensively in renal and heart transplantation with additional data in lung, and liver transplant patients. Therapeutic doses between 1.5 and 3.0 mg/day have been thoroughly evaluated. The use of everolimus in heart transplant patients showed significantly less thickening of the intima in the coronary arteries of transplanted patients in comparison with the control group. In summary, Novartis clinical trials demonstrate the minimum therapeutic level of everolimus with cyclosporine to be greater than or equal to 3.0 ng/ml. The blood levels of everolimus achieved with oral doses used in clinical trials of organ transplant rejection greatly exceed the *in vivo* systemic exposure with the implantation of XIENCE V. These findings support the safety and effectiveness of everolimus at doses that exceed the levels eluted from the XIENCE V stent.

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4.6 XIENCE V Non-clinical Studies

A series of nonclinical studies were conducted on the XIENCE V EECSS including biocompatibility, *in vivo* animal pharmacokinetics (PK), *in vitro* engineering testing, coating characterization, chemistry, manufacturing, and controls (CMC) testing including stability / shelf life evaluations and sterility testing, and *in vivo* animal studies evaluating safety and vascular response.

4.6.1 Biocompatibility

A series of GLP biocompatibility tests were conducted to demonstrate the components of the XIENCE V Everolimus Eluting Coronary Stent System are non-toxic including:

- Cytotoxicity
- Sensitization
- Intracutaneous Reactivity
- Systemic Toxicity
- Pyrogenicity
- Hemocompatibility / Hemolysis
- Implantation
- Genotoxicity
- Reproductive Toxicity (Teratology)
- Carcinogenicity

Tests were conducted on ethylene oxide (EtO) sterilized XIENCE V OTW Everolimus Eluting Coronary Stent System (EECSS), XIENCE V RX EECSS, XIENCE V everolimus eluting 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 containing 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. The results of the biocompatibility studies, including a 26-week carcinogenicity study and reproductive toxicity study, indicated that the XIENCE V EECSS was biologically safe and acceptable for clinical use.

4.6.2 Preclinical Pharmacokinetic Studies

In vivo pharmacokinetic studies were performed in the porcine coronary artery model to determine the percent everolimus released from the XIENCE V stent over time, the tissue concentrations of everolimus over time, and the impact, if any, of systemic exposure of everolimus following implantation of maximum dose XIENCE V stents on platelet function. The tissues that were evaluated include blood, the stented artery, the artery 5 mm proximal and 5 mm distal from the edge of the stent, myocardium subjacent to the stented artery, myocardium distal to the stented artery, spleen, lung, liver, and kidney.

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Platelet function was determined by performing two coagulation assays, prothrombin time and activated partial thromboplastin time, and obtaining platelet counts at baseline and at various predetermined endpoints (1, 3, 7, and 14 days). As studied, no adverse effects on platelet function were seen.

The *in vivo* % Drug Release (DR) profile of the XIENCE V as measured in animal studies is illustrated in Figure 4-2. Seventy-five to eighty percent of everolimus is released during the first 28 days post implantation with > 99% of drug released by 120 days (Table 4-3). Everolimus is optimally released during the key cellular phases of restenosis which consists of platelet deposition (0-14 days), leukocyte recruitment (3-30 days), SMC proliferation and migration (7-60 day), and extra-cellular matrix deposition (> 28 days) (Figure 4-3).

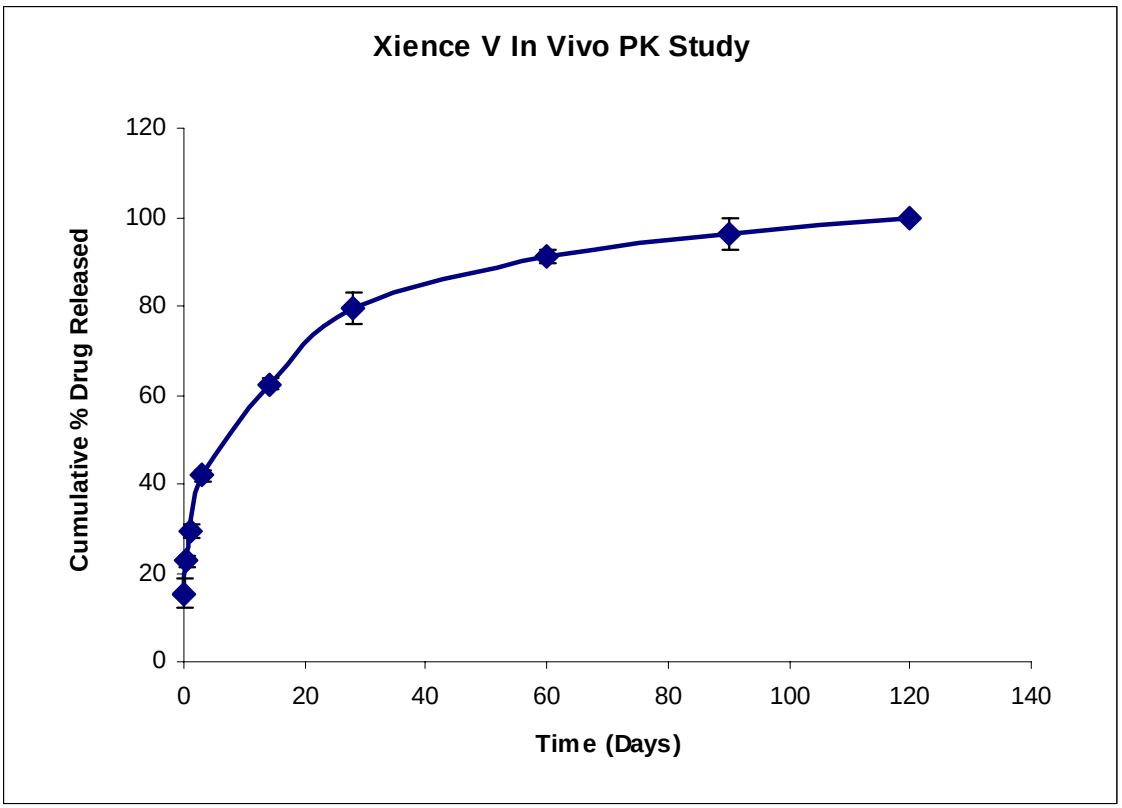

Figure 4-2 *In Vivo* % Drug Released (DR) Over Time as shown in Animal Pharmacokinetic Studies

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Table 4-3 Mean (± SD) % Drug Released Over Time

Time Point (Day)	Cumulative Percent Drug Release Mean ± SD n = 5 - 6
0.125	15.2 ± 3.3
0.25	22.6 ± 1.3
1	29.5 ± 1.6
3	41.8 ± 1.3
14	62.5 ± 1.2
28	79.5 ± 3.4
60	91.3 ± 1.4
90	96.1 ± 3.4
120	99.7 ± 0.2

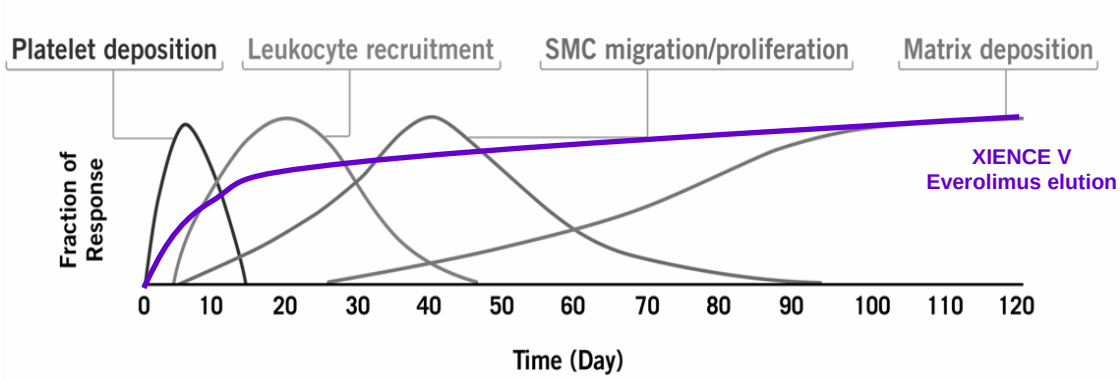

Figure 4-3 Controlled Release of Everolimus from the XIENCE V Stent During the Key Cellular Phases of Restenosis[7]

Systemic exposure to everolimus is minimal following implantation with XIENCE V stents. Peak blood levels (C_{max} = 1.67 ng/mL) were measured at 30 minutes post-stenting and quickly declined to non-detectable levels beyond 72 hours (Figure 4-4, Table 4-4). A peak blood level of 1.67 ng/mL is far less than the minimum systemic level of everolimus (Certican) (3-8 ng/mL recommended therapeutic range) that must be sustained to prevent organ transplant rejection when delivered orally which demonstrates the safety of everolimus in tandem with the vascular response safety data.

[7] Forrester JS et al. A Paradigm for Restenosis based on Cell Biology: Clues for the Development of New Preventative Therapies. JACC 1991, Vol 17, No 3, 758-69

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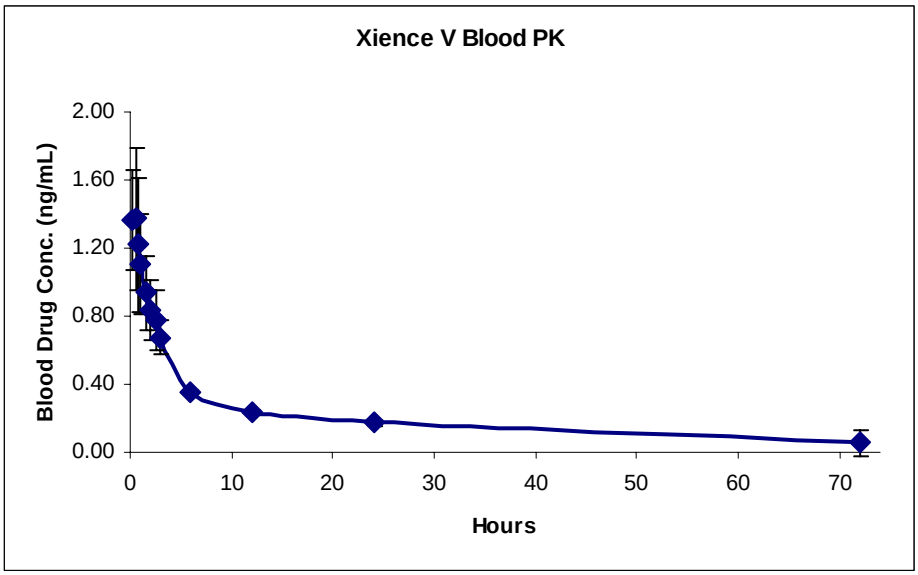

Figure 4-4 Blood Levels of Everolimus Following Implantation with XIENCE V Stents (3 - 3.0 x 12mm, 57 µg) in Porcine Coronary Arteries

Table 4-4 Mean Everolimus Blood Concentration

Time Point (Hour)	Blood Concentration (ng/mL) Mean ± SD n = 2
0.25	1.37 ± 0.29
0.5	1.38 ± 0.42
0.75	1.22 ± 0.40
1	1.11 ± 0.29
1.5	0.94 ± 0.22
2	0.83 ± 0.17
2.5	0.78 ± 0.18
3	0.67 ± 0.10
6	0.35 ± 0.01
12	0.24 ± 0.01
24	0.17 ± 0.02
72	0.08 ± 0.04

Average peak arterial tissue concentration (7.1 ng/mg) was achieved within the first 3 hours following stenting. Arterial tissue concentrations were maintained at approximately 0.7-2.2 ng/mg between the first day and 28 days post stenting (Table 4-5, Figure 4-5). Minimal levels of everolimus were present in the arterial tissue by 120 days post stenting.

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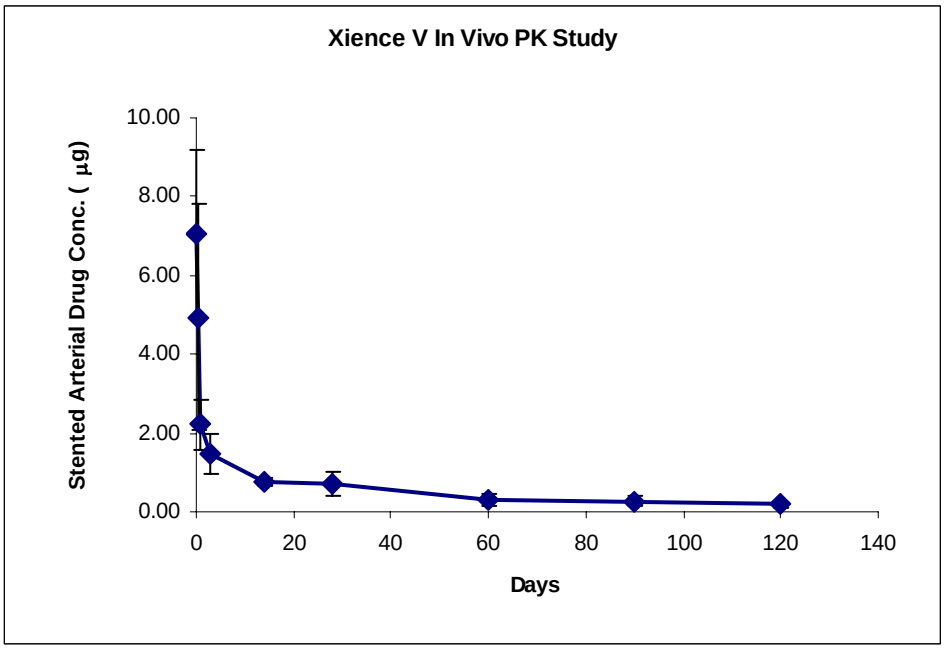

Figure 4-5 Stented Artery Everolimus Concentration: 3 hours-120 days

Table 4-5 Mean Everolimus Tissue Concentration in Stented Vessel

Time Point (Day)	Mean Tissue Concentration (ng/mg) Mean ± SD n = 5 - 6
0.125	7.06 ± 2.14
0.25	4.94 ± 2.85
1	2.21 ± 0.65
3	1.48 ± 0.53
7	1.62 ± 0.37
14	0.75 ± 0.09
28	0.69 ± 0.30
60	0.31 ± 0.16
90	0.27 ± 0.13
120	0.19 ± 0.08

Myocardial levels of everolimus were at least 10 fold lower than that in the stented artery at all time points during the first week post stenting. Everolimus levels in the myocardium downstream of the stented artery ranged from non-detectable to minimal (< 0.5 ng/mg). In addition, extremely low levels to non-measurable levels (< 0.5 ng/g) of everolimus were measured in the spleen, liver, lung, and kidney. These data demonstrate that everolimus remains in the target tissue, the stented artery, with minimal distribution to surrounding myocardium and other non-target organs.

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4.6.3 Engineering Testing

In vitro engineering testing and coating characterization studies, 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, were conducted on the XIENCE V stent except where the testing could be leveraged from the approved MULTI-LINK VISION or MULTI-LINK MINI VISION stent. Supplementary *in vitro* engineering tests were also performed on the XIENCE V delivery systems containing the XIENCE V stent mounted on a delivery catheter. The XIENCE V EECSS met all relevant product specifications. The following engineering test reports have been provided to FDA:

Material Characterization Testing

- Material Analysis
- Mechanical Properties: Tensile Strength and Elongation
- Corrosion Testing

Stent Dimensional and Functional Attributes

- Stent Dimensional Inspection
- Stent Percent Surface Area
- Stent Uniformity of Expansion
- Stent Percent Length Change (Foreshortening)
- Stent Percent Recoil
- Stent Radial (Hoop) Strength
- Finite Element Analysis (FEA)
- Accelerated Fatigue
- Magnetic Resonance Imaging (MRI)
- Radiopacity

Delivery System Dimensional and Functional Attributes

- Balloon Rated Burst Pressure (RBP)
- Unconstrained Balloon Fatigue
- Stent Diameter vs. Balloon Pressure (Compliance)
- Soft Tip Tensile
- Distal Delivery System Tensile
- Proximal Delivery System Tensile
- Delivery System Crossing Profile – Crimped Stent Outer Diameter
- Delivery System Balloon Inflation/Deflation Times
- Stent Dislodgement
- Delivery System Guiding Catheter Pullback
- Delivery, Deployment, and Retraction
- Delivery System Preparation
- Delivery System Shaft Pressure
- Delivery System Inner Member Collapse
- Delivery System Coating Friction (Hydrophilic)
- Delivery System Coating Dry Adhesion (Hydrophilic)

Stent Coating Durability

- Coating Physical Structure and Chemical Properties
- Coating Adhesion

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- Coating Surface Integrity
- Coating Integrity after Balloon Rupture
- Accelerated Coating Fatigue (radial, single)
- Particulate - Beaker Method (Over-expansion)
- Particulate – Tracking Method (Simulated Use)
- Embolic Fatigue (Overlap Configuration)

4.6.4 Chemistry, Manufacturing, & Controls (CMC)

The drug substance, everolimus, is a novel semi-synthetic macrolide immunosuppressant obtained through chemical modification of rapamycin. Everolimus is a drug that has been evaluated in clinical trials in the US and outside the US for use in conjunction with other medications to prevent heart and renal transplant rejection. Everolimus (Certican) has obtained market approval in over 65 countries and is under review for market approval in the United States. Novartis continues to work with the FDA towards a final NDA decision using additional clinical data from prospective transplant trials that evaluate a regimen of everolimus with therapeutic drug monitoring and reduced dose Neoral (cyclosporine) to support the NDA review. Novartis supplied a letter granting permission to FDA to review relevant sections of their drug substance sections within the IND and NDAs filed with FDA.

Information related to the XIENCE V EECSS drug product and the drug product components were provided to FDA including manufacturing information, analytical test methods and supporting validation data, control information, stability studies, and product specifications. Each lot of the XIENCE V manufactured for distribution in the United States will be tested according a pre-determined set of release tests and must meet the final product specifications prior to distribution.

The XIENCE V Everolimus Eluting Coronary Stent System is sterilized using ethylene oxide (EtO) sterilization and has been validated to demonstrate that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, bacterial endotoxins were verified to be within the specification limits per USP. Packaging studies were conducted to demonstrate that the packaging configuration will maintain a sterile barrier throughout transportation and storage through the proposed shelf-life.

4.6.5 *In Vivo* Animal Studies

In vivo animal studies were conducted to demonstrate the safety of the XIENCE V EECSS from implant to two years post implantation. Studies were conducted in a porcine non-atherosclerotic coronary artery model to determine the clinical dose of everolimus to incorporate into XIENCE V, to determine the pharmacokinetics of XIENCE V and to evaluate the safety of XIENCE V. Safety was defined by angiographic, arterial histomorphometric, arterial and myocardial histopathology, and expression of endothelial cell markers.

Porcine coronary safety studies range from acute performance to two years, and include 28 day, 90 day, 180 day, 1 year, and 2 year time points. Single XIENCE V stents, overlapping XIENCE V stents, maximum dose XIENCE V stents, polymer only and

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bulk polymer safety studies were all conducted in porcine coronary arteries with select supportive safety studies conducted in rabbit iliac arteries at 28 and 90 days to evaluate the histological response to single stent and overlapping stents. A total of thirty-five *in vivo* animal studies were conducted to evaluate the safety of the XIENCE V EECSS. Abbott Vascular has determined that there are 24 major supportive *in vivo* animal studies that are representative of the clinical dose selected. All studies were conducted in accordance with 21 CFR, Part 58 (Good Laboratory Practices), unless specified otherwise.

Overall, the animal studies have demonstrated the safety of the XIENCE V stent in two animal models at multiple time points. Everolimus when delivered off of a stent platform has a wide safety margin as demonstrated by animal studies evaluating dose formulations of 100 $\mu g/cm^2$ (1X dose - the clinical dose selected for the XIENCE V), 200 $\mu g/cm^2$, 260 $\mu g/cm^2$, and 803 $\mu g/cm^2$ (8X dose – the maximum dose formulation). Pharmacokinetic studies show that everolimus remains largely localized within the stented arterial wall. Everolimus is eluted off of the stent with the majority cleared from the tissue by 120 days post-implantation. Extensive safety studies consistently demonstrate that vessels implanted with XIENCE V (1X - 8X dose) maintain a patent lumen, and XIENCE V is rapidly incorporated by an endothelialized smooth muscle cell rich neointima. The vessel has reached a healed quiescent phase by 180 days consistent with complete drug elution off of the stent and clearance from the tissue.

To further understand the healing response, *in vivo* research studies were conducted to specifically evaluate endothelial cell coverage and function following implantation with XIENCE V stents as compared to metallic stents and commercially available drug eluting stents (either FDA approved or CE marked). Overall XIENCE V re-endothelialized more rapidly compared to other DES as indicated by scanning electron microscopy, expression of platelet endothelial cell adhesion molecule (PECAM) and decreased expression of vascular endothelial growth factor (VEGF). Levels of thrombomodulin and eNOS were similar for all DES evaluated.

Summary of Overall Animal Health

All animal studies were conducted in compliance with 21 CFR, Part 58, except where noted. Animal care was conducted in accordance with the Animal Welfare Act (Public Law 89-544 and its subsequent amendments), the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy Press, 1996), and the testing facilities' Standard Operating Procedures (SOP).

Animal health was monitored daily. Complete Blood Count (CBC) and Serum Chemistry analysis was performed to assess general health, to provide a baseline of blood parameters at study initiation, and to evaluate for any adverse effects of the device at study termination. Additionally, a full necropsy with histopathologic examination of select key metabolic organs was performed on all animals at study termination.

The overall morbidity and mortality rate was low for these studies. The most frequent

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observation was subclinical pneumonia in the pigs which is considered to be a common finding in farm animals, and unrelated to stent implantation. The myocardium was assessed grossly and histologically in all porcine studies and met acceptance criteria.

Clinical Dose Selection

The XIENCE V EECSS contains 100 μg/cm^2 of everolimus of which approximately 80% of the drug elutes off of the stent during the first 28 days post-stenting. This formulation was selected based on animal studies conducted in a high injury porcine coronary artery model. In this model, stents were implanted at a 1.3:1.0 balloon to artery ratio (30% overstretch) in order to incite a robust neointimal response post stenting. Three formulations of everolimus eluting stents (100 μg/cm^2, n=11; 200 μg/cm^2, n=11; and 260 μg/cm^2, n=11) were implanted into the 30% overstretch model and compared to a metallic stent control (n=8) at 28 days. All three formulations were equally effective at reducing the neointimal response (Figure 4-6 and Figure 4-7). The mean percent area stenosis was markedly reduced (> 60%) with all everolimus eluting stents (mean range 13-17%) as compared to the MULTI-LINK VISION control (mean 48%). Moreover, all three formulations resulted in a similar histological response at 28 days characterized by a patent lumen and healthy neointima covering all stent struts.

The neointima was comprised of smooth muscle cells oriented circumferentially in a mild proteoglycan and collagen-rich extracellular matrix. Mild to moderate peri-strut fibrin was observed, consistent with a drug associated biological effect. Inflammation was minimal. There was no evidence of strut associated thrombus, medial thinning, or necrosis. All lumens were patent and the luminal surfaces were completely endothelialized. Based on these findings, the evaluated minimal effective dose of 100 μg/cm^2 was chosen for the XIENCE V EECSS.

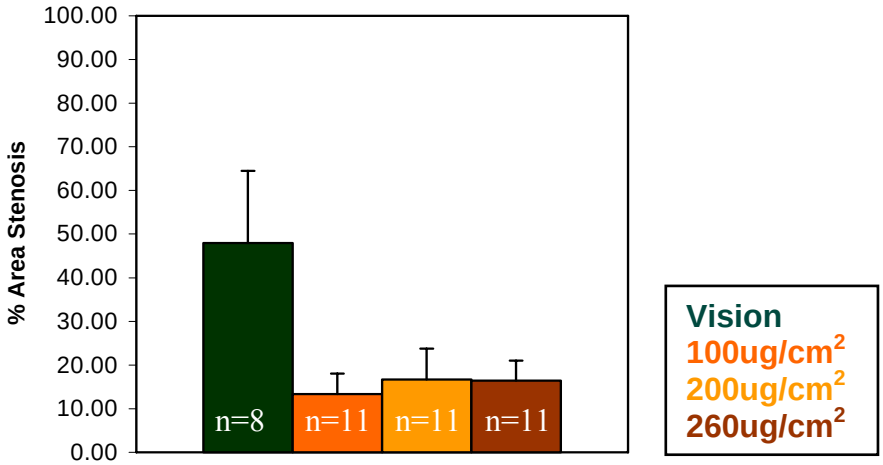

Figure 4-6 Percent Area Stenosis at 28 days (Mean ± SD)

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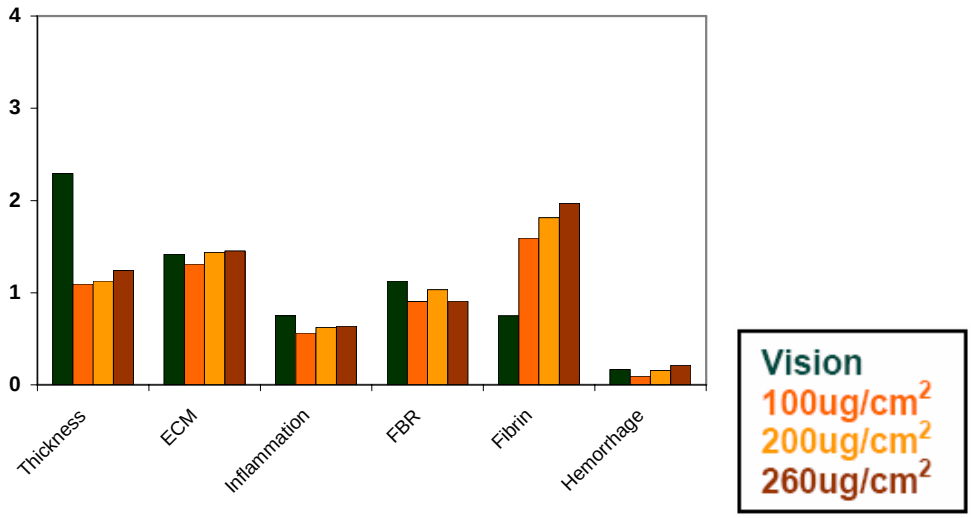

Figure 4-7 Vascular Response Scores (Mean)

Key for Figures:
% Area Stenosis: Morphometric determination of vessel luminal narrowing. % Stenosis= Neointimal Area/Internal Elastic Lamina Area x 100
Thickness: Semi-quantitative assessment of neointimal thickness on a scale of 0-3
ECM: Semi-quantitative assessment of extracellular matrix (proteoglycan/collagen) on a scale of 0-3
Inflammation: Semi-quantitative assessment of vessel wall inflammation on a scale of 0-4
FBR: Semi-quantitative assessment of foreign body response (macrophages/giant cells) adjacent to stent struts
Fibrin: Semi-quantitative assessment of peri-strut fibrin on a scale of 0-3
Hemorrhage: Semi-quantitative assessment of peri-strut hemorrhage on a scale of 0-3

Acute Performance

Acute performance testing (R110303-PDD) was performed in a porcine vascular model to evaluate the performance and deployment of XIENCE V compared to the MULTI-LINK VISION and two competitive stent systems (Cordis CYPHER® and Boston Scientific TAXUS® Express) of comparable diameter and lengths. The evaluation was conducted by an independent interventional cardiologist. Stents were delivered and deployed into the right and left internal mammary arteries (IMA) and into the right brachial artery. All stents were rated acceptable or better for performance and deployment. Key delivery criteria such as system integrity, push-ability, track-ability, wire movement, and retraction from stented site were rated good and equivalent for all evaluated devices. The operator deemed that the deliverability and performance of the XIENCE V was superb overall, and equivalent to, or better than, the VISION metallic control, CYPHER, and TAXUS Express.

Safety

Comprehensive preclinical testing demonstrates the safety of the XIENCE V EECSS out to two years. XIENCE V stents have been evaluated in two animal models at multiple time points. The vascular response to XIENCE V stents was evaluated at 28, 90, 180 days, 1 year, and 2 years in a low injury porcine coronary artery model (10% overstretch), and at 28 and 90 days in a non-atherosclerotic rabbit iliac model. The vascular response to overlapped XIENCE V stents (target 4 mm overlap) was evaluated at 28, 90 and 180 days in a low injury porcine coronary artery model and in a non-

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atherosclerotic rabbit iliac model at 28 and 90 days. In addition, the safety margin of the XIENCE V stent was demonstrated by maximum dose studies in which stents coated with the 8X dose (803 μg/cm^2) were evaluated at 28, 90 and 180 days. All 24 safety studies were designed to assess the arterial response to the XIENCE V stent by angiography, histomorphometry, and histologic parameters. In all studies, the response to the XIENCE V was compared to the response to the MULTI-LINK VISION metallic stent. The criteria by which the arterial response was assessed include the following specific parameters:

- Angiographic Criteria
  - No apparent dissections or aneurysms
  - Mean angiographic percent diameter stenosis less than 50%

- Histomorphometric Criteria
  - All parameters (e.g. % area stenosis, neointimal area, neointimal thickness, medial area, injury score) compared to metallic control

- Histologic Criteria
  - Near complete to complete endothelialization
  - No luminal thrombus
  - No evidence of medial thinning or medial necrosis
  - No evidence of positive remodeling
  - Presence of fibrin at 28 days consistent with a drug associated biological effect. Fibrin scored on a scale of 0-3 (none, mild, moderate, severe)
  - Inflammation in neointima, media, and adventitia scored on a scale of 0-4 (none, mild, moderate, severe, granulomas) and compared to metallic control.

All stented vessel sections were scored semi-quantitatively based on the following descriptive parameters, provided in Table 4-6. All parameters were scored on a scale of 0-3 (none, mild, moderate, severe) with the exception of inflammation which was scored on a scale of 0-4.

Table 4-6 Semi-Quantitative Histologic Parameters

Parameter	0	1	2	3	4
Inflammation	None to rare leukocytes	Few scattered leukocytes	Focal areas of increased cellularity	Moderate increase of cellularity	≥ 2 struts with circumferentia l leukocytes that extends into media
Fibrin, Hemorrhage	None	Mild or inconsistent presence around struts	Moderate multifocal to complete, presence around strut	Confluent or bridging presence between struts	NA
Necrosis, Mineralization	None	Minimal to mild, rare foci	Moderate, multifocal or focally extensive	Severe, multifocal to focally extensive	NA

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XIENCE V EECSS Safety Studies

XIENCE V stents were implanted into a low injury porcine coronary artery model (10 % overstretch) for 28, 90, and 180 days, 1 and 2 years, and evaluated by angiography, histomorphometry, and histopathology to assess the overall safety of the system. Additionally, XIENCE V stents were implanted into a non-atherosclerotic rabbit iliac artery model for 28 and 90 days, and similarly evaluated. The XIENCE V stents yielded acceptable results in both animal models confirming the safety of the XIENCE V stents. The XIENCE V stents elicit a benign neointimal response, with all stent struts incorporated by a thin to moderate smooth muscle cell rich neointima. The amount of neointima produced in response to XIENCE V stents is comparable to that produced in response to VISION stents at all time points, in both the low injury porcine model and the non-atherosclerotic rabbit model (Table 4-7 and 4-8 respectively). The luminal surfaces are endothelialized at all time points evaluated as determined with scanning electron microscopy.

Angiographic Evaluation

Patent lumens with TIMI 3 flow were observed angiographically at all time points evaluated. There was no angiographic evidence of dissection, aneurysm, angiographic filling defects, excessive narrowing, thrombosis, or stent migration at follow-up (performed only in the porcine model). Additionally, no stent fractures were observed, either angiographically or via radiographs of explanted stented arteries, with XIENCE V or VISION (single or overlapping stents) at any time point evaluated out to 2 years, a critical observation to further confirm the overall safety of the stents.

Arterial Histomorphometric Evaluation

Numerous morphometric measurements were obtained to quantify the neointimal response to XIENCE V compared to VISION at multiple time points. Percent area stenosis and neointimal thickness measurements revealed that the neointimal response is overall low at all time points evaluated and as expected is similar for XIENCE V and VISION at all time points evaluated in both the low injury porcine coronary and rabbit iliac models. The VISION stent has thin struts and is highly conformable and as such, causes minimal injury to the vessel wall upon deployment resulting in a mild neointimal response. The thin struts are readily incorporated within a neointima and are rapidly re-endothelialized.

Table 4-7 Mean Percent Area Stenosis (Morphometry) in the Porcine Model

Time point	28 day	90 day	180 day	1 Year	2 year
VISION	29.1 ± 18.3 (n = 43)	22.5 ± 8.0 (n = 31)	20.7 ± 9.0 (n = 41)	28.4 ± 12.0 (n = 12)	27.0 ± 11.6 (n = 11)
XIENCE V	35.3 ± 20.4 (n = 33)	34.12 ± 18.8 (n = 22)	25.65 ± 11.0 (n = 22)	42.96 ± 8.8 (n = 6)	28.6 ± 12.4 (n = 6)

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Table 4-8 Mean Percent Area Stenosis (Morphometry) in the Rabbit Model

Time point	28 day	90 day
VISION	15.8 ± 4.4 (n = 5)	15.0 ± 2.3 (n = 6)
XIENCE V	17.4 ± 3.7 (n = 5)	15.6 ± 1.6 (n = 6)

In addition, the amount of neointima in response to stenting is comparable for VISION and XIENCE V at all time points evaluated in both the porcine model (Figure 4-8) and the rabbit iliac model (Figure 4-9).

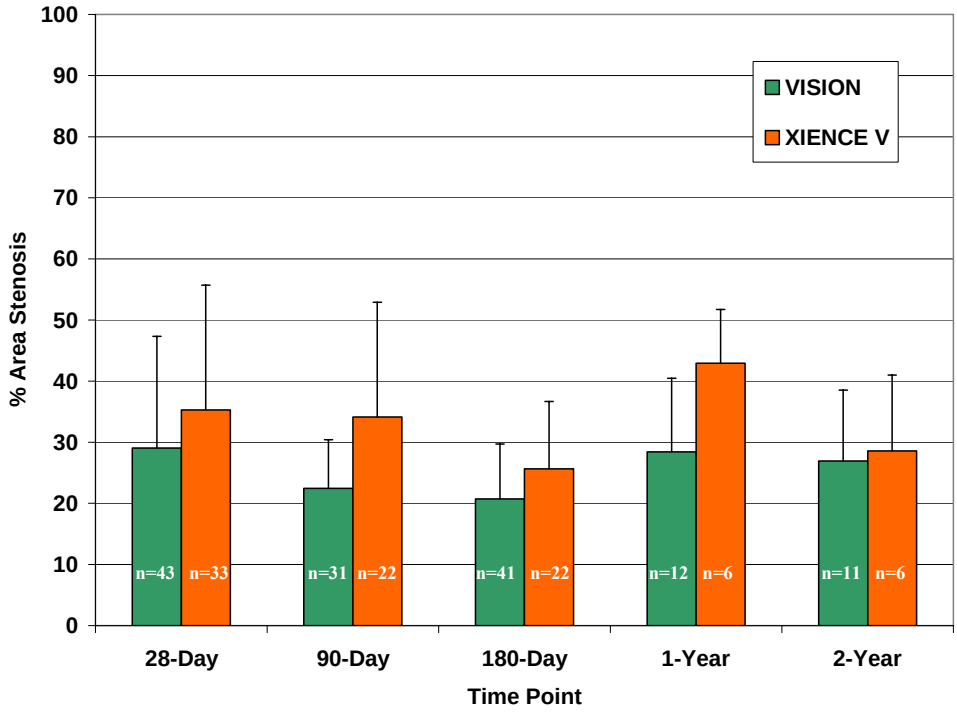

Figure 4-8 Percent Area Stenosis (mean ± SD) in the Porcine Model (28 days, 90 days, 180 days, 1 year, and 2 years)

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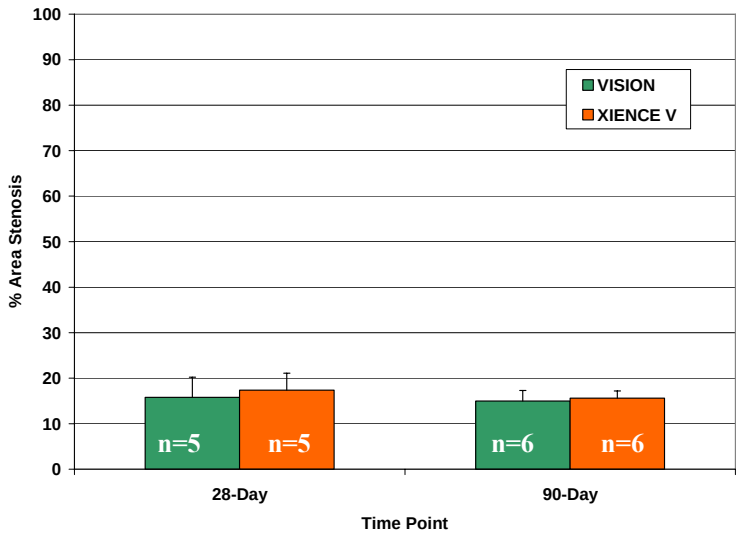

Figure 4-9 Percent Area Stenosis (mean ± SD) in the Rabbit Iliac Model (28 and 90 days)

Arterial Histopathology

All vessels had patent lumens with all stent struts incorporated in a well endothelialized neointima from 28 days to 2 years. Consistent with rapid healing of the vessel wall, luminal endothelialization was confirmed by evaluation of both cross sections of stented vessels under light microscopy and scanning electron microscopy of the luminal surface. There was no evidence of luminal thrombus or strut-associated thrombus consistent with rapid healing of the vessel wall.

The thin XIENCE V stent struts were rapidly incorporated in an endothelialized neointima by 28 days. The neointima was comprised of smooth muscle cells in a proteoglycan/collagen extracellular matrix which gradually increased in maturity concomitant with the clearance of drug from the tissue. By 180 days, the neointimal response to the XIENCE V stent was characterized by a thin, quiescent, concentric layer of parallel aligned smooth muscle cells on a minimal to scant amount of collagen rich extra-cellular matrix. This mature neointima was unchanged at one and two years post implantation, which is consistent with a healed vessel wall.

Everolimus was present in the arterial wall at levels of 1-2 ng/mg during the first 28 days following stent implantation and could be detected at very low levels out to 120 days post stenting. Accordingly, a biological effect attributable to everolimus could be detected in the arterial wall. At 28 days, peri-strut fibrin, an indicator of the biological activity of everolimus in the vessel wall, was evident in the arterial wall of vessels implanted with a XIENCE V stent. The fibrin was localized to the peri-strut region within the neointima. By 90 days, peri-strut fibrin was detectable in minimal amounts consistent with the complete elution of everolimus from the stent and by 180 days was rarely detected (Figure 4-10). At no time point were there lesions indicative of drug toxicity, such as medial thinning, medial necrosis or positive remodeling. The media was healthy at all time points, which translates into a structurally and physiologically

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healthy vessel.

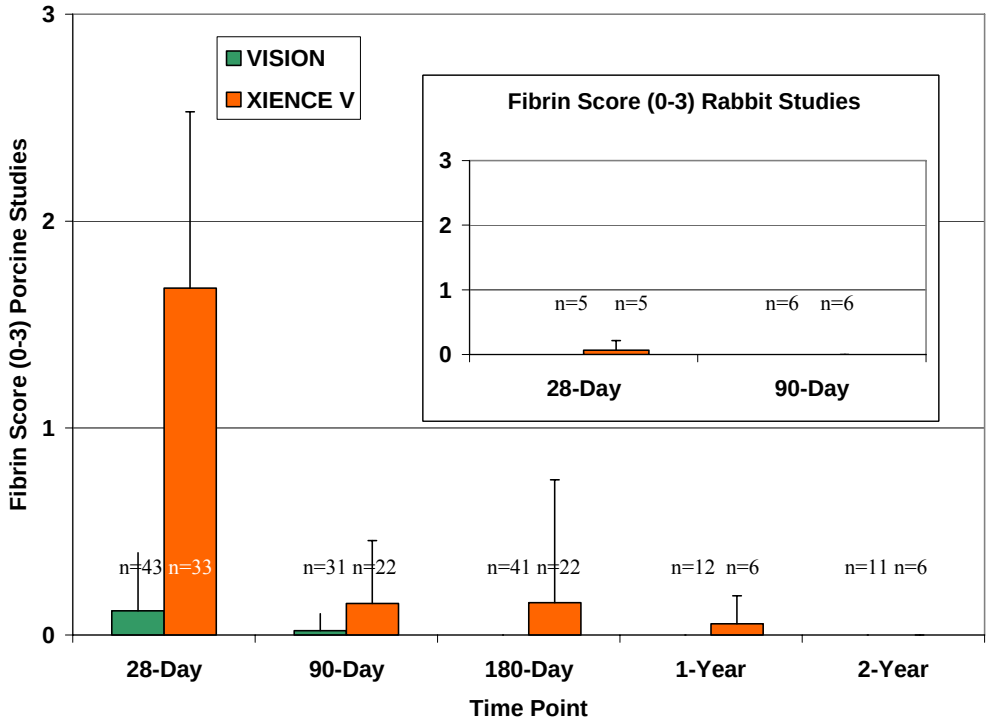

Figure 4-10 Peri-strut Fibrin (mean ± SD) in Response to Stenting in the Porcine Model (28 days, 90 days, 180 days, 1 year, and 2 years) and the Rabbit Model (28 and 90 days)

The inflammatory response was similar for XIENCE V and VISION at all time points evaluated in both the porcine and rabbit models (Figure 4-11 and Figure 4-12 respectively). The mean inflammation score was greater in the porcine model than that observed in the rabbit model; however, the trends were similar. Peak inflammation was observed at 28 and 90 days with resolution by 180 days which persisted to the one and two year time points. As the drug is completely eluted from the stent by 120 days and minimal to trace amounts of drug are present in the vessel wall at 120 days, the lack of inflammation beyond 180 days indicates that the system, and in particular, the polymer, is biocompatible. No late inflammatory effects have been noted. In addition, mineralization directly attributable to the stent was a rare to non-existent observation at all time points evaluated. In summary a benign vascular response to the XIENCE V stent was obtained, with histological appearance from 180 days to two years indicating a healed quiescent vessel.

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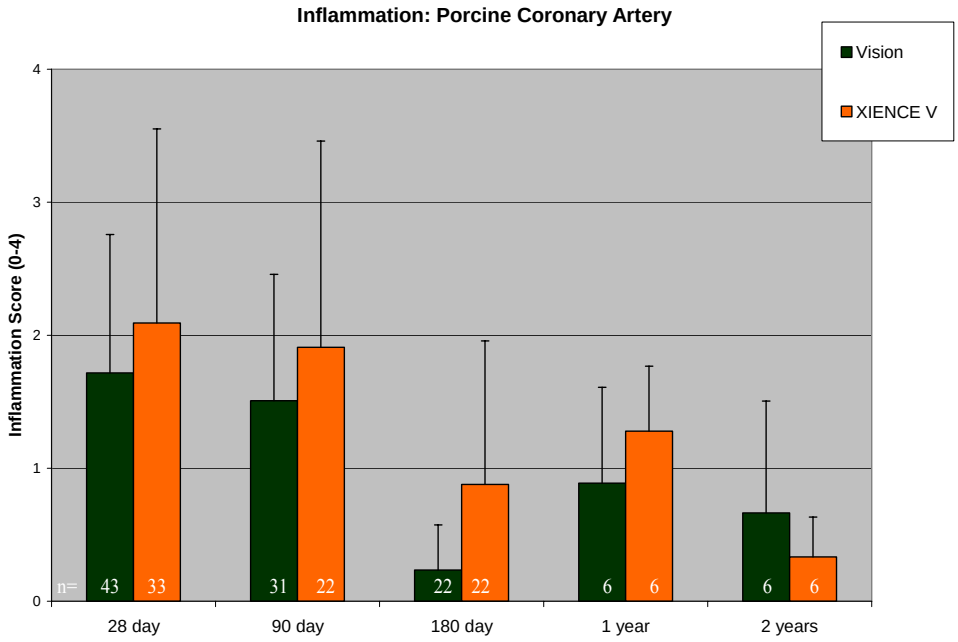

Figure 4-11 Inflammation (mean ± SD) in Response to Stenting in the Porcine Model (28 days, 90 days, 180 days, 1 year, and 2 years
Note: Inflammation scored on a scale of 0-4; ≤ 1 considered background levels of inflammation

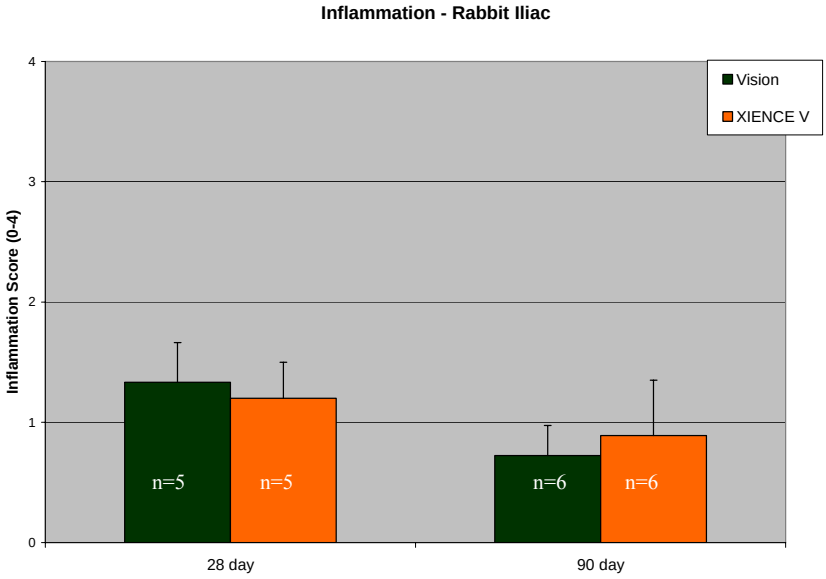

Figure 4-12 Inflammation (mean ± SD) in Response to Stenting in the Rabbit Model (28 and 90 days)
Note: Inflammation scored on a scale of 0-4; ≤ 1 considered background levels of inflammation

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Overlapping XIENCE V Safety Studies
XIENCE V stents were implanted in an overlapping configuration with a minimum of 4 mm of stent overlap into a low injury porcine coronary artery model (10% overstretch) for 28, 90, and 180 days and evaluated by angiography, histomorphometry, and histopathology to assess the overall safety of the system. Additionally, XIENCE V overlapping stents were implanted into a non-atherosclerotic rabbit iliac artery model for 28 and 90 days and evaluated by angiography, histomorphometry, and histopathology to confirm the overall safety of the system. Overlapping of XIENCE V stents yielded acceptable results in both animal models further demonstrating the safety of the system. Patent lumens with TIMI 3 flow were observed angiographically at all three time points evaluated. There was no angiographic evidence of dissection, aneurysm, angiographic filling defects, excessive narrowing, thrombosis, stent migration, or stent fractures at follow-up.

Overlapped XIENCE V stents resulted in a moderate neointimal response with all stent struts covered with a smooth muscle cell rich neointima. The amount of neointima produced in response to overlapped XIENCE V stents was equivalent to that produced in response to overlapped VISION stents at all time points in both the low injury porcine model and the non-atherosclerotic rabbit model.

All vessels with overlapping stents had patent lumens with near complete to complete luminal endothelialization (> 98%) by 28 days in both porcine and rabbit models, and complete luminal endothelialization by 90 and 180 days. There was no evidence of luminal thrombus, or strut associated thrombus at any time point. There was evidence of an active biological effect secondary to the elution of everolimus as demonstrated by the presence of peri-strut fibrin at 28 days (mean < 2, scale of 0-3). Fibrin, when present, tended to remain localized to the peri-strut region within the neointima. The fibrin resolved over the 180 days evaluated. Minimal fibrin was observed at the 90-day time point and rare fibrin was observed by 180 days. There was no evidence of local vessel toxicity at any time point. There were no to rare observations of mineralization within the vessel wall. There was no evidence of medial thinning or of medial necrosis. The media were comprised of healthy smooth muscle cells oriented longitudinally. The inflammation score was similar in response to both the XIENCE V and the VISION stent in the porcine model at all time points evaluated. Minimal inflammation was observed in response to the XIENCE V and the VISION stents in the rabbit model. These observations are within expectations for the respective models.

XIENCE V EECSS Maximum Dose Safety Studies
The safety of a maximum dose everolimus eluting stent system was evaluated in a low injury porcine coronary artery model to assess the arterial response to a high dose of everolimus. The maximum dose XIENCE V stent contains 803 $\mu g/cm^2$ everolimus, eight times the dose density of everolimus than in the XIENCE V stent. Importantly, the release kinetics of the maximum dose stent is similar to the XIENCE V stent as demonstrated by a short term *in vivo* study in which maximum dose stents were implanted into porcine coronary arteries for one, seven, and fourteen days. The cumulative percent drug released over time for the maximum dose system is similar to

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the XIENCE V with approximately 80% (expected based on the % DR curve) released by 28 days. Similar release kinetics between the maximum dose system and the XIENCE V ensured that a true assessment of a maximum dose XIENCE V would be obtained. As expected, higher arterial tissue concentrations of everolimus were measured following implantation with a maximum dose stent. The tissue concentrations of everolimus were approximately 3 times greater than those obtained following implantation with the XIENCE V. Despite higher arterial tissue concentrations, the vascular response was benign with no evidence of drug associated vascular toxicity. The data obtained from the maximum dose studies compliment the data obtained from the overlapping stent safety studies in terms of understanding the response to a high drug load.

Maximum dose XIENCE V stents were implanted into a low injury porcine coronary artery model (10% overstretch) for 28, 90, and 180 days and evaluated by angiography, histomorphometry, and histopathology to assess the overall safety of the system, and determine the safety margin of the system in terms of drug loading.

Patent lumens with TIMI 3 flow were observed angiographically at all three time points evaluated in the porcine model. There was no angiographic evidence of dissection, aneurysm, angiographic filling defects, excessive narrowing, thrombosis, or stent migration observed. The maximum dose XIENCE V stents and bulk polymer stents resulted in a benign neointimal response with all stent struts covered with a thin to moderate smooth muscle cell rich neointima. The amount of neointima produced in response to maximum dose XIENCE V stents was equivalent to that produced in response to VISION stents at all time points, as expected in both the low injury porcine model.

All vessels had patent lumens with near complete to complete luminal endothelialization (> 99 %) at all time points evaluated. There was no evidence of luminal thrombus, or strut associated thrombus at any time point. There were no to rare observations of mineralization within the vessel wall. There was no evidence of medial thinning or of medial necrosis. The inflammatory response to the maximum dose XIENCE V stent was overall mild, and comparable to that observed with a VISION stent.

Summary of Polymer Safety Studies

The safety of the polymer was evaluated in formulations ranging from 1X (equivalent load to that of XIENCE V), 2X, and 3X in a porcine model at various time points out to 2 years. The 1X polymer stents were evaluated at 180 days, 1 and 2 years, 2X polymer stents were evaluated at 28 and 90 days, and 3X polymer stents were evaluated at 28, 90, and 180 days. The percent area stenosis (neointimal response) is similar for all 3 loads of polymer at the various time points evaluated in the porcine model. The struts were rapidly incorporated in an endothelialized smooth muscle cell rich neointima by 28 days. Minimal inflammation was observed at all time points out to 2 years indicating the overall biocompatibility of the polymer. Overall the neointimal response was benign with no adverse effects noted.

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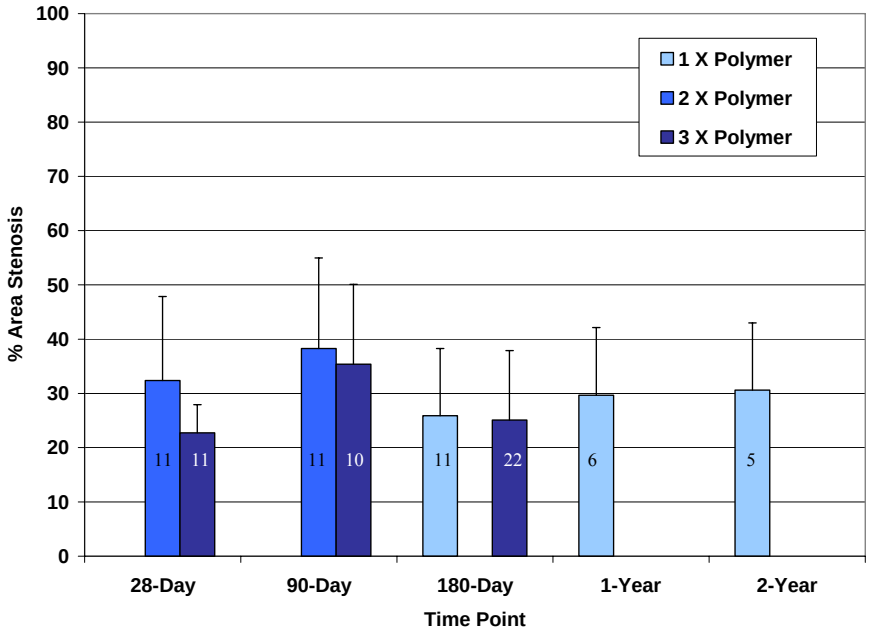

Figure 4-13 Percent Area Stenosis Associated With Various Loads of Polymer, the XIENCE V Polymer in the Porcine Model

Acute Thrombogenicity

Research studies were conducted to assess the relative acute thrombogenicity of XIENCE V as compared to VISION and other commercially available drug eluting stents (FDA approved or CE marked) in *ex vivo* models. A porcine *ex vivo* arterial shunt loop model was utilized to assess relative thrombogenicity[8]. The study results demonstrate that XIENCE V is acutely thromboresistant (0-30 minutes) and is overall less thrombogenic than a metallic stent. These test results can be attributed to the structurally intact, hemocompatible properties of the XIENCE V polymer. Additional supportive data was generated in a Chandler Loop *ex vivo* model[9] in which the stents are exposed to circulating heparinized porcine whole blood for 2 hours in a physiologically controlled loop system. The XIENCE V demonstrated decreased relative thrombogenicity compared to VISION stents as well as to commercially available DES (CYPHER, TAXUS, Endeavor) as measured by overall adherent thrombus weight at 2 hours. Both *ex vivo* models confirm the relative thromboresistance of the XIENCE V stent.

[8] International Standard, ISO 10993-4, Biological Evaluation of Medical Devices – Part 4: Selection of Tests for Interaction with Blood.
[9] Chandler, AB. "In Vitro Thrombotic Coagulation of the Blood: A method for producing a thrombus." Lab Invest, 1958; 7:110-114.

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Endothelial Cell Coverage and Function[10,11,12,13]

Research studies were conducted to assess the healing response to XIENCE V. Long term safety can be characterized by a benign neointimal response with mild inflammation, minimal persistent fibrin and return of a complete and functional endothelium. Preclinical studies were conducted to assess the relative rate of re-endothelialization for XIENCE V as compared to VISION, and to other commercially available drug eluting stents (FDA approved or CE marked). XIENCE V, VISION, CYPHER, TAXUS, and Endeavor stents were implanted into a non-atherosclerotic rabbit iliac model following balloon denudation for 14 and 28 days. The stented vessels were cut longitudinally and endothelial cell coverage was assessed by scanning electron microscopy (SEM). A rabbit model was chosen as the best model to assess re-endothelialization for the following reasons: 1) rabbit arteries heal slower than pig arteries enabling differentiation of the rates of re-endothelialization between treatment arms and 2) earlier work conducted by Abbott Vascular demonstrated that a 14 day time point allowed for the greatest differentiation in terms of healing between a bare metallic stent and a drug eluting stent. As such, the 14 day rabbit iliac model has proven to be very useful to evaluate relative rates of healing / re-endothelialization, which likely translate into relative rates of healing in the clinical setting albeit on a different time scale.

Evaluations of scanning electron micrographs of the luminal surface of various DES demonstrated differences in endothelial cell coverage among DES. As depicted in Figure 4-14, XIENCE V stents had the greatest coverage compared to CYPHER, TAXUS, and Endeavor. Endothelial cell coverage was further assessed by high magnification SEM (up to 200X) in order to clearly identify and differentiate endothelial cells from smooth muscle cells, leukocytes, and platelets. The percentage of endothelial cell coverage was determined both 'above struts' and 'between struts'. As shown in Figure 4-15, XIENCE V had significantly greater endothelial cell coverage above stent struts as compared to CYPHER, TAXUS, and Endeavor, as well as greater coverage in between the struts. The endothelial cell coverage for XIENCE V was not significantly different from VISION.

[10] Joner, M et al., Competitive Comparison Of Reendothelialization in Drug Eluting Stents, AHA Abstract 2006
[11] Virmani R, Endothelium and inflammation in the light of coronary DES safety assessment. EuroPCR 2007
[12] Virmani R, Safety of drug-eluting stents: one year after Barcelona: The pathologist viewpoint: an update. ESC 2007
[13] Virmani R, In Vitro and In Vivo Assessment of Endothelium from Structure to Function, TCT 2007

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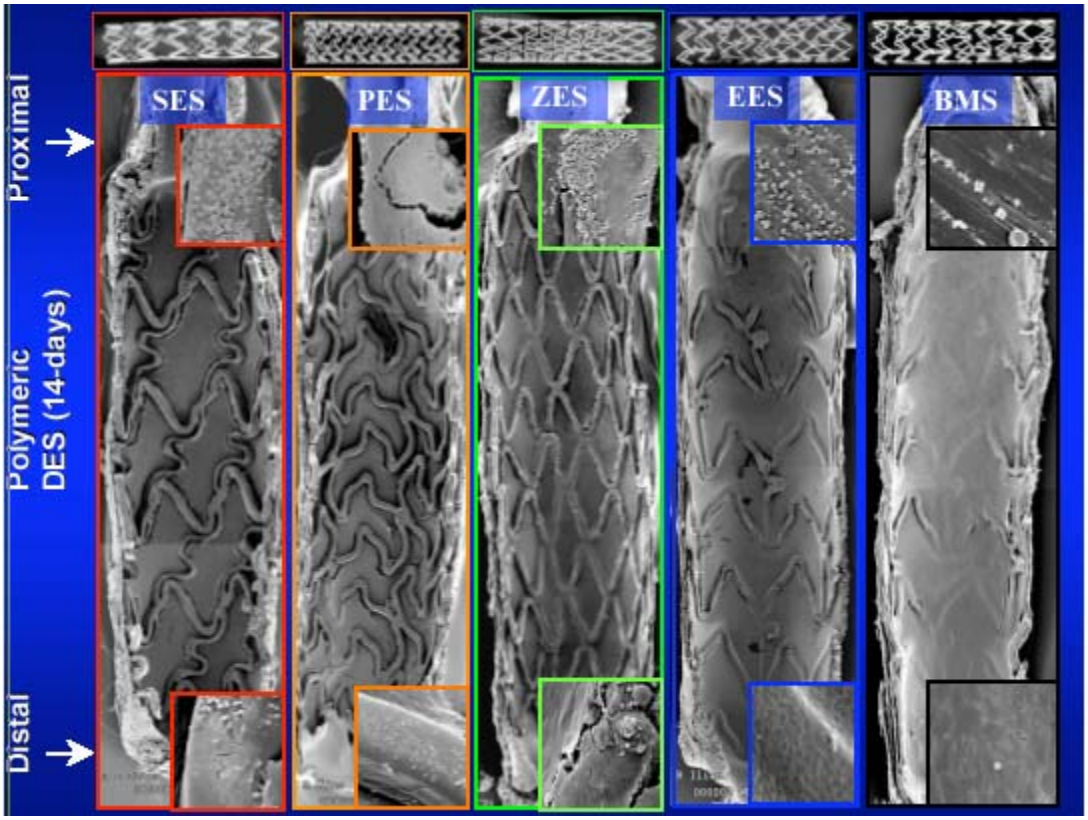

Figure 4-14 Scanning electron micrographs of the luminal surface of various Drug Eluting stents at 14 days in a rabbit iliac model
Note: SES: Sirolimus eluting stent; PES: Paclitaxel eluting stent; ZES: Zotarolimus eluting stent; EES: Everolimus eluting stent (XIENCE V); BMS: Bare metallic stent (VISION)

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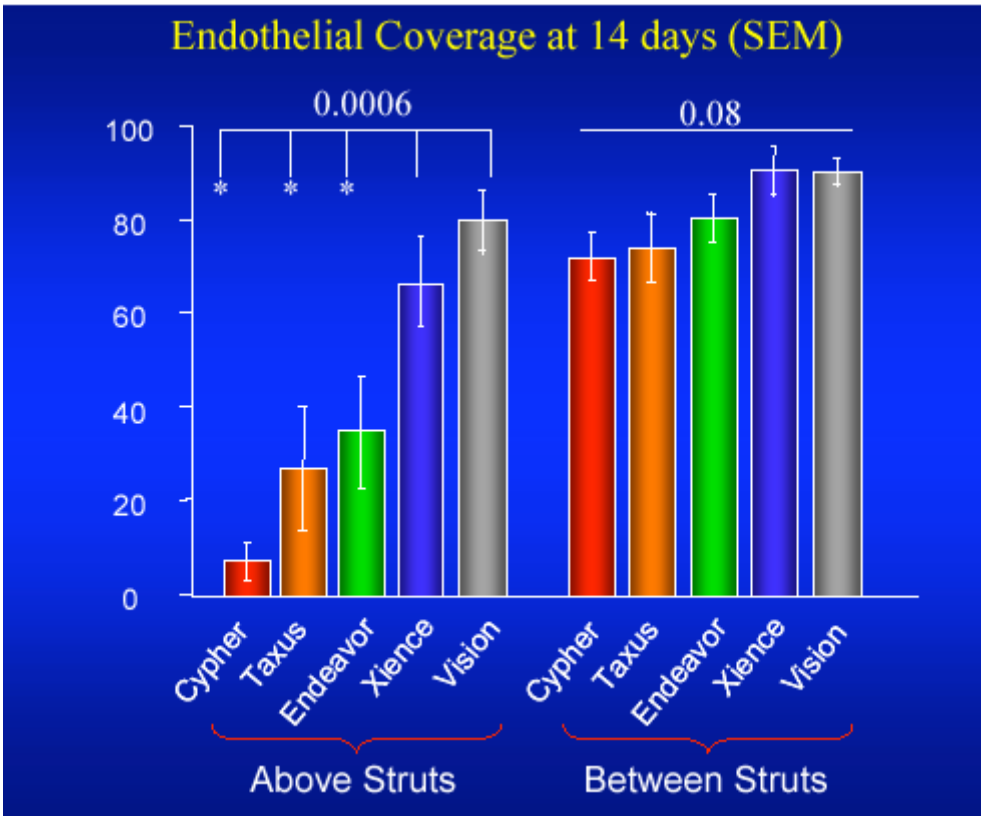

Figure 4-15 Quantitative assessment of the endothelial cell coverage "Above Struts' and "Between Struts for various Drug Eluting Stents

The faster re-endothelialization associated with the XIENCE V is likely due, at least in part, to the thin stent struts of the XIENCE V. A thin stent strut will be incorporated in neointima more rapidly, and will require less neointima to completely cover the struts. Similarly, endothelial cells should migrate up and over to incorporate a thin strut more rapidly[14].

To confirm the SEM data and to evaluate the maturity of the endothelial cells, the expression of Platelet-Endothelial Cell Adhesion Molecule (PECAM/CD31) and Thrombomodulin was determined by immunohistochemical techniques. PECAM is a major constituent of the endothelial cell intercellular junctions and plays an important role as an inhibitory factor of platelet aggregation and hemostasis. Thrombomodulin is a transmembrane endothelial glycoprotein expressed on the surface of the endothelium which suppresses intravascular thrombosis by converting thrombin from a procoagulant into an anti-coagulant enzyme. As shown in Figure 4-16, there is significantly greater expression of PECAM/CD31 in association with XIENCE V above the struts, compared to CYPHER, TAXUS, and Endeavor at 14 days consistent with the SEM data. At 28 days, all endothelial cells expressed PECAM/CD31 in XIENCE V stented vessels indicative of a more mature endothelial cell layer lining the luminal surface.

[14] Palmaz, J. Long-Term Effects Medical Implants, 10(1): 143-151 (2000).

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Thrombomodulin (protein) expression and eNOS (mRNA) was decreased in all DES evaluated, compared to VISION. Additionally, in these studies, production of vascular endothelial growth factor (VEGF) (protein and mRNA) was similar for XIENCE V and VISION at 28 days consistent with an endothelialized vessel wall.

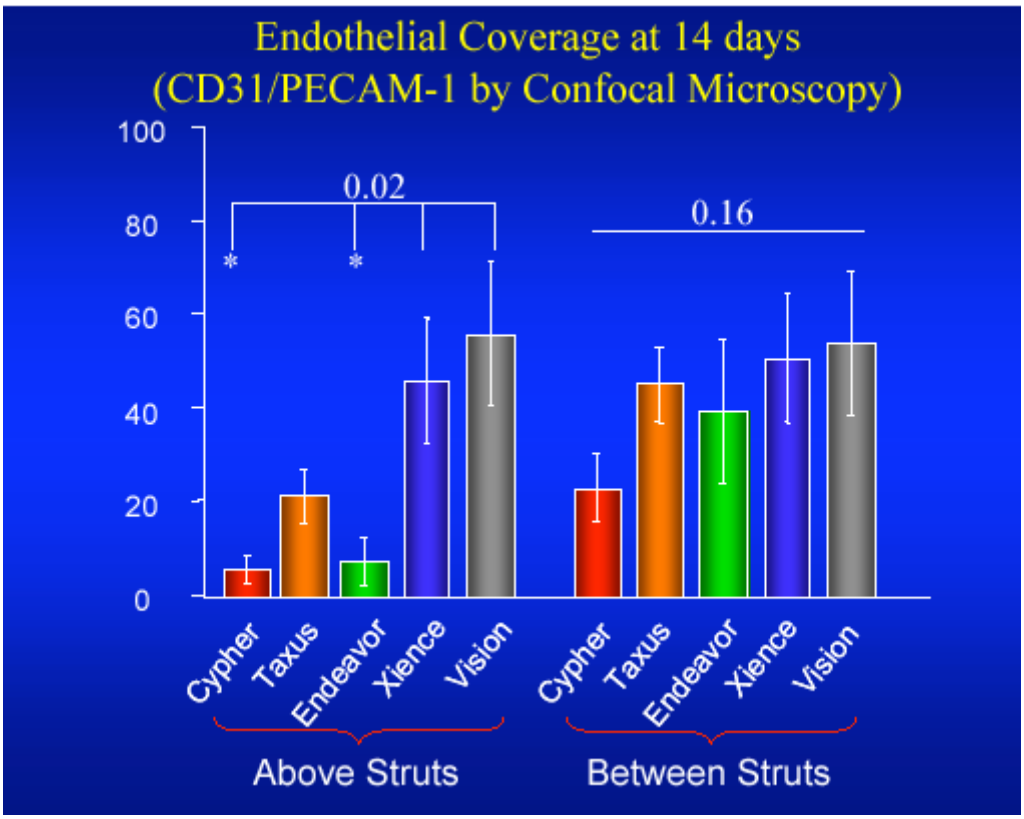

Figure 4-16 Quantification of PECAM/CD31 Positive Cells at 14 Days in a Rabbit Iliac Model Following Implantation with Various DES as Compared to VISION

***In Vivo* Animal Study Conclusions**

Animal studies have demonstrated the safety of the XIENCE V EECSS from implant to 2 years post implantation. Everolimus when delivered off of a stent platform has a wide safety and therapeutic margin as demonstrated by animal studies evaluating dose formulations of 100 $\mu g/cm^2$ (XIENCE V), 200 $\mu g/cm^2$, 260 $\mu g/cm^2$ and 803 $\mu g/cm^2$ (maximum dose formulation). The neointimal response is benign with rapid healing as demonstrated by a consistent vascular response at 180 days, 1 year, and 2 years. Long term polymer studies have further demonstrated the overall biocompatibility of the system. Endothelial cell coverage and function studies have demonstrated that XIENCE V stented vessels rapidly re-endothelialize with a mature endothelium. Overall, the system met all safety acceptance criteria in two animal models.

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4.7 XIENCE V EECSS Clinical Experience

The XIENCE-SPIRIT family of trials is a robust clinical program that includes more than 16,000 patients with over 14,000 patients assigned to XIENCE V EECSS. This global clinical trials program consists of eight studies that have either completed enrollment, are currently enrolling or are designed as post-approval studies.

The initial clinical safety and performance of XIENCE V EECSS were demonstrated in the **SPIRIT FIRST** clinical trial, a randomized, controlled, single-blinded evaluation of XIENCE V in the treatment of patients with *de novo* native coronary artery lesions. A total of 60 patients (28 in the XIENCE V treatment group and 32 in the VISION bare metal stent control group) were enrolled at 9 investigational sites outside the United States. The primary endpoint was in-stent late loss at 6 months. The SPIRIT FIRST trial showed a significant benefit for XIENCE V over the VISION stent. In-stent late loss of 0.10 ± 0.23 mm in the everolimus eluting stent group represented an 88% reduction relative to the control group (0.85 ± 0.36 mm) ($p < 0.0001$). A low 6-month major adverse cardiac event (MACE) rate of 7.7% supported the clinical safety of the XIENCE V EECSS. The SPIRIT FIRST trial has demonstrated that the clinical safety observed at 6 months was sustained out to 3 years as demonstrated by no observations of late stent thrombosis events, and continued low TVF and MACE rates.

The **SPIRIT II** clinical trial was a continuation in the assessment of the safety and performance of the XIENCE V EECSS versus the TAXUS EXPRESS^2 Paclitaxel-Eluting Coronary Stent System (PECSS) in the treatment of patients with a maximum of two *de novo* native coronary artery lesions located in two different epicardial vessels (from 2.5 mm to 4.25 mm in diameter and up to 28 mm in length, including overlapping stents). A total of 300 subjects were enrolled into the SPIRIT II clinical study at 28 international sites. Of the 300 subjects enrolled, 223 were randomized to receive the XIENCE V EECSS and 77 were randomized to receive the TAXUS PECSS (3:1 XIENCE V:TAXUS randomization). The primary endpoint was in-stent late loss at 180 days. The data indicated that XIENCE V ECCSS was non-inferior to the TAXUS PECSS for in-stent late loss at 180 days. Pre-specified secondary analysis also showed superiority in terms of in-stent late loss for the XIENCE V EECSS compared to the TAXUS PECSS. The XIENCE V in-stent late loss was 0.11 mm while the TAXUS in-stent late loss was 0.36, which represents a 72% reduction in late loss. Lower rates on key clinical endpoints were observed for the XIENCE V compared to the TAXUS such as ischemia driven MACE (2.7% and 6.5%, respectively) and protocol-defined stent thrombosis (0.5% and 1.3%). Ischemia-drive MACE at 180 days was sustained through 1 year for XIENCE V, and no new instances of late stent thrombosis were observed in either group at 1 year.

The **SPIRIT III** clinical trial was designed to demonstrate safety and effectiveness of the XIENCE V EECSS. The SPIRIT III clinical trial is a prospective, randomized, active-controlled, single-blinded, parallel two-arm multi-center clinical trial utilizing either the XIENCE V stent on a Rapid Exchange (RX) delivery system or the FDA approved, commercially available TAXUS EXPRESS^2 Paclitaxel-Eluting Coronary Stent System. The SPIRIT III protocol allowed for dual vessel treatment and planned

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stent overlap.

The SPIRIT III RCT study was designed to enroll 1,002 subjects (randomized 2:1 XIENCE V:TAXUS) at up to 80 sites in the US. The primary endpoint for the SPIRIT III RCT was in-segment late loss at 240 days, and the major secondary endpoint was ischemia-driven Target Vessel Failure (TVF) at 270 days. The XIENCE V in-segment late loss at 240 days was 0.14 mm, compared to the TAXUS EXPRESS^2 in-segment late loss of 0.28 mm. These data demonstrated non-inferiority (p-value < 0.0001) and superiority (p-value =0.0037) for the XIENCE V in terms of in-segment late loss at 240 days. XIENCE V was also found to be non-inferior (p-value <0.0001) to TAXUS EXPRESS^2 in terms of the major secondary endpoint, with ischemia-driven TVF rates of 7.6% and 9.7%, respectively. The rates of late stent thrombosis through 393 days for XIENCE V vs. TAXUS were 0.3% vs 0.6% by protocol definitions, and 1.1% vs. 0.6% by the Academic Research Consortium (ARC) definitions (definite plus probable).

The primary endpoint for the SPIRIT III 4.0 mm non- randomized arm was in-segment late loss at 240 days. The XIENCE V 4.0 mm non-randomized arm in-segment late loss was 0.17 mm and is non inferior (p-value <0.0001) to the TAXUS EXPRESS^2 in-segment late loss of 0.28 mm. The XIENCE V in-segment late loss in the 4.0 mm arm is comparable to the XIENCE V in-segment late loss in the SPIRIT III RCT.

Clinical pharmacokinetic substudies were conducted in three different geographies to demonstrate the elution of everolimus from the XIENCE V stent. SPIRIT II conducted outside the United States and SPIRIT III conducted in the United States (RCT) and Japan (registry) contained pharmacokinetic substudies. 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.

Taken together, these three studies have demonstrated superiority of XIENCE V in the following angiographic measures:

- In-stent late loss compared to VISION in SPIRIT FIRST
- In-stent late loss compared to TAXUS in SPIRIT II
- In-segment late loss compared to TAXUS in SPIRIT III

The studies also show consistent angiographic, clinical, and pharmacokinetic results for XIENCE V across all geographies. The observed lower MACE rates compared to TAXUS, and the low incidence of late stent thrombosis confirm the safety of XIENCE V.

Greater than 13,000 additional patients will be studied in four continued access / post-approval studies and one post-approval surveillance registry.

The **SPIRIT IV** Clinical Trial is a continued access study for continued access and was initiated on August 14, 2006 to further evaluate the safety and effectiveness of the

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XIENCE V Everolimus Eluting Coronary Stent System and to enroll SPIRIT III-like subjects in order to support the SPIRIT III major secondary endpoint (270 day TVF). The SPIRIT IV Clinical Trial is a single-blinded, multi-center clinical trial and will enroll approximately 3,690 subjects at up to 70 sites in the United States. This trial is randomized (2:1 XIENCE V EECSS:TAXUS EXPRESS^2 PECSS) in subjects with a maximum of three *de novo* native coronary artery lesions, maximum of two lesions per epicardial vessel, and in some cases, lesions that are located at areas of bifurcation, with reference vessel diameters (RVD) ≥ 2.5 mm to ≤ 4.25 mm, lesion lengths ≤ 28 mm. Overlapping stents were allowed for XIENCE V subjects with lesions > 22 mm. The primary endpoint of the trial is ischemia-driven major adverse cardiac event (MACE) at 270 days. Patients will be followed out to five years. This study has enrolled approximately 2000 patients.

SPIRIT V is an international (outside the US) study with a target of 3000 patients. Of these, 2700 will be enrolled in a registry assessing a composite endpoint of death, MI and target vessel revascularization with 5 year follow up. ARC defined stent thrombosis and other clinical outcome parameters will also be evaluated. An additional 300 patients with diabetes will participate in a randomized study of XIENCE V vs. TAXUS in a 2:1 randomization with a 9 month angiographic endpoint of late loss. Over 2000 patients have been enrolled to date.

XIENCE V SPIRIT WOMEN is a 2000 female patient all-comers study being conducted in Europe and the Asia-Pacific countries. Of these, 1550 will be enrolled in a single arm registry assessing a composite endpoint of death, MI and target vessel revascularization with 5 year follow up. ARC defined stent thrombosis and other clinical parameters will also be studied. Additionally, 450 patients will participate in a trial of XIENCE V vs. CYPHER in a 2:1 randomization with a 9 month end point of angiographic late loss. Enrollment commenced in July 2007 and follow-up will be for 5 years.

XIENCE V India is a 1000 patient registry of all-comers in India. Follow-up is for 5 years. The study protocol is similar to that for the US post-approval registry, XIENCE V USA, which will assess ARC defined stent thrombosis, device-oriented and patient-oriented outcomes, patient compliance and therapy interruptions with dual antiplatelet therapy, major bleeding complications, clinical device and procedural success and patient health status using the Seattle Angina Questionnaire. Enrollment is expected to begin January 2008.

Finally, **XIENCE V USA** is a 5000 patient post-approval registry with 5 year follow up. This study is a prospective, open-label, multi-center, observational, single-arm registry designed to evaluate the continued safety and effectiveness of the XIENCE V during commercial use in real world settings. Physicians with a range of coronary stenting experience will be invited to participate. The study will assess ARC defined stent thrombosis, device-oriented and patient-oriented outcomes (including death, myocardial infarction and revascularization), patient compliance and therapy interruptions with dual antiplatelet therapy, major bleeding complications, clinical

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device and procedural success and patient health status using the Seattle Angina Questionnaire.

In total, the XIENCE V SPIRIT family of trials provides comprehensive evaluation of more than 16,000 patients world-wide as shown in Table 4-9

Table 4-9 Overview of Total XIENCE V SPIRIT Family Enrollment

	Total (XIENCE V + Control)	XIENCE V	Planned Follow-up
SPIRIT FIRST	60	28	5 Years
SPIRIT II	300	223	5 Years
SPIRIT III	1002	668	5 Years
SPIRIT IV	3690	2460	5 Years
SPIRIT V	3000	2900	5 Years
XIENCE V SPIRIT Women	2000	2000	5 Years
XIENCE V India	1000	1000	5 Years
XIENCE V USA	5000	5000	5 Years
TOTAL	**16052**	**14279**	

4.7.1 Effectiveness and Safety Results

The SPIRIT III is the pivotal study for United States. The following information focuses on principal effectiveness and safety results from the randomized control trial (RCT). Within the SPIRIT III RCT, the XIENCE V EECSS when placed in single or multiple *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 late loss (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 7.6% (50/657) for the XIENCE V arm and 9.7% (31/320) for the TAXUS arm (non-inferiority $p < 0.0001$). The ischemia-driven TVF rate through 393 days continues to be lower in the XIENCE V arm compared to the TAXUS arm, with rates of 8.6% and 11.3%, respectively. Table 4-10 provides the effectiveness and safety data out to 393 days for the SPIRIT III RCT. Please note that within this table 194 days represents the maximum 6 month window, 284 days represents the maximum 9 month window, and 393 days represents the maximum 12 month window.

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Table 4-10 Principal Effectiveness and Safety Results - All Lesions within the SPIRIT III RCT for the 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 (primary endpoint) 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]
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 Days[1] - Per-Subject Analysis			
TVF-free	92.4%	90.5%	1.98% [-1.80%, 5.76%]
TLR-free	97.3%	95.0%	2.24% [-0.44%, 4.92%]
Revascularization[2]-free	94.7%	93.5%	1.21% [-1.98%, 4.41%]
Cardiac Death-free	99.4%	99.4%	0.01% [-1.04%, 1.05%]

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Table 4-10 Principal Effectiveness and Safety Results - All Lesions within the SPIRIT III RCT for the Intent-To-Treat Population (cont'd)

Measurements	XIENCE V (N=669) (M=772)	TAXUS (N=333) (M=383)	Difference [Precision]
Clinical Endpoints to 284 Days[1] - Per-Subject Analysis (cont'd)			
MACE-free	95.0%	91.4%	3.62% [0.15%, 7.09%]
Per-Subject Analysis Clinical Endpoints to 393 Days[4]			
TVF-free	91.5%	88.9%	2.62% [-1.41%, 6.65%]
TLR-free	96.7%	94.4%	2.26% [-0.61%, 5.12%]
Revascularization[2]-free	93.9%	92.5%	1.39% [-2.02%, 4.79%]
Cardiac Death-free	99.2%	99.1%	0.17% [-1.08%, 1.41%]
MACE-free	94.1%	89.8%	4.27% [0.51%, 8.02%]
Safety Measures - Per-Subject Analysis			
TVF in-hospital[3]	0.9% (6/669)	2.4% (8/330)	-1.53% [-3.33%, 0.28%]
TVF through 37 days	1.6% (11/667)	3.3% (11/330)	-1.68% [-3.85%, 0.48%]
TVF through 194 days	4.1% (27/663)	5.5% (18/326)	-1.45% [-4.35%, 1.45%]
TVF through 284 days (major secondary endpoint)	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]
TVF through 393 days	8.6% (56/653)	11.3% (36/320)	-2.67% [-6.75%, 1.40%]
MACE in-hospital[3]	0.9% (6/669)	2.4% (8/330)	-1.53% [-3.33%, 0.28%]
MACE through 37 days	1.3% (9/667)	3.0% (10/330)	-1.68% [-3.73%, 0.37%]
MACE through 194 days	2.9% (19/663)	5.2% (17/326)	-2.35% [-5.08%, 0.38%]
MACE through 284 days	5.0% (33/657)	8.8% (28/320)	-3.73% [-7.24%, -0.21%]
MACE through 393 days	6.0 % (39/653)	10.3% (33/320)	-4.34% [-8.14%, -0.54%]
Stent Thrombosis 0 to 30 days	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Stent Thrombosis 31 to 284 days	0.2% (1/653)	0.0% (0/319)	0.15% [Assump. not met]
Stent Thrombosis 31 to 393 days	0.3% (2/646)	0.6% (3/317)	-0.32% [Assump. not met]
Bleeding Complication to 284 days	3.1% (20/653)	5.0% (16/319)	-1.95% [-4.69%, 0.78%]
Bleeding Complication to 393 days	3.3% (21/646)	5.4% (17/316)	-2.3% [-4.97%, 0.71%]
Vascular Complication to 284 days	0.9% (6/654)	0.9% (3/319)	-0.02% [Assump. not met]
Vascular Complication to 393 days	0.9% (6/647)	1.6% (5/316)	-0.65% [-2.22%, 0.91%]
CVA to 284 days	0.8% (5/653)	0.6% (2/319)	0.14% [Assump. not met]
CVA to 393 days	1.1% (7/646)	0.6% (2/316)	0.45% [Assump. not met]

[1] Kaplan-Meier estimates for analysis to 284 days.
[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.
[4] Kaplan-Meier estimates for analysis to 393 days.

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-p1)/n11+(1-p2)/n21]; CI=exp(ln(RR)±1.96*SE)
· Difference = XIENCE V- TAXUS; Binomial: SE=sqrt(p1*q1/n1+p2*q2/n2); Normal: SE=sqrt(Sp2(1/n1+1/n2)); Survival: SE=sqrt(SE_1^2+SE_2^2); Binomial/Survival: CI=Diff±1.96*SE; Normal: CI=Diff±$t_{0.025}$*SE
· ABR (angiographic binary restenosis): A follow-up percent diameter stenosis of ≥ 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

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functional ischemia test or ischemic symptoms, and having an angiographic minimal lumen diameter stenosis ≥ 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 ≥ 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.

4.7.2 Consistency Across Trials

The results for In-Stent and In-Segment Late Loss, TVF, MACE, and Cardiac Death and MI are consistent across all studies and all geographies. Comparability and consistency across studies can be justified because SPIRIT II and SPIRIT III studies were designed as randomized controlled clinical trials. The subjects that were enrolled in SPIRIT II and SPIRIT III met similar inclusion and exclusion criteria and had similar baseline and angiographic characteristics. The studies were analyzed using common endpoint definitions for both effectiveness and safety. Finally, poolability for the meta-analysis that combined SPIRIT II and SPIRIT III can be justified because these two studies were designed as randomized controlled clinical trials comparing XIENCE V with TAXUS. See Table 4-11 for the In-Stent and In-Segment Late Loss, TVF, MACE, and Cardiac Death and MI for all studies. For ease of review, XIENCE V has been shaded.

In summary, this robust clinical program shows consistency in clinical data, safety, and clinical superiority for XIENCE V compared to TAXUS, and will enroll a total of over 14,000 XIENCE V patients with 5 year follow up.

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Table 4-11 In-Stent Late Loss, In-Segment Late Loss, TVF, MACE and Cardiac + MI Across SPIRIT Trials

	Time Point	SPIRIT FIRST	SPIRIT II		SPIRIT III		SPIRIT III 4.0 mm	Combined SPIRIT II & III RCT	
			XIENCE V	TAXUS	XIENCE V	TAXUS		XIENCE V	TAXUS
in-stent late loss (Analysis Lesion)	6M	0.10 ± 0.23 (23)	0.10 ± 0.27 (201)	0.36 ± 0.39 (73)	-	-	-	-	-
MACE	6M	7.7% (2/ 26)	2.7% (6/222)	6.5% (5/77)	2.6% (17/663)	4.6% (15/326)	5.9% (4/68)	-	-
Cardiac Death + MI	6M	3.8% (1/ 26)	0.9% (2/222)	3.9% (3/77)	1.5% (10/663)	3.1% (10/326)	5.9% (4/68)	-	-
TVF	6M	7.7% (2/ 26)	3.6% (8/222)	6.5% (5/77)	3.8% (25/663)	4.9% (16/326)	5.9% (4/68)	-	-
in-stent late loss (Analysis Lesion)	8M	-	-	-	0.16 ± 0.41 (301)	0.31 ± 0.55 (134)	0.12 ± 0.34 (49)	-	-
in-segment late loss (Analysis Lesion)	8M	-	-	-	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	0.17 ± 0.38 (49)	-	-
MACE	9M	7.7% (2/ 26)	2.7% (6/220)	6.6% (5/76)	5.0% (33/657)	8.8% (28/320)	5.9% (4/68)	4.4% (39/877)	8.6% (34/397)
Cardiac Death + MI	9M	3.8% (1/ 26)	0.9% (2/220)	3.9% (3/76)	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	2.4% (21/877)	3.8% (15/397)
TVF	9M	7.7% (2/ 26)	4.5% (10/220)	6.6% (5/76)	7.6% (50/657)	9.7% (31/320)	5.9% (4/68)	6.8% (60/877)	9.3% (37/397)
MACE	12M	15.4% (4/26)	2.7% (6/220)	9.2% (7/76)	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	5.3% (46/873)	10.1% (40/397)
Cardiac Death + MI	12M	7.7% (2/26)	0.9% (2/220)	3.9% (3/76)	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	2.7% (24/873)	4.5% (18/397)
TVF	12M	15.4 (4/26)	4.5% (10/220)	9.2% (7/76)	8.6% (56/653)	11.3 (36/320)	5.9% (4/68)	7.7% (67/873)	10.8% (43/397)

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4.8 Conclusions

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.

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 XIENCE V does not show evidence of toxicity and everolimus when delivered off of a stent platform has a wide safety and therapeutic margin. The neointimal response is benign with rapid healing as demonstrated by a consistent vascular response at 180 days, 1 year, and 2 years. Endothelial cell coverage and function studies have demonstrated that XIENCE V stented vessels rapidly re-endothelializes with a mature endothelium.

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 XIENCE V has demonstrated robust mechanical, functional, and coating integrity.

The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released. The drug substance, polymer excipients, and drug product have been well characterized and are stable. The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use through the labeled shelf life.

The clinical pharmacokinetics showed that the C_{max} never reached the minimum therapeutic value necessary for effective systemic administration to prevent organ rejection. 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. Furthermore, the XIENCE V EECSS when placed in single or multiple *de novo* native coronary artery lesions was found to be statistically superior to the TAXUS PECSS in terms of the primary endpoint of in-segment late loss at 240 days and non-inferior with regard to the major secondary endpoint of ischemia-driven TVF. The clinical testing conducted demonstrated the safety and effectiveness when used as indicated in accordance with the Instructions for Use.

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