XIENCE Skypoint™

Everolimus Eluting Coronary Stent System

Rx ONLY

INSTRUCTIONS FOR USE

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15.0 REUSE PRECAUTION STATEMENT

THE COMPONENTS OF THE XIENCE Skypoint™ EVEROLIMUS ELUTING CORONARY STENT SYSTEM ARE STERILE.

1.0 PRODUCT DESCRIPTION

The XIENCE Skypoint™ Everolimus Eluting Coronary Stent System (EECSS) is comprised of two main components: the drug-coated stent and the balloon expandable delivery system. The XIENCE Skypoint EECSS uses a similar stent design, as well as the identical stent contacting balloon materials, and the identical drug coating formulation and drug dose density (100 ug/cm²) as the XIENCE Sierra™ EECSS. The XIENCE Skypoint EECSS is available in a Rapid Exchange (RX) delivery system configuration.

The XIENCE Skypoint EECSS includes:

Product	Stent Diameter (mm)	Stent Length (mm)	Reference Vessel Diameter (RVD mm)	Lesion Length (mm)
XIENCE Skypoint	2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 4.5*, 5.0*	8, 12, 15, 18, 23, 28, 33, 38, 48**	≥ 2.25 and ≤ 5.25	≤ 44

* 4.5 mm and 5.0 mm stent diameter are not available in 8 mm and 38 mm stent length

** 48 mm stent length are not available in 2.25 mm, 3.25 mm, 4.5 mm, 5.0 mm stent diameters

Hereafter, the XIENCE Skypoint Everolimus Eluting Coronary Stent System is referred to as the XIENCE Skypoint EECSS or the XIENCE Skypoint stent. The XIENCE Skypoint EECSS are device / drug combination products consisting of a drug-coated stent and a balloon expandable delivery system. The stent is coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer, which is identical to the FDA approved XIENCE Sierra™, XIENCE Alpine™, XIENCE Xpedition™, XIENCE PRIME™ and XIENCE V™ Everolimus Eluting Coronary Stent Systems.

1.1 Device Component Description

The device component consists of a medical grade L-605 cobalt chromium (CoCr) drug-coated stent mounted onto the XIENCE Skypoint stent delivery system. The device component characteristics are summarized in *Table 1.1-1*.

Table 1.1-1: XIENCE Skypoint EECSS Product Description

	XIENCE Skypoint EECSS	
Available Stent Lengths (mm)	8, 12, 15, 18, 23, 28, 33, 38, 48	
Available Stent Diameters (mm)	2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 4.5, 5.0	
Stent Material	A medical grade L-605 cobalt chromium CoCr alloy identical to the material used in the XIENCE Sierra, XIENCE Alpine, XIENCE Xpedition, XIENCE PRIME, and XIENCE V stent	
Drug Component	A conformal coating of a non-erodible polymer loaded with 100 µg/cm^2 of everolimus with a maximum nominal drug content of 300 µg on the large stent (4.0 x 48 mm)	
Delivery System Working Length	145 cm	
Delivery System Design	RX: Single access port to inflation lumen; guide wire exit notch is located 25.5 cm from tip; designed for guide wires ≤ 0.014”.	
Stent Delivery System Balloon	A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length	
Balloon Inflation Pressure	Rated Burst Pressure (RBP): 16 atm (1621 kPa)	
	Stent Diameter (mm)	***In vitro* Stent Nominal Pressure (atm)**
	2.25	9
	2.5	9
	2.75	12
	3.0	12
	3.25	12
	3.5	12
	4.0	12
	4.5	12
	5.0	12
Minimum Guiding Catheter Inner Diameter	2.25 – 4.0 mm Stent Diameters 8-38 mm Stent Lengths: 5 F (0.056” / 1.42 mm ID) 2.5 – 4.0 mm Stent Diameters 48 mm Stent Lengths: 6 F (0.070’’ / 1.78 mm ID) 4.5 – 5.0 mm Stent Diameters 12-33 mm Stent Lengths: 6 F (0.070’’ / 1.78 mm ID)	
Catheter Shaft Outer Diameter	2.25 – 4.0 mm Stent Diameters Mid Shaft: 0.039” (0.99 mm) Proximal Shaft (RX): 0.029” (0.74 mm) 4.5 – 5.0 mm Stent Diameters Mid Shaft: 0.042” (1.07 mm) Distal Shaft: 0.041” (1.04 mm) Proximal Shaft (RX): 0.029” (0.74 mm)	

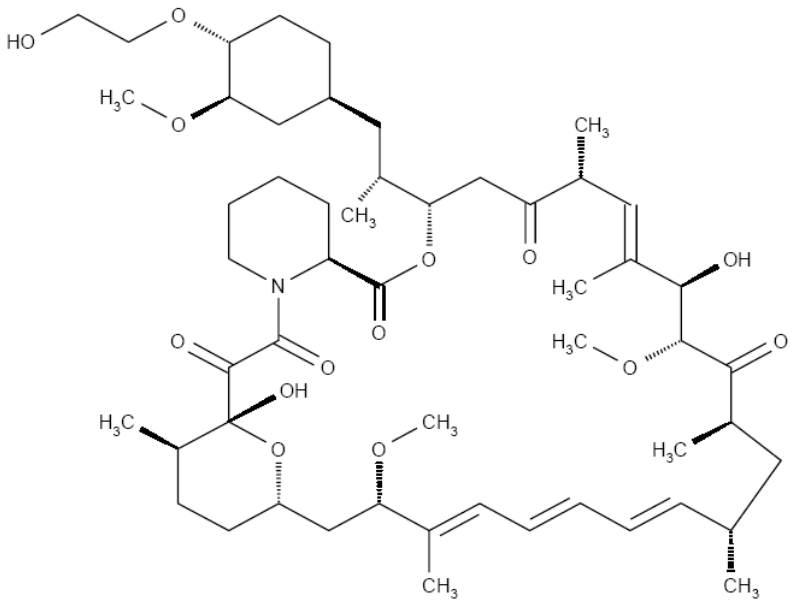
1.2 Drug Component Description

The XIENCE Skypoint stent is coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

1.2.1 Everolimus

Everolimus is the active pharmaceutical ingredient in the XIENCE Skypoint stent. It is a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin (sirolimus). The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in *Figure 1.2.1-1* below.

Figure 1.2.1-1: Everolimus Chemical Structure

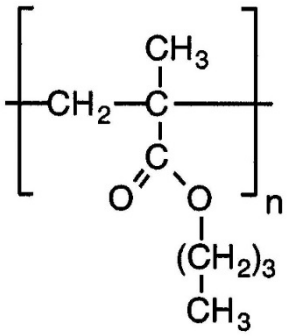


1.2.2. Inactive Ingredients – Non-erodible Polymer

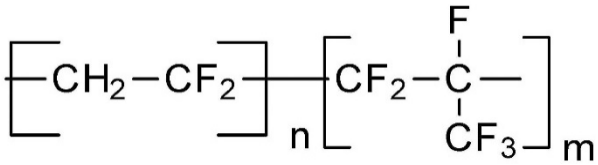
The XIENCE Skypoint stent contains inactive ingredients, including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (MW) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semicrystalline random copolymer with a molecular weight (MW) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA-coated stent surface. The drug load is 100 µg/cm^2 for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in *Figure 1.2.2-1* below.

Figure 1.2.2-1: Non-erodible Polymer Chemical Structures

PBMA



PVDF-HFP



1.2.3 Product Matrix and Everolimus Content

Table 1.2.3-1: XIENCE Skypoint EECSS Product Matrix and Everolimus Content

Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
2.25	8	39
2.5		39
2.75		39
3.0		39
3.25		39
3.5		53
4.0		53
2.25	12	58
2.5		58
2.75		58
3.0		58
3.25		58
3.5		72
4.0		72
4.5		72
5.0		72
2.25	15	72
2.5		72
2.75		72
3.0		72
3.25		72
3.5		99
4.0		99
4.5		99
5.0		99
2.25	18	85
2.5		85
2.75		85
3.0		85
3.25		85
3.5		117
4.0		117
4.5		117
5.0		117
2.25	23	111
2.5		111
2.75		111
3.0		111
3.25		111
3.5		145
4.0		145
4.5		145
5.0		145
2.25	28	131
2.5		131
2.75		131
3.0		131
3.25		131
3.5		181
4.0		181
4.5		181
5.0		181

Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content (µg)
2.25	33	157
2.5		157
2.75		157
3.0		157
3.25		157
3.5		209
4.0		209
4.5		209
5.0		209
2.25	38	177
2.5		177
2.75		177
3.0		177
3.25		177
3.5		236
4.0		236
2.5	48	223
2.75		223
3.0		223
3.5		300
4.0		300

2.0 INDICATIONS

The XIENCE Skypoint™ stent system is indicated for improving coronary artery luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease due to *de novo* native coronary artery lesions ≤ 44 mm in length with reference vessel diameters of ≥ 2.25 mm to ≤ 5.25 mm and for high bleeding risk patients with coronary arteries lesions ≤ 32 mm in length with a reference vessel diameter of ≥ 2.25 mm and ≤ 5.25 mm. In addition, the XIENCE Skypoint stent system is indicated for treating *de novo* chronic total coronary occlusions.

3.0 CONTRAINDICATIONS

The XIENCE Skypoint™ stent system is contraindicated for use in:

- Patients with hypersensitivity or contraindication to everolimus or structurally-related compounds, or known hypersensitivity to stent components (cobalt, chromium, nickel, tungsten, methacrylic polymer, and fluoropolymer), or with contrast hypersensitivity.
- Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or the post-procedural antiplatelet regimen

4.0 WARNINGS

- **The XIENCE Skypoint™ stent and the delivery system are for single use only.** Do not reuse, reprocess, or resterilize. Note the product “Use by” date on the package. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and / or delivery system and / or lead to device failure, which may result in patient injury, illness, or death. Reuse, reprocessing, or resterilization may also create a risk of contamination of the device and / or cause patient infection or cross-infection, including,

but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device and / or delivery system may lead to injury, illness, or death of the patient.

- Antiplatelet therapy should be administered post-procedure. (See *Section 10.0 Individualization of Treatment.)*
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.
- Judicious selection of patients is necessary, since the use of this device carries the associated risk of stent thrombosis, vascular complications, and / or bleeding events.
- It is not recommended to treat patients having a lesion that prevents complete inflation of an angioplasty balloon.
- The XIENCE Skypoint stent is coated with an everolimus and polymer coating at the full implant stent length. The distal and intermediate portions of the device, the tip, and tapers of the balloon are coated with HYDROCOAT™ Hydrophilic Coating. Refer to *Section 13.3 Preparation* for further information on how to prepare and use this device to ensure it performs as intended. Failure to abide by the warnings in this labeling might result in damage to the device coating, which may necessitate intervention or result in serious adverse events.

5.0 PRECAUTIONS

5.1 Stent Handling

- Implantation of the stent should be performed only by physicians who have received appropriate training.
- Stent placement should be performed at centers where emergency coronary artery bypass graft surgery (CABG) can be readily performed.
- **The foil pouch is not a sterile barrier.** The inner header bag (pouch) within the foil pouch is the sterile barrier. **Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.**
- To confirm sterility has been maintained, ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important during catheter removal from packaging, placement over the guide wire, and advancement through the rotating hemostatic valve adapter and guiding catheter hub.
- **Do not manipulate, touch, or handle the stent**, as this may cause coating damage, contamination, or dislodgement of the stent from the delivery balloon.
- Avoid wiping the device with dry gauze or excessive wiping of the device as this may damage the device coating.
- Avoid using alcohol, antiseptic solutions, or other solvents to pre-treat the device because this may cause unpredictable changes in the coating which could affect the device safety and performance.

- Avoid soaking the XIENCE Skypoint™ stent. See instructions in *Section 13.3.2 Guide Wire Lumen Flush.*
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon, as this may cause uneven expansion and difficulty in deployment of the stent. If gaseous medium is used and balloon rupture occurs, there is the potential of causing air embolism and / or vessel injury.
- After use, this device, its accessories and packaging should be appropriately classified for disposal (e.g. biohazard, sharp, non-hazardous waste, etc.) and carefully disposed of in compliance with facility procedures and applicable laws and regulations.

5.2 Stent Placement

- Use guiding catheters which have lumen sizes that are suitable to accommodate the stent delivery system
- **Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed.** Use the balloon purging technique described under *Section 13.3.3 Delivery System Preparation*.
- When pre-dilatation is performed, an appropriate balloon size should be used. Failure to do so may increase the difficulty of stent placement and cause procedural complications.
- The decision to pre-dilate the lesion with an appropriately sized balloon should be based on patient and lesion characteristics. Direct stenting in less complex coronary lesions with a predicate device has been shown to be as effective and safe as stenting with pre-dilation for device lengths up to 28 mm in real-world settings. If pre-dilation is performed, limit the length of pre-dilation by the percutaneous transluminal coronary angioplasty (PTCA) balloon to avoid creating a region of vessel injury that is outside the boundaries of the implanted stent.
- When introducing the delivery system into the vessel, do not induce negative pressure on the delivery system. This may cause dislodgement of the stent from the balloon.
- Do not torque the catheter more than one (1) full turn.
- Implanting a stent may lead to dissection of the vessel distal and / or proximal to the stent, and may cause abrupt closure / total occlusion of the vessel, requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- An unexpanded stent may be retracted into the guiding catheter one time only. An unexpanded stent should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter should not be performed, as the stent may be damaged or dislodged during retraction back into the guiding catheter.
- Should **resistance** be felt **at any time** during removal of the undeployed coronary stent system, refer to the steps provided in *Section 5.4 Stent / System Removal*.

- Do not expand the stent if it is not properly positioned in the vessel. (See *Section 5.4 Stent / System Removal.)*
- The inflated balloon diameter of the system used to deploy the stent should approximate the diameter of the vessel. Oversizing of the stent can result in a ruptured vessel. To ensure full expansion of the stent, the balloon should be inflated to a minimum of nominal pressure.
- **Do not exceed the Rated Burst Pressure (RBP) as indicated on the product label.** Monitor balloon pressures during inflation. Use of pressures higher than specified on the product label may result in a ruptured balloon, with possible intimal damage and dissection.
- Although the stent delivery system balloon is strong enough to expand the stent without rupture, a circumferential balloon tear distal to the stent and prior to complete stent expansion could cause the balloon to become tethered to the stent, requiring surgical removal. In case of balloon rupture, it should be withdrawn and if necessary, a new dilatation catheter exchanged over the guide wire to complete the expansion of the stent.
- Do not dilate the stent beyond the limits indicated in *Section 13.5 Deployment Procedure*.
- When performed, post-dilatation should be performed at high pressure with a noncompliant balloon.
- Underexpansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure that the stent is in full contact with the arterial wall upon deflation of the balloon. All efforts should be made to ensure that the stent is not underdilated. Refer to *Section 13.0 Clinician Use Information.*
- Placement of a stent has the potential to compromise side branch patency.
- Stent retrieval methods (use of additional wires, snares, and / or forceps) may result in additional trauma to the coronary vasculature and / or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- When treating multiple lesions within the same vessel, stent the distal lesion prior to stenting the proximal lesion. Stenting in this order obviates the need to cross the proximal stent during placement of the distal stent and reduces the chance of damaging or dislodging the proximal stent.
- Ensure the stented area covers the entire lesion / dissection site and that no gaps exist between stents.
- When multiple drug-eluting stents are required, only stent materials with similar composition (e.g., XIENCE™ Everolimus Eluting Coronary Stent Systems with the identical cobalt-chromium stent substrate and identical drug-eluting polymer coating) should be used. Potential interaction with other drug-eluting stents or coated stents has not been evaluated and should be avoided. Placing multiple stents of different metals in contact with each other may increase the potential for corrosion *in vivo*, although *in vitro* corrosion tests using an L-605 CoCr alloy stent in combination with a 316L stainless steel alloy stent did not appear to increase corrosion.

- The extent of the patient's exposure to drug and polymer is directly related to the number of stents implanted. A patient can receive up to three 48 mm XIENCE Skypoint stents or four other everolimus eluting coronary stents from the XIENCE Family of Stents (i.e., XIENCE V™, XIENCE PRIME™, XIENCE Xpedition™, XIENCE Alpine™, XIENCE Sierra™ and XIENCE Skypoint™) ≤ 38 mm depending on the number of vessels treated and the lesion length. Those patients receiving bailout stenting will receive additional XIENCE Family of Stents. The use of multiple XIENCE Family of Stents will result in the patient receiving larger amounts of drug and polymer.
- The safety and effectiveness of the XIENCE Skypoint stents in patients with prior brachytherapy of the target lesion, or the use of brachytherapy for restenosis in a site treated with XIENCE Skypoint stents have not been established. Both vascular brachytherapy and the implanted XIENCE Skypoint stent alter arterial remodeling. The potential combined effect on arterial remodeling by these two treatments is not known.

5.3 Use in Conjunction with Other Procedures

- While vessel preparation in complex lesions may include the use of various mechanical atherectomy devices, the safety and effectiveness of the XIENCE Skypoint stents have not been established in clinical trials with the use of either mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters.

5.4 Stent / System Removal

- **Stent delivery system removal prior to stent deployment:** If removal of a stent system is required prior to deployment, ensure that the guiding catheter is coaxially positioned relative to the stent delivery system, and cautiously withdraw the stent delivery system into the guiding catheter. Should unusual resistance be felt at any time when withdrawing the stent into the guiding catheter, the stent delivery system and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.

- **Withdrawal of the stent delivery system / post-dilatation balloon from the deployed stent:**

1. Deflate the balloon by pulling negative on the inflation device. Larger and longer balloons will take more time (up to 30 seconds) to deflate than smaller and shorter balloons. Confirm balloon deflation under fluoroscopy and wait 10 – 15 seconds longer.

2. Position the inflation device to "negative" or "neutral" pressure.

3. Stabilize the guiding catheter position and anchor in place. Maintain the guide wire placement across stent segment.

4. Gently remove the stent delivery system / post-dilatation balloon with slow and steady pressure.

5. Tighten the rotating hemostatic valve.

Notes:

1. **If during withdrawal of the catheter from the deployed stent, resistance is encountered, use the following steps to improve balloon rewrap:**

    - Re-inflate the balloon up to nominal pressure, deflate and change pressure to neutral.
    - Repeat steps 1 through 5 above.

2. After successful withdrawal of the balloon from the deployed stent, should any resistance be felt at any time when withdrawing the stent delivery system or post-dilatation balloon into the guiding catheter, remove the entire system as a single unit.

- Failure to follow these steps and / or applying excessive force to the delivery system can potentially result in loss or damage to the stent and / or delivery system components.

- If it is necessary to retain guide wire position for subsequent artery / lesion access, leave the guide wire in place and remove all other system components.

5.5 Post-Implant

- If necessary to **cross a newly deployed stent** with a guide wire, balloon delivery system, or imaging catheters, exercise care to avoid disrupting the stent geometry.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of stents is unknown at present.
- If the patient requires imaging, see *Section 5.9 Magnetic Resonance Imaging (MRI) Safety Information.*

5.6 Use in Special Populations

5.6.1 Pregnancy

Pregnancy Category C: see *Section* 5.7.4 *Preg*nancy. There are no adequate everolimus or XIENCE Skypoint stent-related studies in pregnant women. Effects on the developing foetus have not been studied.[1] This product has not been tested in pregnant women or in men intending to father children. The XIENCE Skypoint stent should be used in pregnant women only if potential benefits of the stent outweigh potential risks.

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[1] Certican‡ UK SmPC, Afinitor‡ UK SmPC, Votubia‡ UK SmPC, Afinitor‡ US label, and Zortress‡ US label. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SmPC/labels.

5.6.2 Lactation

See *Section 5.7.5 Lactation*. It is unknown whether everolimus is distributed in human milk. A decision should be made whether or not to discontinue nursing prior to stent implantation, considering the importance of the stent to the mother.

5.6.3 Ethnicity

Insufficient subject numbers prevent meaningful ethnicity-related analyses of the XIENCE Family of Stents safety and effectiveness. *Table 5.6.3-1* provides an overview of all non-Caucasians enrolled in the SPIRIT Trials.

Table 5.6.3-1: Non-Caucasians in the SPIRIT and XIENCE V USA Trials

	Non-Caucasian Population
SPIRIT III	8.8% (88/1001)
SPIRIT IV	6.4% (236/3687)
SPIRIT Small Vessel	9.9% (14/142)
SPIRIT PRIME CSR	7.7% (29/375)
SPIRIT PRIME LLR	8.3% (8/96)
XIENCE V USA	12.3% (990/8027)
EXPERT CTO	19.8% (44/222)
XIENCE 90	11.6% (197/1693)
XIENCE 28	42.0% (585/1392)
SPIRIT 48	37.2% (39/105)

5.6.4 Gender

A gender analysis was not pre-specified in the SPIRIT PRIME clinical study. However, post-hoc analyses were conducted to evaluate gender-specific outcomes associated with the XIENCE PRIME stents in the SPIRIT PRIME trials, and the XIENCE V stent in the pooled data from the SPIRIT II, SPIRIT III, and SPIRIT IV trials (see *Section 9.6 Gender-Based Analysis of the SPIRIT Family of Clinical Trials*). Additional gender-specific data associated with the EXPERT CTO trial, XIENCE Short DAPT Program (including XIENCE 90, XIENCE 28 USA, and XIENCE 28 Global trials), and SPIRIT 48 trial can be found in the respective subsections within *Section 9.0 XIENCE Family of Clinical Trials* of this IFU.

5.6.5 Pediatric Use

The safety and effectiveness of the XIENCE Skypoint stent in pediatric subjects have not been established.

5.6.6 Geriatric Use

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

5.6.7 Lesion / Vessel Characteristics

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

- Unresolved vessel thrombus at the lesion site
- Coronary artery reference vessel diameters < 2.25 mm or > 5.25 mm
- Lesion lengths > 44 mm
- Lesions located in saphenous vein grafts
- Lesions located in unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation
- Previously stented lesions
- Diffuse disease or poor flow (TIMI < 1) distal to the identified lesions
- Excessive tortuosity proximal to or within the lesion
- Recent acute myocardial infarction (AMI) or evidence of thrombus in the target vessel
- Multivessel disease
- In-stent restenosis

In the all-inclusive, real-world XIENCE V USA post-approval study, several pre-specified subgroup analyses (including the above-mentioned AMI, multivessel disease and in-stent restenosis) were conducted. See *Section 9.7.3 Pre-specified XIENCE V USA Subgroup Analysis* for the clinical outcomes of XIENCE V in those clinical settings.

5.6.8 Off-Label Use

When XIENCE Skypoint EECSS are used outside the specified indications for use, patient outcomes may differ from the results observed in the SPIRIT family of clinical trials. Compared to use within the specified indications for use, the use of the XIENCE Skypoint EECSS in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.

5.7 Drug Interactions

5.7.1 Interactions with Drugs or Other Substances

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the liver and to some extent in the intestinal wall, and is a substrate for the counter transporter P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of everolimus may be influenced by

drugs that also affect CYP3A4 and PgP pathways. Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Formal drug interaction studies have not been performed with the XIENCE Skypoint stent because of limited exposure to everolimus eluted from the stent (see *Section 6.2 Pharmacokinetics*). Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall, when deciding to place the XIENCE Skypoint stent in a patient taking a drug with known interaction, with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a XIENCE Skypoint stent.

Everolimus, when prescribed as an oral medication, may interact with the following drugs or foods, including the following but not limited to:

- CYP3A4 / PgP isozyme inhibitors
  - Antifungal agents (e.g., fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole)
  - Macrolide antibiotics (e.g., erythromycin, clarithromycin, telithromycin)
  - Calcium channel blockers (e.g., verapamil, nicardipine, diltiazem)
  - Protease inhibitors (e.g., ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir, amprenavir, fosamprenavir)
  - Other (e.g., cyclosporine, nefazodone, cisapride, metoclopramide, bromocriptine, cimedtidine, danazol, sildenafil, terfenadine, astemizole, grapefruit / grapefruit juice, digoxin)

- CYP3A4 / P-gP isozyme inducers
  - Antibiotics (e.g., rifampin, rifabutin, ciprofloxacin, ofloxacin)
  - Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin)
  - Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine)
  - Glucocorticoids (e.g., dexamethasone, prednisone, prednisolone)
  - HMGCoA reductase inhibitors (e.g., simvastatin, lovastatin)
  - Other (e.g., St. John's Wort)

For more detailed drug interaction information, reference the most recent everolimus drug label.[2]

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

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[2] Certican‡ UK SmPC, Afinitor‡ UK SmPC, Votubia‡ UK SmPC, Afinitor‡ US label, and Zortress‡ US label. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SmPC/labels.

5.7.2 Immune Suppression Potential

Everolimus, the XIENCE Skypoint stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the XIENCE family of clinical trials. However, for patients who receive several XIENCE Skypoint stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

5.7.3 Lipid Elevation Potential

Oral everolimus use in renal transplant and advanced renal cell carcinoma patients was associated with increased serum cholesterol and triglyceride levels, which in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the XIENCE Skypoint stent is expected to be significantly lower than concentration exposure usually obtained in transplant patients. Increased serum cholesterol and triglyceride levels were not observed in the SPIRIT and XIENCE family of clinical trials. Oral administration of everolimus in combination with cyclosporine has been associated with increased serum cholesterol and triglyceride levels.

5.7.4 Pregnancy

Pregnancy Category C: There are no adequate everolimus or XIENCE Skypoint stent-related studies in pregnant women. Effects on the developing foetus have not been studied.[3] Effects of a similar stent, XIENCE V, on prenatal and postnatal rat development were no different than the controls (see *Section 5.8 Carcinogenicity, Genotoxicity, and Reproductive Toxicity*). When administered at oral doses of 0.1 mg/kg or above to animals, everolimus has shown reproductive toxicity effects including embryotoxicity and foetotoxicity.

Effective contraception is recommended to be initiated before implanting a XIENCE Skypoint stent and continued for one year post-implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time[3].

5.7.5 Lactation

It is unknown whether everolimus is distributed in human milk. Everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to XIENCE Skypoint stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate procedure.

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[3] Certican‡ UK SmPC, Afinitor‡ UK SmPC, Votubia‡ UK SmPC, Afinitor‡ US label, and Zortress‡ US label. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SmPC/labels.

5.8 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

The carcinogenicity, genotoxicity, and reproductive toxicity of the XIENCE Skypoint stent have not been evaluated; however, long-term carcinogenicity and teratology studies were performed with the similar XIENCE V stent. The test results from the XIENCE V stent, as described below, are applicable to the stent of the XIENCE Skypoint EECSS, due to similar stent design, delivery system materials, and identical stent coating technology.

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

Genotoxicity studies were conducted on the XIENCE V stent in mammalian cells and bacteria. These studies included gene mutations in bacteria (Ames Test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. Based on the results of these studies, the XIENCE V stent is not genotoxic.

In addition, a reproductive toxicity (teratology) study was conducted in female Sprague-Dawley rats. The XIENCE V stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (XIENCE V stent) and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of *in utero* mortality. Additionally, the XIENCE V stent did not cause any reproductive toxicity in the offspring in this study.

5.9 Magnetic Resonance Imaging (MRI) Safety Information

MRI Safety Information

Non-clinical testing has demonstrated that the **XIENCE Skypoint** stent is MR Conditional for single and overlapping lengths up to 91 mm in length. A person with the **XIENCE Skypoint** stent may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	**XIENCE Skypoint** stent
Static Magnetic Field Strength (B_0)	1.5 T or 3 T
Maximum Spatial Field Gradient	30 T/m (3,000 gauss/cm)
Maximum Gradient Slew Rate	200 T/m/s per axis
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	There are no Transmit Coil restrictions
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2.0 W/kg (normal operating mode)
Scan Duration	60 minutes of continuous RF scanning with 2 W/kg whole-body average SAR (Under the scan conditions defined above, the XIENCE Skypoint stent is expected to produce a maximum temperature rise of 2.4 °C after 15 minutes of continuous scanning.)
MR Image Artifact	In non-clinical testing, the image artifact caused by the device extends approximately 5 mm from the XIENCE Skypoint stent when imaged with a gradient echo or spin echo pulse sequence and a 3 Tesla MRI system.

The XIENCE Skypoint stent should not migrate in this MRI environment. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the XIENCE Skypoint stent.

6.0 DRUG INFORMATION

6.1 Mechanism of Action

The mechanism by which the XIENCE Skypoint™ stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FKBP-12 Rapamycin Associated Protein (FRAP), also known as mammalian target of rapamycin (mTOR), leading to inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 stage.

6.2 Pharmacokinetics

Pharmacokinetic studies have not been performed using the XIENCE Skypoint stent, but were conducted on the similar XIENCE V™ stent. The XIENCE Skypoint stent is similar to the XIENCE V stent with regards to the stent design, identical stent coating technology (dosing and drug to polymer ratio), and similar delivery system materials. Given these similarities, the findings from the XIENCE V stent pharmacokinetic studies, as described below, are applicable to the XIENCE Skypoint stent. Everolimus pharmacokinetics, when eluted from the XIENCE V stent post-implantation, have been evaluated in three different substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the United States randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The third pharmacokinetic substudy was conducted as part of the SPIRIT II clinical trial at sites in Europe, India, and New Zealand. Whole blood everolimus pharmacokinetic parameters determined from subjects receiving the XIENCE V stent are provided in *Table 6.2-1*.

Table 6.2-1: Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation

SPIRIT III RCT and 4.0 Arm							
	Dose (µg)	**t_{max} (h)**	**C_{max} (ng/mL)**	**$t_{1/2}$ (h)[a]**	**AUC_{0-t}[a] (ng.h/mL)**	**$AUC_{0-\infty}$[a] (ng.h/mL)**	**CL (L/h)[a]**
		median (range)	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
2.5 – 3.0 x 18 mm (n = 3[b])	88 µg	0.050 (0.50 – 1.88)	0.3867 ± 0.09866		5.31 ± 4.114		
3.5 – 4.0 x 28 mm (n = 6[c])	181 µg	0.50 (0.07 – 1.00)	1.175 ± 0.6817	79.08 ± 57.24	23.73 ± 13.63	44.00 ± 28.67	5.130 ± 2.114
SPIRIT III Japanese Arm							
	Dose (µg)	**t_{max} (h)**	**C_{max} (ng/mL)**	**$t_{1/2}$ (h)[a]**	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$[a] (ng.h/mL)**	**CL (L/h)**
		median (range)	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
2.5 – 3.0 x 18 mm (n = 6)	88 µg	1.00 (0.50 – 1.02)	0.5017 ± 0.1398	45.22 ± 35.08	5.049 ± 2.138	12.98 ± 7.078	9.286 ± 6.069
3.5 – 4.0 x 18 mm (n = 4[b])	113 µg	0.51 (0.50 – 0.53)	0.6500 ± 0.08756	53.57 ± 19.34	11.02 ± 4.002	19.97 ± 7.890	6.471 ± 2.807
SPIRIT II Clinical Trial							
	Dose (µg)	**t_{max} (h)**	**C_{max} (ng/mL)**	**$t_{1/2}$ (h)[a]**	**AUC_{last} (ng.h/mL)**	**$AUC_{0-\infty}$[a] (ng.h/mL)**	**CL (L/h)[a]**
		median (range)	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**	**mean ± SD**
2.5 – 3.0 x 18 mm (n = 13)	88 µg	0.50 (0.13 – 2.17)	0.4369 ± 0.1507	54.08 ± 35.78	8.255 ± 5.863	19.60 ± 15.30	8.066 ± 6.443
3.5 – 4.0 x 18 mm (n = 4[c])	113 µg	0.50 (0.50 – 0.50)	0.5850 ± 0.2630	47.60 ± 62.13	42.54 ± 58.83	22.79 ± 31.47	16.96 ± 13.07
3.5 – 4.0 x 28 mm (n = 4)	181 µg	0.46 (0.17 – 1.00)	0.7925 ± 0.1406	103.4 ± 64.17	28.07 ± 13.18	52.71 ± 27.40	5.332 ± 5.048

[a] Accurate determination not possible due to rapid disappearance of everolimus from the blood
[b] n = 5 for $t_{1/2}$ and CL
[c] n = 3 for $t_{1/2}$ and CL
t_{max} (h) = time to maximum concentration
C_{max} = maximum observed blood concentration
$t_{1/2}$ (h) = terminal phase half-life
AUC_{0-t} or AUC_{last} = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration
$AUC_{(0-\infty)}$ = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time
CL = total blood clearance

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, one subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all three studies, the C_{max} value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection in patients taking Certican‡. The pharmacokinetic parameters representing elimination, $t_{½}$, AUC_{0-t}, AUC_{last}, AUC_{∞}, and CL, could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

Everolimus disappearance from circulation following XIENCE V stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies. The same results are expected for the XIENCE Skypoint stent due to the similarities with the XIENCE V stent stated above.

6.3 Interactions with Drugs or Other Substances

For information on interactions with drugs or other substances, see *Section 5.7.1 Interactions with Drugs or Other Substances*.

7.0 OVERVIEW OF CLINICAL EXPERIENCE

SPIRIT PRIME is a prospective, open-label, multicenter, non-randomized clinical trial using the core size XIENCE PRIME™ and XIENCE PRIME™ LL EECSS. Approximately 500 subjects at up to 75 sites were to be enrolled in the Core Size Registry or Long Lesion Registry. Each subject was to receive treatment in up to two *de novo* native coronary lesions, each in a different epicardial vessel. The Core Size Registry was to enroll approximately 400 subjects in which all were to be treated with core size XIENCE PRIME EECSS (stent diameters 2.25, 2.5, 3.0, 3.5 or 4.0 mm with stent lengths 8, 18, or 28 mm[4]). The Long Lesion Registry was to enroll approximately 100 subjects in which all were to be treated with at least one XIENCE PRIME LL EECSS (stent diameters 2.5, 3.0, 3.5 or 4.0 mm with stent lengths 33 or 38 mm). Treatment of a second target lesion with a core size XIENCE PRIME EECSS was recommended. The primary endpoint was target lesion failure (TLF) at 1 year. Secondary endpoints included clinical outcomes at 30 and 180 days and annually from 1 to 3 years. Final follow-up through 3 years is presented here. The SPIRIT PRIME clinical trial is Abbott Vascular's pivotal United States trial evaluating XIENCE PRIME EECSS.

The XIENCE PRIME stent is similar to the FDA approved XIENCE V™ EECSS. The XIENCE V EECSS has been studied extensively in four clinical trials: SPIRIT FIRST, SPIRIT II, SPIRIT III, and SPIRIT IV. Initial clinical safety and performance of the XIENCE V EECSS stent was demonstrated in the SPIRIT FIRST clinical trial in which the XIENCE V EECSS was compared to the VISION bare metal stent. 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‡ stent. The SPIRIT III clinical trial was a pivotal clinical trial to demonstrate the safety and effectiveness of the XIENCE V EECSS. SPIRIT IV further evaluated the safety and effectiveness of XIENCE V EECSS in a large population of complex subjects. The SPIRIT family of trials evaluating the XIENCE V EECSS is ongoing, inclusive of Investigational Device Exemption (IDE) and post-marketing trials. For more information on the XIENCE V EECSS, refer to the XIENCE V EECSS Instructions for Use (IFU).

Principal XIENCE V EECSS safety and effectiveness information is derived from the SPIRIT III clinical trial and confirmed by the SPIRIT IV clinical trial. These studies evaluated the performance of XIENCE V EECSS in subjects with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics for SPIRIT III and SPIRIT IV are summarized below and listed in *Table 7-1*.

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS Express stent (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III RCT was a prospective, randomized

[4] The 28 mm length stent was studied in the XIENCE PRIME Core Size Registry. The results of the Core Size Registry are presented in *Tables 9.1-2* to *9.1-3*.

(2:1; XIENCE V:TAXUS), active-controlled, single-blinded, multicenter, clinical trial in the US designed to evaluate the safety and efficacy of the XIENCE V stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. The RCT study was designed to enroll 1,002 subjects at up to 80 sites in the US. The primary endpoint in the RCT was in-segment late loss at 240 days, and the co-primary endpoint was ischemia-driven Target Vessel Failure (TVF, defined as the composite of cardiac death, MI, or ischemia-driven Target Vessel Revascularization [TVR]) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and annually from 1 to 5 years), as well as angiographic results and Intravascular Ultrasound (IVUS) results at 240 days. Five-year results are available, completing follow-up for SPIRIT III RCT.

The SPIRIT IV trial was a prospective, randomized, active-controlled, single-blinded, multicenter evaluation of the XIENCE V stent compared to the TAXUS Express stent[5] (TAXUS stent) in the treatment of up to three *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 4.25 mm. The SPIRIT IV trial was randomized 2:1 (XIENCE V:TAXUS) and designed to enroll 3,690 subjects at up to 80 sites in the US. Subjects were stratified by diabetes mellitus (diabetic vs. non-diabetic) and lesion characteristics (complex vs. non-complex). Complex lesion characteristics included triple vessels treatment, or dual lesions per vessel treatment, or lesions involving RCA-aorto-ostial locations, or bifurcation lesions. The primary endpoint was Target Lesion Failure (TLF) at 1 year. The major secondary endpoints were ID-TLR at 1 year and the composite of cardiac death or target vessel MI at 1 year. Formal non-inferiority and superiority testing were planned for the primary and the two major secondary endpoints by following a fixed sequence. Secondary endpoints included clinical outcomes at 30, 180, 270 days and annually from 1 to 3 years. Three-year results are available, completing follow-up for the SPIRIT IV trial.

The SPIRIT Small Vessel (SV) Registry was a prospective, single-arm, open-label, US multicenter registry study using 2.25 mm diameter XIENCE V EECSS. The trial enrolled a total of 150 subjects, of which 69 subjects were included in an angiographic follow-up cohort, at 33 sites. The SPIRIT SV trial allowed for target and non-target lesion treatment. The target lesion was identified as that lesion intended to be treated by the 2.25 mm XIENCE V EECSS and the non-target lesion was identified as that lesion intended to be treated by the commercial XIENCE V EECSS. The SPIRIT SV trial allowed for single target lesion or two lesion treatment (two target lesions or one target and one non-target lesion) in separate epicardial vessels. The primary endpoint was target lesion failure (TLF, defined as the composite of cardiac death, target vessel myocardial infarction and clinically indicated target lesion revascularization) at 1 year. Three-year results are available, completing follow-up for SPIRIT SV.

The XIENCE V USA study was a prospective, multicenter, FDA mandated post-approval study to evaluate the continued safety and effectiveness of the XIENCE V EECSS in “real-world” settings after commercialization in the US, and also to support the FDA dual antiplatelet therapy (DAPT) initiative. A total of 8,040 patients were consecutively enrolled from 191 sites in the US in two enrollment stages (5,042 patients from the first stage and 2,998 patients from the second stage). There were three cohorts in this study: (1) phase I cohort (from index procedure to 1 year), consisting of all enrolled patients from both enrollment stages; (2) long-term follow-up cohort (from 1 year to 4 years), consisting of patients from the first enrollment stage who were not transferred to HCRI-DAPT study and remained in the study beyond 1 year; (3) AV-DAPT

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[5] In the TAXUS stent arm, there was 1 subject who received 1 TAXUS‡ Liberté‡ stent.

cohort (from 1 year to 33 months), consisting of patients from the second enrollment stage who were eligible and randomized to the AV-DAPT study. Patients were considered enrolled upon signing the Institutional Review Board (IRB)-approved informed consent form (ICF) and upon completion of the index procedure utilizing only XIENCE V EECSS was (were) implanted during the index procedure. There were no angiographic inclusion and exclusion criteria for this study. For the phase I and the long-term follow-up cohorts, the primary endpoint was the annual rate of Academic Research Consortium (ARC)-defined stent thrombosis (definite and probable), and the co-primary endpoint was the annual composite rate of cardiac death or any MI. The study design of the AV-DAPT cohort follows the HCRI-DAPT study (IDE#G080186). Final clinical follow-up through 4 years is available for all the enrolled patients (long-term follow-up cohort).

The SPIRIT 48 clinical trial was a prospective, single-arm, open-label, multi-center clinical investigation in 107 subjects at 25 global sites to evaluate the safety and effectiveness of 48 mm stent length of XIENCE Skypoint in the treatment of *de novo* native coronary artery long lesions. This trial registered subjects with a maximum of two *de novo* coronary artery lesions, of which, only one target lesion was allowed and required to be treated by 48 mm stent length of XIENCE Skypoint. The other lesion, if any, was required to be a non-target lesion in a separate epicardial coronary vessel and treated by stents other than 48 mm stent length of XIENCE Skypoint. The primary endpoint of the SPIRIT 48 clinical trial was TLF (composite of cardiac death, target vessel myocardial infarction per Society for Cardiovascular Angiography and Interventions (SCAI) definition, and clinically indicated target lesion revascularization) at 1 year. In addition, the study is evaluating TLF in hospital, at 30 days, 180 days, and 2 years as descriptive secondary endpoints. The SPIRIT 48 study completed the 1-year primary endpoint follow-up and is currently ongoing through the 2-year follow-up.

Table 7-1 summarizes the clinical trial designs for the SPIRIT family of trials. *Table 7-2* summarizes the clinical trial design for the XIENCE V USA post-approval study.

Table 7-1: SPIRIT Family Clinical Trial Designs

	SPIRIT PRIME Clinical Trial		SPIRIT III Clinical Trial		SPIRIT IV Clinical Trial	SPIRIT Small Vessel Registry	SPIRIT 48 Clinical Trial
	Core Size Registry	**Long Lesion Registry**	**RCT (Pivotal)**	**4.0 Arm (Registry)**			
Study Type / Design	• Multicenter • Single-arm • Open-label	• Multicenter • Single-arm • Open-label	• Multicenter • Randomized • Single-blinded • Active-control	• Multicenter • Single-arm • Open-label	• Multicenter • Randomized • Single-blinded • Active-Control	• Multicenter • Non-randomized • Open-label • Non-blinded • Single-arm	• Multicenter • Single-arm • Open-label
Number of Subjects Enrolled	Total: 400	Total: 100	Total: 1,002 XIENCE V: 668 TAXUS Express Control: 334	Total: 80	Total: 3,690 XIENCE V: 2,460 TAXUS Express Control: 1,230[**]	Total : 150 No Control	Total : 107
Treatment	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Up to two *de novo* lesions in different epicardial vessels	Up to three *de novo* lesions, maximum of two lesions per epicardial vessel	Up to two *de novo* lesions in different epicardial vessels	One single *de novo* native coronary target lesion
Lesion Size	RVD: ≥ 2.25 ≤ 4.25 mm Length: ≤ 22 mm	XIENCE PRIME CS: RVD: ≥ 2.25 ≤ 4.25 mm Length: ≤ 22 mm XIENCE PRIME LL: RVD: ≥ 2.5 ≤ 4.25 mm Length: > 22 mm and ≤ 32 mm	RVD: ≥ 2.5 ≤ 3.75 mm Length: ≤ 28 mm	RVD: > 3.75 ≤ 4.25 mm Length: ≤ 28 mm	RVD: ≥ 2.5 ≤ 4.25[§] mm Length: ≤ 28 mm	RVD: ≥ 2.25 < 2.50 mm Length: ≤ 28 mm	RVD: ≥ 2.5 mm and ≤ 4.25 mm Length: > 32 mm and ≤ 44 mm
Stent Sizes (XIENCE PRIME / XIENCE V / XIENCE Skypoint)	**XIENCE PRIME** Diameter: 2.25, 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28*** mm	**XIENCE PRIME LL** Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 33, 38 mm	**XIENCE V** Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm	**XIENCE V** Diameter: 4.0 mm Length: 8, 18, 28 mm	**XIENCE V** Diameter: 2.5, 3.0, 3.5, 4.0[§] mm Length: 8, 18, 28 mm	**XIENCE V** Diameter: 2.25 mm Length: 8, 18, 28 mm	**XIENCE Skypoint 48** Diameter: 2.5, 2.75, 3.0, 3.50, 4.0 mm Length: 48 mm
Post-Procedure Antiplatelet Therapy	Clopidogrel 12 months minimum (or ticlopidine per site standard), aspirin 3 years	Clopidogrel 12 months minimum (or ticlopidine per site standard), aspirin 3 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), aspirin 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), aspirin 5 years	Clopidogrel 12 months minimum (or ticlopidine per site standard), [#] aspirin 3 years	Clopidogrel 12 months minimum (or ticlopidine per site standard), aspirin indefinitely	Post-procedure antiplatelet medication per latest American College of Cardiology / American Heart Association (ACC/AHA) / SCAI guidelines

	SPIRIT PRIME Clinical Trial		SPIRIT III Clinical Trial		SPIRIT IV Clinical Trial	SPIRIT Small Vessel Registry	SPIRIT 48 Clinical Trial
	Core Size Registry	**Long Lesion Registry**	**RCT (Pivotal)**	**4.0 Arm (Registry)**			
Primary Endpoint • **Primary Analysis** • **Major Secondary Analysis 1** • **Major Secondary Analysis 2**	• TLF (Target lesion failure) at 1 year • TLF (per ARC) at 1 year compared to PG* of 9.2% • TLF (per protocol) at 1 year compared to PG* of 9.2% • TLF (per ARC) at 1 year compared to PG* of 15.3%	• TLF (Target Lesion failure) at 1 year • TLF (per ARC) at 1 year compared to PG* of 19.2% • TLF (per protocol) at 1 year compared to PG* of 19.2% • TLF (per ARC) at 1 year compared to PG* of 26%	In-segment late loss at 240 days	In-segment late loss at 240 days	TLF (Target Lesion failure) at 1 year	Clinically indicated target lesion failure at 1 year (composite of cardiac death, target vessel MI and clinically indicated TLR)	Target lesion failure (TLF) (composite of cardiac death, target vessel myocardial infarction per SCAI definition, and clinically indicated target lesion revascularization, CI-TLR) at 1 year compared to pre-specified PG of 20%
Co-Primary Endpoint	None	None	TVF (Target vessel Failure) at 270 days	None	None	None	None
Major Secondary Endpoint	None	None	None	None	• Ischemia-driven Target Lesion Revascularization (ID-TLR) at 1 year • Composite endpoint of cardiac death or target vessel MI at 1 year	None	TLF in hospital, at 30 days, 180 days, and 2 years (descriptive without a pre-specified statistical assumption)
Clinical Follow-up	30, 180 days, 1 to 3 years	30, 180 days, 1 to 3 years	30, 180, 240, 270 days, 1 to 5 years	30, 180, 240, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 3 years	30, 240 days, 1 to 3 years	30 days, 180 days, 1 year, and 2 years
Status	1, 2, and 3 years reported	1, 2, and 3 years reported	1, 2, 3, 4, and 5 years reported	1, 2, 3, 4, and 5 years reported	1, 2, and 3 years reported	1, 2, and 3 years reported	1 and 2 years reported

* Performance Goal (PG)
** In the TAXUS arm, there was 1 patient who received 1 TAXUS‡ Liberté‡ stent.
*** The 28 mm length stent was studied in the Core Size Registry. The results of the Core Size Registry are presented in *Tables 9.1-2* to *9.1-3*.
§ RVD ≥ 2.5 mm to ≤ 3.75 mm and stent sizes up to 3.5 mm until 4.0 mm TAXUS is commercially available.
# All subjects receiving a study stent were to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of 6 months, and per the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) guidelines it was strongly recommended that subjects should be treated with clopidogrel bisulfate up to 12 months if they are not at high risk for bleeding.

Table 7-2: XIENCE V USA Post-Approval Study Design

	XIENCE V USA Phase I Cohort	XIENCE V USA Long-Term Follow-up Cohort	XIENCE V USA AV-DAPT Cohort
Study Type / Design	• Multicenter • Prospective	• Multicenter • Prospective	• Multicenter • Randomized • Double-blinded • Placebo Control
Number of Subjects Enrolled	Total: 8040	Total: 4663	Total: 868
Treatment	Only XIENCE V EECSS implanted during the index procedure; otherwise per site standard care	Only XIENCE V EECSS implanted during the index procedure; otherwise per site standard care	Only XIENCE V EECSS implanted during the index procedure; otherwise per site standard care. At 1 year, patients were randomized to receive either thienopyridine or placebo treatment for additional 18 months along with aspirin.
Lesion Size	No angiographic restrictions	No angiographic restrictions	No angiographic restrictions
Stent Sizes (XIENCE V)	Diameter: 2.5, 2.75, 3.0, 3.5, 4.0 mm Length: 8, 12, 15, 18, 23, 28 mm	Diameter: 2.5, 2.75, 3.0, 3.5, 4.0 mm Length: 8, 12, 15, 18, 23, 28 mm	Diameter: 2.5, 2.75, 3.0, 3.5, 4.0 mm Length: 8, 12, 15, 18, 23, 28 mm
Post-Procedure Antiplatelet Therapy	Per site standard	Per site standard	Patients were randomized to receive either thienopyridine or placebo treatment between 12 and 30 months. Thienopyridine or placebo will be discontinued between 30 and 33 months. Aspirin is required through 33 months.
Primary Endpoint	ARC definite and probable stent thrombosis up to 1 year	ARC definite and probable stent thrombosis from year 1 to 4	MACE (composite of all death, MI and stroke) 12 – 33 months
Co-Primary Endpoint	Composite rate of cardiac death or any MI at 1 year	Composite rate of cardiac death or any MI from year 1 to 4	ARC definite and probable ST 12 – 33 months
Major Safety Endpoint	None	None	Major bleeding (GUSTO severe and moderate bleeding combined) 12 – 33 months
Major Secondary Endpoint	None	None	None
Clinical Follow-up	14, 30, 180 days, and 1 year	2, 3, and 4 years	15, 24, 30, and 33 months
Angiographic Follow-up	None	None	None
IVUS Follow-up	None	None	None
Pharmacokinetic Study	None	None	None
Status	1 year reported	2, 3, and 4 years reported	15, 24, 30, and 33 months reported

8.0 ADVERSE EVENTS

8.1 Observed Adverse Events

Principal adverse event information is derived from the SPIRIT PRIME Core Size Registry, SPIRIT IV, SPIRIT III, and SPIRIT SV clinical trials and is shown in *Table 8.1-1*. Principal adverse events from the XIENCE V USA clinical trial are presented in *Table 8.1-2*. See also *Section 8.3 Potential Adverse Events*. See *Section 9.0 XIENCE FAMILY OF CLINICAL TRIALS* for more complete study design descriptions and results.

Note: Information on adverse events for subjects in the SPIRIT PRIME Long Lesion Registry is in *Table 9.1-4*.

Table 8.1-1: SPIRIT Family:
Principal Adverse Events from Post-Procedure to Latest Follow-up

	SPIRIT PRIME	SPIRIT IV		SPIRIT III (RCT)			SPIRIT SV
	Core Size Registry[§] (N = 401)	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	2.25 mm XIENCE V (N = 144)
In-Hospital Adverse Events							
TLF	2.0% (8/401)	1.4% (35/2451)	1.9% (23/1224)	0.9% (6/669)	1.8% (6/330)	4.1% (3/73)	1.4% (2/143)
MACE	2.0% (8/401)	1.4% (35/2451)	1.9% (23/1224)	0.9% (6/669)	1.8% (6/330)	4.1% (3/73)	1.4% (2/143)
TVF	NA	1.5% (36/2451)	2.0% (24/1224)	0.9% (6/669)	1.8% (6/330)	4.1% (3/73)	1.4% (2/143)
All Death	0.0% (0/401)	0.0% (0/2451)	0.0% (0/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/143)
Cardiac Death	0.0% (0/401)	0.0% (0/2451)	0.0% (0/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/143)
Non-Cardiac Death	0.0% (0/401)	0.0% (0/2451)	0.0% (0/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/143)
MI	1.7% (7/401)	1.4% (35/2451)	1.8% (22/1224)	0.7% (5/669)	1.8% (6/330)	4.1% (3/73)	1.4% (2/143)
QMI	0.2% (1/401)	0.1% (3/2451)	0.2% (2/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.7% (1/143)
NQMI	1.5% (6/401)	1.3% (32/2451)	1.6% (20/1224)	0.7% (5/669)	1.8% (6/330)	4.1% (3/73)	0.7% (1/143)
Cardiac Death or MI	1.7% (7/401)	1.4% (35/2451)	1.8% (22/1224)	0.7% (5/669)	1.8% (6/330)	4.1% (3/73)	1.4% (2/143)
Ischemia-Driven Revascularization	0.5% (2/401)	0.4% (9/2451)	0.5% (6/1224)	0.1% (1/669)	0.0% (0/330)	0.0% (0/73)	0.7% (1/143)
Ischemia-Driven TLR	0.2% (1/401)	0.3% (8/2451)	0.4% (5/1224)	0.1% (1/669)	0.0% (0/330)	0.0% (0/73)	0.0% (0/143)
Ischemia-Driven TVR, Non-TL	0.2% (1/401)	0.1% (3/2451)	0.2% (2/1224)	0.0% (0/669)	0.0% (0/330)	0.0% (0/73)	0.7% (1/143)
Stent Thrombosis (Per Protocol)	0.5% (2/401)	0.1% (3/2451)	0.4% (5/1224)	0.1% (1/669)	0.0% (0/330)	1.4% (1/73)	0.0% (0/143)

	SPIRIT PRIME	SPIRIT IV		SPIRIT III (RCT)			SPIRIT SV
	Core Size Registry[§] (N = 401)	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	2.25 mm XIENCE V (N = 144)
30-Day TLF	2.2% (9/401)	1.6% (38/2451)	2.7% (33/1222)	1.2% (8/667)	2.1% (7/330)	4.1% (3/73)	2.1% (3/140)
6-Month TLF[1]	3.8% (15/399)	2.5% (62/2435)	5.1% (62/1208)	2.3% (15/663)	4.3% (14/326)	6.8% (5/73)	NA
9-Month TLF[2]	NA	3.4% (83/2419)	6.1% (73/1201)	4.1% (27/657)	7.8% (25/321)	6.8% (5/73)	7.2% (10/139)
30-Day TVF	NA	1.9% (46/2451)	2.9% (36/1222)	1.5% (10/667)	2.7% (9/330)	4.1% (3/73)	2.9% (4/140)
6-Month TVF	NA	3.4% (82/2435)	6.0% (73/1208)	3.8% (25/663)	4.9% (16/326)	6.8% (5/73)	NA
9-Month[5] TVF	NA	4.6% (111/2419)	7.1% (85/1201)	7.2% (47/657)	9.0% (29/321)	6.8% (5/73)	9.4% (13/139)
1-Year Subject Counts of Adverse Events							
TLF[3]	4.5% (18/399)	4.0% (97/2416)	6.8% (81/1195)	5.2% (34/653)	9.7% (31/320)	6.8% (5/73)	8.1% (11/136)
TVF	NA	5.5% (134/2416)	7.7% (92/1195)	8.6% (56/653)	11.3% (36/320)	6.8% (5/73)	11.0% (15/136)
All Death	0.8% (3/399)	1.0% (25/2416)	1.3% (15/1195)	1.2% (8/655)	1.2% (4/321)	1.4% (1/73)	1.5% (2/136)
Cardiac Death	0.3% (1/399)	0.4% (10/2416)	0.4% (5/1195)	0.8% (5/655)	0.9% (3/321)	1.4% (1/73)	1.5% (2/136)
Non-Cardiac Death	0.5% (2/399)	0.6% (15/2416)	0.8% (10/1195)	0.5% (3/655)	0.3% (1/321)	0.0% (0/73)	0.0% (0/136)
All MI	1.8% (7/399)	1.9% (45/2416)	3.1% (37/1195)	2.8% (18/653)	4.1% (13/320)	4.1% (3/73)	1.5% (2/136)
QMI	0.3% (1/399)	0.1% (3/2416)	0.4% (5/1195)	0.3% (2/653)	0.3% (1/320)	0.0% (0/73)	0.7% (1/136)
NQMI	1.5% (6/399)	1.7% (42/2416)	2.8% (33/1195)	2.5% (16/653)	3.8% (12/320)	4.1% (3/73)	0.7% (1/136)
Target Vessel MI	1.8% (7/399)	1.8% (44/2416)	2.9% (35/1195)	NA	NA	NA	1.5% (2/136)
Cardiac Death or all MI	2.0% (8/399)	2.2% (54/2416)	3.3% (39/1195)	3.4% (22/653)	4.7% (15/320)	5.5% (4/73)	2.9% (4/136)
ID* TVR	4.5% (18/399)	3.9% (94/2416)	5.9% (70/1195)	6.1% (40/653)	7.5% (24/320)	2.7% (2/73)	8.8% (12/136)
ID* TLR	2.5% (10/399)	2.5% (61/2416)	4.6% (55/1195)	3.4% (22/653)	5.6% (18/320)	2.7% (2/73)	5.1% (7/136)
ID* Non-TLR TVR	2.8% (11/399)	2.3% (56/2416)	3.1% (37/1195)	3.1% (20/653)	4.4% (14/320)	0.0% (0/73)	5.9% (8/136)
Protocol Defined Stent Thrombosis[4]	0.5% (2/399)	0.17% (4/2389)	0.85% (10/1181)	0.8% (5/647)	0.6% (2/317)	1.4% (1/72)	2.2% (3/136)
ARC Definite+Probable Stent Thrombosis[4]	0.5% (2/399)	0.29% (7/2391)	1.10% (13/1181)	1.1% (7/652)	0.6% (2/319)	0.0% (0/72)	1.5% (2/136)
ARC Definite Stent Thrombosis[4]	0.5% (2/399)	0.25% (6/2391)	0.85% (10/1181)	0.8% (5/652)	0.0% (0/319)	0.0% (0/72)	0.7% (1/138)

	SPIRIT PRIME	SPIRIT IV		SPIRIT III (RCT)			SPIRIT SV
	Core Size Registry[§] (N = 401)	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	2.25 mm XIENCE V (N = 144)
2-Year Subject Counts of Adverse Events							
TLF[3]	6.4% (25/392)	7.0% (167/2388)	10.0% (119/1190)	7.1% (45/637)	12.8% (39/305)	8.6% (6/70)	8.3% (11/133)
TVF	NA	9.6% (230/2388)	11.8% (140/1190)	11.3% (72/637)	16.4% (50/305)	10.0% (7/70)	12.0% (16/133)
All Death	2.0% (8/392)	2.1% (51/2388)	2.7% (32/1190)	2.0% (13/642)	2.6% (8/309)	6.9% (5/72)	1.5% (2/133)
Cardiac Death	0.5% (2/392)	0.9% (22/2388)	1.3% (15/1190)	1.1% (7/642)	1.3% (4/309)	2.8% (2/72)	1.5% (2/133)
Vascular Death	0.5% (2/392)	NA	NA	NA	NA	NA	NA
Non-Cardiac Death	1.0% (4/392)	1.2% (29/2388)	1.4% (17/1190)	0.9% (6/642)	1.3% (4/309)	4.2% (3/72)	0.0% (0/133)
All MI	2.0% (8/392)	2.6% (61/2388)	3.9% (47/1190)	3.3% (21/637)	5.9% (18/305)	4.3% (3/70)	1.5% (2/133)
QMI	0.5% (2/392)	0.1% (3/2388)	0.8% (9/1190)	0.5% (3/637)	0.7% (2/305)	0.0% (0/70)	0.8% (1/133)
NQMI	1.5% (6/392)	2.4% (58/2388)	3.4% (40/1190)	2.8% (18/637)	5.2% (16/305)	4.3% (3/70)	0.8% (1/133)
Target Vessel MI	1.8% (7/392)	2.3% (56/2388)	3.5% (42/1190)	NA	NA	NA	1.5% (2/133)
Cardiac Death or all MI	2.6% (10/392)	3.4% (82/2388)	4.6% (55/1190)	4.1% (26/637)	6.9% (21/305)	7.1% (5/70)	3.0% (4/133)
ID* TVR	6.9% (27/392)	7.0% (168/2388)	8.9% (106/1190)	8.8% (56/637)	11.1% (34/305)	4.3% (3/70)	9.8% (13/133)
ID* TLR	4.1% (16/392)	4.4% (106/2388)	6.9% (82/1190)	4.6% (29/637)	7.5% (23/305)	2.9% (2/70)	5.3% (7/133)
ID* Non-TLR TVR	4.3% (17/392)	3.9% (94/2388)	4.3% (51/1190)	4.9% (31/637)	6.6% (20/305)	1.4% (1/70)	6.8% (9/133)
3-Year Subject Counts of Adverse Events							
TLF[3]	8.5% (33/390)	9.5% (223/2348)	11.9% (138/1158)	8.9% (56/629)	15.1% (46/305)	8.8% (6/68)	12.1% (16/132)
TVF	NA	13.3% (312/2348)	14.5% (168/1158)	14.3% (90/629)	20.0% (61/305)	11.8% (8/68)	16.7% (22/132)
All Death	3.1% (12/390)	3.4% (81/2348)	5.2% (60/1158)	2.8% (18/636)	4.5% (14/312)	8.5% (6/71)	3.8% (5/132)
Cardiac Death	0.8% (3/390)	1.4% (34/2348)	1.9% (22/1158)	1.6% (10/636)	1.9% (6/312)	2.8% (2/71)	3.8% (5/132)
Vascular Death	0.5% (2/390)	NA	NA	NA	NA	NA	NA
Non-Cardiac Death	1.8% (7/390)	2.0% (47/2348)	3.3% (38/1158)	1.3% (8/636)	2.6% (8/312)	5.6% (4/71)	0.0% (0/132)
All MI	3.1% (12/390)	3.1% (73/2348)	4.7% (55/1158)	3.8% (24/629)	6.6% (20/305)	4.4% (3/68)	1.5% (2/132)
QMI	1.0% (4/390)	0.3% (6/2348)	0.9% (11/1158)	0.5% (3/629)	0.7% (2/305)	0.0% (0/68)	0.8% (1/132)

	SPIRIT PRIME	SPIRIT IV		SPIRIT III (RCT)			SPIRIT SV
	Core Size Registry[§] (N = 401)	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	2.25 mm XIENCE V (N = 144)
NQMI	2.6% (10/390)	2.9% (67/2348)	4.0% (46/1158)	3.3% (21/629)	5.9% (18/305)	4.4% (3/68)	0.8% (1/132)
Target Vessel MI	2.6% (10/390)	2.8% (65/2348)	4.1% (48/1158)	NA	NA	NA	1.5% (2/132)
Cardiac Death or all MI	3.8% (15/390)	4.5% (105/2348)	6.0% (70/1158)	5.1% (32/629)	8.2% (25/305)	7.4% (5/68)	5.3% (7/132)
ID* TVR	9.5% (37/390)	10.1% (238/2348)	10.6% (123/1158)	11.1% (70/629)	14.8% (45/305)	5.9% (4/68)	12.1% (16/132)
ID* TLR	5.4% (21/390)	6.3% (148/2348)	7.9% (92/1158)	5.7% (36/629)	9.2% (28/305)	2.9% (2/68)	6.8% (9/132)
ID* Non-TLR TVR	5.9% (23/390)	5.6% (132/2348)	5.4% (63/1158)	6.7% (42/629)	8.9% (27/305)	2.9% (2/68)	8.3% (11/132)
4-Year Subject Counts of Adverse Events							
TLF[3]	NA	NA	NA	11.9% (73/615)	17.2% (52/302)	8.8% (6/68)	NA
TVF	NA	NA	NA	18.5% (114/615)	22.5% (68/302)	11.8% (8/68)	NA
All Death	NA	NA	NA	4.9% (31/628)	6.1% (19/311)	8.5% (6/71)	NA
Cardiac Death	NA	NA	NA	2.5% (16/628)	2.6% (8/311)	2.8% (2/71)	NA
Non-Cardiac Death	NA	NA	NA	2.4% (15/628)	3.5% (11/311)	5.6% (4/71)	NA
All MI	NA	NA	NA	4.4% (27/615)	6.6% (20/302)	4.4% (3/68)	NA
QMI	NA	NA	NA	1.0% (6/615)	0.7% (2/302)	0.0% (0/68)	NA
NQMI	NA	NA	NA	3.4% (21/615)	6.0% (18/302)	4.4% (3/68)	NA
Target Vessel MI	NA	NA	NA	NA	NA	NA	NA
Cardiac Death or all MI	NA	NA	NA	6.5% (40/615)	8.9% (27/302)	7.4% (5/68)	NA
ID* TVR	NA	NA	NA	14.3% (88/615)	16.6% (50/302)	5.9% (4/68)	NA
ID* TLR	NA	NA	NA	8.0% (49/615)	10.6% (32/302)	4.4% (3/68)	NA
ID* Non-TLR TVR	NA	NA	NA	7.8% (48/615)	9.6% (29/302)	2.9% (2/68)	NA
5-Year Subject Counts of Adverse Events							
5-Year TLF[3]	NA	NA	NA	13.4% (81/605)	20.6% (59/286)	10.4% (7/67)	NA
TVF	NA	NA	NA	20.3% (123/605)	26.6% (76/286)	11.9% (8/67)	NA
All Death	NA	NA	NA	6.0% (37/621)	10.3% (31/300)	8.6% (6/70)	NA

	SPIRIT PRIME	SPIRIT IV		SPIRIT III (RCT)			SPIRIT SV
	Core Size Registry[§] (N = 401)	XIENCE V (N = 2458)	TAXUS (N = 1229)	XIENCE V (N = 669)	TAXUS (N = 333)	XIENCE V 4.0 mm Arm (N = 73)	2.25 mm XIENCE V (N = 144)
Cardiac Death	NA	NA	NA	2.7% (17/621)	4.3% (13/300)	2.9% (2/70)	NA
Non-Cardiac Death	NA	NA	NA	3.2% (20/621)	6.0% (18/300)	5.7% (4/70)	NA
All MI	NA	NA	NA	4.6% (28/605)	7.0% (20/286)	4.5% (3/67)	NA
QMI	NA	NA	NA	1.0% (6/605)	0.7% (2/286)	0.0% (0/67)	NA
NQMI	NA	NA	NA	3.8% (23/605)	6.3% (18/286)	4.5% (3/67)	NA
Target Vessel MI	NA	NA	NA	NA	NA	NA	NA
Cardiac Death or all MI	NA	NA	NA	7.1% (43/605)	11.2% (32/286)	7.5% (5/67)	NA
ID* TVR	NA	NA	NA	15.7% (95/605)	19.9% (57/286)	6.0% (4/67)	NA
ID* TLR	NA	NA	NA	8.9% (54/605)	12.9% (37/286)	4.5% (3/67)	NA
ID* Non-TLR TVR	NA	NA	NA	8.8% (53/605)	11.9% (34/286)	3.0% (2/67)	NA

Notes:

- Population for SPIRIT PRIME Core Size Registry consists of those subjects who were treated with at least one XIENCE PRIME stent and had cardiac enzyme data between 8-hour post-index procedure and hospital discharge. SPIRIT III and IV based on intent-to-treat population (all subjects randomized, regardless of the treatment they actually received).
- In-hospital is defined as hospitalization less than or equal to 7-day post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s) / lesion(s) for subjects with two or more target vessels / lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- TLF includes cardiac death, target vessel MI (per protocol definition) and ischemia-driven TLR. For SPIRIT III 4.0 mm arm, MACE (cardiac death, all MI [per protocol definition] and ischemia-driven TLR) is reported, as TLF was not an endpoint.
- SPIRIT SV based on full analysis set (FAS) population.
- For SPIRIT III, cardiac death is defined as the number of patients experiencing cardiac death through the follow-up time point / (the number of patients experiencing cardiac death through the follow-up time point + the number of patients followed through the follow-up time point without cardiac death + the number of patients terminated prior to the follow-up time point who did not experience cardiac death but experienced non-cardiac death, MI, ID or non-ID TLR, or ID or non-ID TVR).
- Deaths were adjudicated in SPIRIT PRIME as cardiac, vascular, and non-cardiovascular. SPIRIT III, IV, and SV adjudicated deaths as cardiac or non-cardiac.

[1] SPIRIT III and SPIRIT IV include 14-day window. SPIRIT PRIME includes 28-day window.
[2] SPIRIT III and SPIRIT IV includes 14-day window.
[3] SPIRIT III, SPIRIT IV, and SPIRIT PRIME include 28-day window.
[4] See *Section 8.2 Stent Thrombosis Definitions*.
[5] SPIRIT SV 8-month data are presented, as follow-up was not required at 9 months.
§ For Long Lesion Registry data, see *Table 9.1-4*.
* For SPIRIT PRIME, it is captured as clinically indicated (CI).

Table 8.1-2: XIENCE V USA Post-Approval Study
Principal Adverse Events from Post-Procedure to 4 Years

	XIENCE V USA				
	XIENCE V (N = 8040)				XIENCE V (N = 5020)
	In-Hospital	30 Days	6 Months	1 Year	4 Years
TLF	2.7% (214/8001)	3.5% (275/7963)	6.2% (490/7854)	9.4% (707/7522)	19.3% (875/4530)
All Death	0.02% (2/8001)	0.4% (28/7963)	1.4% (108/7854)	2.6% (194/7522)	10.9% (494/4530)
Cardiac Death	0.01% (1/8001)	0.3% (25/7963)	0.9% (69/7854)	1.4% (108/7522)	5.4% (244/4530)
Vascular Death	0.0% (0/8001)	0.01% (1/7963)	0.1% (6/7854)	0.2% (12/7522)	0.7% (32/4530)
Non-Cardiovascular Death	0.01% (1/8001)	0.03% (2/7963)	0.4% (33/7854)	1.0% (74/7522)	4.8% (218/4530)
MI	2.7% (216/8001)	3.3% (266/7963)	4.7% (372/7854)	6.3% (475/7522)	11.3% (511/4530)
QMI	0.2% (18/8001)	0.3% (25/7963)	0.4% (30/7854)	0.5% (39/7522)	1.5% (68/4530)
NQMI	2.5% (198/8001)	3.0% (241/7963)	4.4% (346/7854)	5.9% (442/7522)	10.1% (457/4530)
Cardiac Death or MI	2.7% (216/8001)	3.6% (286/7963)	5.4% (422/7854)	7.2% (545/7522)	14.9% (676/4530)
Clinically Indicated Revascularization	0.2% (17/8001)	1.0% (81/7963)	4.5% (352/7854)	8.1% (607/7522)	19.9% (901/4530)
Clinically Indicated TLR	0.2% (13/8001)	0.4% (30/7963)	2.2% (173/7854)	4.4% (330/7522)	10.4% (473/4530)
Clinically Indicated TVR, Non -TL	0.02% (2/8001)	0.2% (15/7963)	1.0% (82/7854)	2.1% (161/7522)	6.1% (277/4530)
Stent Thrombosis (ARC Definite and Probable)	0.11% (9/8000)	0.40% (32/7951)	0.58% (45/7790)	0.81% (60/7380)	1.56% (64/4093)
Stent Thrombosis (ARC Definite)	0.11% (9/8000)	0.23% (18/7951)	0.35% (27/7790)	0.54% (40/7380)	1.05% (43/4093)

Notes:
- In-hospital is defined as hospitalization less than or equal to 7-day post-index procedure.
- 30-day window is through 37 days (7-day window).
- 6-month window is through 194 days (14-day window).
- 1-year window is through 407 days (42-day window) or randomization date if occurred within 407 days for the second enrollment phase. 4-year window is through 1502 days (42-day window).
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- ARC MI definition was used for MI and MI related endpoints.
- TLF includes cardiac death, target vessel MI and clinically indicated TLR.

8.2 Stent Thrombosis Definitions

Protocol-defined Stent Thrombosis (ST) was categorized as acute (< 1 day), subacute (1–30 days) and late (> 30 days) and was defined as any of the following[6]:

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (angiographic appearance of thrombus within or adjacent to a previously treated target lesion)
- In the absence of angiography, any unexplained death, or acute MI (ST segment elevation or new Q-wave)[7] in the distribution of the target lesion within 30 days

All stent thrombosis events were also classified using the ST definitions proposed by the Academic Research Consortium (ARC)[8]. This was performed by an independent event committee blinded to the treatment group of the individual subject. The committee categorized each incident of ST by timing and level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

Timing:

- Early ST: 0 to 30 days post-stent implantation
- Late ST: 31 days to 1 year post-stent implantation
- Very late ST: > 1 year post-stent implantation

Level of probability:

- Definite ST – considered to have occurred by either angiographic or pathologic confirmation
- Probable ST – considered to have occurred after intracoronary stenting in the following cases:
  - Any unexplained death within the first 30 days
  - Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause
- Possible ST – considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up[9]

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6 For SPIRIT FIRST Stent Thrombosis is defined as total occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers, and ECG changes consistent with MI.

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

8 Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circ* 2007;115:2344-51.

9 All data within these Instructions for Use are presented as definite+probable only.

8.3 Potential Adverse Events

Adverse events that may be associated with percutaneous coronary intervention (PCI) treatment procedures and the use of a stent in native coronary arteries include, but are not limited to, the following:

- Allergic reaction or hypersensitivity to latex, contrast agent, anesthesia, device materials (cobalt, chromium, nickel, tungsten, methacrylic polymer, and fluoropolymer), and drug reactions to everolimus, anticoagulation, or antiplatelet drugs
- Vascular access complications which may require transfusion or vessel repair, including:
    - Catheter site reactions
    - Bleeding (ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage)
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
    - Embolism (air, tissue, plaque, thrombotic material or device)
    - Peripheral nerve injury
    - Peripheral ischemia
- Coronary artery complications which may require additional intervention, including:
    - Total occlusion or abrupt closure
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
    - Tissue prolapse / plaque shift
    - Embolism (air, tissue, plaque, thrombotic material, or device)
    - Coronary or stent thrombosis (acute, subacute, late, very late)
    - Stenosis or restenosis
- Pericardial complications which may require additional intervention, including:
    - Cardiac tamponade
    - Pericardial effusion
    - Pericarditis
- Cardiac arrhythmias (including: aspecific, conduction disorders, atrial and ventricular arrhythmias)
- Cardiac ischemic conditions, including:
    - Myocardial ischemia
    - Myocardial infarction (including acute)
    - Coronary artery spasm
    - Unstable or stable angina pectoris
- Stroke / cerebrovascular accident (CVA) and transient ischemic attack (TIA)
- System organ failures:
    - Cardio-respiratory arrest
    - Cardiac failure
    - Cardiopulmonary failure (including pulmonary edema)
    - Renal insufficiency / failure
    - Shock
- Bleeding
- Blood cell disorders (including heparin induced thrombocytopenia [HIT])
- Hypotension / hypertension
- Infection

- Nausea and vomiting
- Palpitations, dizziness, and syncope
- Chest pain
- Fever
- Pain
- Death

Adverse events associated with daily oral administration of everolimus in doses varying from 1.5 mg to 10 mg daily can be found in the Summary of Product Characteristics (SmPC) and labels for the drug[10]. The risks described below include the anticipated adverse events relevant for the cardiac population referenced in the contraindications, warnings and precaution sections of the everolimus labels / SmPCs and / or observed at incidences ≥ 10% in clinical trials with oral everolimus for different indications. Refer to the drug SmPCs and labels for more detailed information and less frequent adverse events.

- Abdominal pain
- Anemia
- Angioedema (increased risk with concomitant angiotensin converting enzyme [ACE] inhibitor use)
- Arterial thrombotic events
- Bleeding and coagulopathy (including hemolytic uremic syndrome [HUS], thrombotic thrombocytopenic purpura [TTP], and thrombotic microangiopathy; increased risk with concomitant cyclosporine use)
- Constipation
- Cough
- Diabetes mellitus
- Diarrhea
- Dyspnea
- Embryo-fetal toxicity
- Erythema
- Erythroderma
- Headache
- Hepatic artery thrombosis (HAT)
- Hepatic disorders (including hepatitis and jaundice)
- Hypersensitivity to everolimus active substance, to other rapamycin derivates
- Hypertension
- Infection (bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens). Polyoma virus-associated nephropathy (PVAN), JC virus-associated progressive multiple leukoencephalopathy (PML), fatal infections and sepsis have been reported in patients treated with oral everolimus
- Kidney arterial and venous thrombosis
- Laboratory test alterations (elevations of serum creatinine, proteinuria, hypokalemia, hyperkalemia; hyperglycemia, dyslipidemia including hypercholesterolemia and

[10] Certican‡ UK SmPC, Afinitor‡ UK SmPC, Votubia‡ UK SmPC, Afinitor‡ US label, and Zortress‡ US label. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SmPC/labels.

hypertriglyceridemia; abnormal liver function tests; decreases in hemoglobin, lymphocytes, neutrophils, and platelets)
- Lymphoma and skin cancer
- Male infertility
- Menstrual irregularities
- Nausea
- Nephrotoxicity (in combination with cyclosporine)
- Non-infectious pneumonitis (including interstitial lung disease)
- Oral ulcerations
- Pain
- Pancreatitis
- Pericardial effusion
- Peripheral edema
- Pleural effusion
- Pneumonia
- Pyrexia
- Rash
- Renal failure
- Upper respiratory tract infection
- Urinary tract infection
- Venous thromboembolism
- Vomiting
- Wound healing complications (including wound infections and lymphocele)

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

9.0 XIENCE FAMILY OF CLINICAL TRIALS

The SPIRIT PRIME™ clinical trial was conducted to demonstrate the safety and effectiveness of the XIENCE PRIME EECSS. Given the substantial similarities between the XIENCE PRIME and XIENCE V™ EECSS, clinical trials previously conducted on the XIENCE V stent are also relevant and included below.

9.1 SPIRIT PRIME Clinical Trial

The SPIRIT PRIME clinical trial was designed to demonstrate the safety and effectiveness of the XIENCE PRIME EECSS. This global trial consists of two separate arms, the Core Size Registry and the Long Lesion Registry. One-year results are presented here.

Primary Objective: The objective of the SPIRIT PRIME clinical trial is to evaluate the safety and effectiveness of the XIENCE PRIME EECSS in improving coronary luminal diameter in subjects with symptomatic heart disease due to a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel.

Design: The SPIRIT PRIME clinical trial is a prospective, non-randomized, open-label, multicenter study consisting of two separate arms, the Core Size Registry (stent diameters 2.25, 2.5, 3.0, 3.5, 4.0 mm with stent lengths 8, 18, and 28[11] mm) and the Long Lesion Registry (stent diameters 2.5, 3.0, 3.5, 4.0 mm with stent lengths 33 and 38 mm) in approximately 500 subjects at up to 75 global sites. For clinical trial design purposes, the 28 mm length stent is included in the Core Size Registry because the historical data on XIENCE V EECSS used to develop the comparative performance goal includes stent lengths up to 28 mm. The Long Lesion Registry only includes subjects with at least one 33 and 38 mm length stents as there were limited data on these stent lengths from which to develop a comparative performance goal.

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

Subjects in the Long Lesion Registry were allowed to have: one target lesion treated with the XIENCE PRIME EECSS (stent diameters 2.5 – 4.0 mm with stent lengths 33 or 38 mm) or two target lesions in separate epicardial vessels, treated with two XIENCE PRIME EECSS (stent diameters 2.5 – 4.0 mm with stent lengths 33 or 38 mm) or one XIENCE PRIME EECSS (stent diameters 2.5 – 4.0 mm with stent lengths 33 or 38 mm) and one XIENCE PRIME EECSS (stent diameters 2.25 – 4.0 mm with stent lengths 8, 18, 28 mm). All subjects in the Long Lesion Registry were required to be treated with at least one XIENCE PRIME stent of 33 or 38 mm in length. For both the Core Size Registry and Long Lesion Registry, planned overlap was not allowed; however, overlap was allowed in case of bailout stenting.

The primary endpoint is target lesion failure (TLF) at one year, a composite endpoint of cardiac death, Target Vessel Myocardial Infarction (TV-MI), and Clinically Indicated Target Lesion Revascularization (CI-TLR). The primary endpoint rates of TLF at 1 year (per protocol and per ARC definitions) were compared to a set of pre-specified performance goals (PGs) for both Core Size Registry and Long Lesion Registry as shown below.

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

[11] The 28 mm length stent was studied in the XIENCE PRIME Core Size Registry. The results of the Core Size Registry are presented in *Tables 9.1-2 to 9.1-3*.

Table 9.1-1: Analyses of the Primary Endpoint

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

[1] Performance goal developed based on per protocol-defined MI.
[2] Performance goal developed based on per ARC-defined MI.
* The Core Size Registry includes 2.25 – 4.0 mm stent diameters, 8, 18, 28 mm lengths.
** The Long Lesion Registry includes 2.5 – 4.0 mm stent diameters, 33 and 38 mm stent lengths.

Demographics: In the Core Size Registry, the mean age was 62.70 ± 10.23 years, 70.3% (282/401) were male, 29.7% (119/401) were female and 92.3% (346/375) were white. The average body mass index (BMI) was 30.86 ± 5.83 kg/m^2 and 50.3% (192/382) of subjects were obese, with a BMI ≥ 30. Regarding medical risk factors in the Core Size Registry, 19.2% (77/401) were tobacco users, 76.6% (307/401) were hypertensive requiring medication, and 80.3% (322/401) were hypercholesterolemic requiring medication. There were 11.1% (44/397) of subjects having had a prior cardiac intervention on the target vessel and 23.0% (91/395) had a prior MI. In addition, there were 45.6% (183/401) of subjects with stable angina and 24.9% (100/401) of subjects with unstable angina. Furthermore, the Core Size Registry consisted of 34.9% (140/401) diabetics, 29.9% (120/401) diabetics requiring medication and 3.5% (14/401) diabetics requiring diet and exercise only.

In the Long Lesion Registry, the mean age was 63.46 ± 9.44 years, 62.5% (65/104) were male, 37.5% (39/104) were female and 91.7% (88/96) were white. The average body mass index (BMI) was 30.67 ± 5.84 kg/m^2, and 49.5% (50/101) of subjects were obese, with a BMI ≥ 30. Regarding medical risk factors in the Long Lesion Registry, 26.9% (28/104) were tobacco users, 75.0% (78/104) were hypertensive requiring medication, and 80.8% (84/104) were hypercholesterolemic requiring medication. There were 11.8% (12/102) of subjects having had a prior cardiac intervention on the target vessel and 22.5% (23/102) had a prior MI. In addition, there were 49.0% (51/104) of subjects with stable angina and 23.1% (24/104) of subjects with unstable angina. Furthermore, the Long Lesion Registry consisted of 35.6% (37/104) diabetics, 31.7% (33/104) diabetics requiring medication and 1.9% (2/104) diabetics requiring diet and exercise only.

Results: The results are presented in *Table 9.1-2* to *Table 9.1-4*. These analyses are based on the Full Analysis Set (FAS). The FAS population is defined as subjects who have received at least one of the following: the core size XIENCE PRIME™ EECSS (stent diameters 2.25 – 4.0 mm with stent lengths 8, 18, 28 mm) or the XIENCE PRIME™ LL EECSS (stent diameters 2.5 – 4.0 mm with stent lengths 33 or 38 mm), including bailout. SPIRIT PRIME Core Size and Long Lesion Registries met all pre-specified PGs with statistical significance. The observed TLF rate at one year was 4.5% (18/399) (per protocol-defined MI) and 6.5% (26/399) (per ARC-defined MI) in the Core Size Registry, and 7.7% (8/104) (per protocol-defined MI) and 12.5% (13/104) (per ARC-defined MI) in the Long Lesion Registry. At the three-year follow-up visit, the follow-up rate for the CSR was 377 (94.0%) and 99 (95.2%) for the LLR. At 3 years, the observed TLF rate was 8.5% (33/390) (per protocol-defined MI) and 10.8% (42/390) (per ARC-defined MI) in the Core Size Registry, and 9.6% (10/104) (per protocol-defined MI) and 14.4% (15/104) (per ARC-defined MI) in the Long Lesion Registry. In the SPIRIT PRIME clinical trial, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 12 months post-procedure (75 mg per day). Aspirin was administered pre-procedure and continued through 5 years (a minimum of 80 mg per day) to reduce thrombosis risk. At 1 year, dual antiplatelet therapy compliance in the Core Size Registry was 92.8% (360/388) and in the Long Lesion Registry was 89.0% (89/100). Upon subject completion of the study, physicians recommended that the subject remain on the aspirin regimen indefinitely.

Table 9.1-2: SPIRIT PRIME Primary Endpoint Results

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

Notes:
- N is the total number of subjects.
- Population for SPIRIT PRIME consists of those subjects who were treated with at least one XIENCE PRIME stent and had cardiac enzyme data between 8-hour post-index procedure and hospital discharge.
- TLF includes cardiac death, target vessel MI and clinically indicated TLR.
- Time frame includes follow-up window (365 + 28 days).

[1] One-sided p-value against pre-specified performed goals, to be compared at a 0.05 significance level.
[§] Performance Goal developed based on per protocol-defined MI.
[#] Performance Goal developed based on per ARC-defined MI.
* The Core Size Registry includes 2.25 – 4.0 mm stent diameters, 8, 18, 28 mm lengths.
** The Long Lesion Registry includes 2.5 – 4.0 mm stent diameters, 33 and 38 mm stent lengths.

Table 9.1-3: SPIRIT PRIME Core Size Registry Clinical Results*

	Outcomes at 3 Years Core Size Registry* (N = 401)
Composite Effectiveness and Safety	
TLF (per protocol)	8.5% (33/390)
TLF (per ARC)	10.8% (42/390)
Effectiveness	
CI-TLR	5.4% (21/390)
CI-TLR, CABG	1.0% (4/390)
CI-TLR, PCI	4.6% (18/390)
CI-TVR	9.5% (37/390)
Safety	
All Death	3.1% (12/390)
Cardiac Death	0.8% (3/390)
Vascular Death	0.5% (2/390)
Non-Cardiac Death	1.8% (7/390)
Target Vessel MI (per protocol)	2.6% (10/390)
Target Vessel QMI (per protocol)	0.3% (1/390)
Target Vessel NQMI (per protocol)	2.3% (9/390)
All MI (per protocol)	3.1% (12/390)
QMI (per protocol)	1.0% (4/390)
NQMI (per protocol)	2.6% (10/390)
Target Vessel MI (per ARC)	6.2% (24/390)
Target Vessel QMI (per ARC)	0.3% (1/390)
Target Vessel NQMI (per ARC)	5.9% (23/390)
All MI (per ARC)	7.9% (31/390)
QMI (per ARC)	1.0% (4/390)
NQMI (per ARC)	7.4% (29/390)
Cardiac Death or All protocol MI	3.8% (15/390)
Cardiac Death or All ARC MI	8.7% (34/390)
ARC Definite+Probable Stent Thrombosis	
Cumulative through 3 years	0.8% (3/380)
Acute / Subacute (0 – 30 days)	0.5% (2/401)
Late (31 days – 1 year)	0.0% (0/399)
Very Late (1 – 3 years)	0.3% (1/379)

Notes:

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

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

Table 9.1-4: SPIRIT PRIME Long Lesion Registry Clinical Results

	Outcomes at 3 Years Long Lesion Registry* (N = 104)
Composite Effectiveness and Safety	
TLF (per protocol)	9.6% (10/104)
TLF (per ARC)	14.4% (15/104)
Effectiveness	
CI-TLR	4.8% (5/104)
CI-TLR, CABG	1.0% (1/104)
CI-TLR, PCI	4.8% (5/104)
CI-TVR	7.7% (8/104)
Safety	
All Death	2.9% (3/104)
Cardiac Death	0.0% (0/104)
Vascular Death	0.0% (0/104)
Non-Cardiac Death	2.9% (3/104)
Target Vessel MI (per protocol)	4.8% (5/104)
Target Vessel QMI (per protocol)	1.9% (2/104)
Target Vessel NQMI (per protocol)	2.9% (3/104)
All MI (per protocol)	5.8% (6/104)
QMI (per protocol)	2.9% (3/104)
NQMI (per protocol)	3.8% (4/104)
Target Vessel MI (per ARC)	10.6% (11/104)
Target Vessel QMI (per ARC)	1.9% (2/104)
Target Vessel NQMI (per ARC)	8.7% (9/104)
All MI (per ARC)	11.5% (12/104)
QMI (per ARC)	2.9% (3/104)
NQMI (per ARC)	9.6% (10/104)
Cardiac Death or All protocol MI	5.8% (6/104)
Cardiac Death or All ARC MI	11.5% (12/104)
ARC Definite+Probable Stent Thrombosis	
Cumulative through 3 years	0.0% (0/99)
Acute / Subacute (0 – 30 days)	0.0% (0/104)
Late (31 days – 1 year)	0.0% (0/104)
Very Late (1–3 years)	0.0% (0/99)

Notes:

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

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

Study Strengths and Limitations: The SPIRIT PRIME study was a prospective, open-label, multicenter study with two separate arms. All event adjudications were performed by an independent Clinical Event Committee (CEC) with 100% site-reported adjudicable events being source-verified. The study provides important information on the clinical outcomes in patients with long lesions and demonstrates the safety and effectiveness of both the core size and 33 mm and 38 mm XIENCE PRIME stents. The study is limited by being a small study with no head-to-head comparison with other DES platforms. In addition, due to the small population size, subgroup analysis can at best be considered exploratory.

9.2 SPIRIT III Pivotal Clinical Trial

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V™ stent to the TAXUS‡ Express stent (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consists of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy. Enrollment is complete in the RCT, the 4.0 mm diameter stent arm, and the Japan arm.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subject subset derived from the RCT[12] and Japan non-randomized arm (see *Section 6.2 Pharmacokinetics*). Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan). Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level at pre-determined sites.

9.2.1 SPIRIT III Randomized Clinical Trial (RCT)

Primary Objective: The objective of the SPIRIT III RCT was to demonstrate the non-inferiority in in-segment late loss at 240 days and target vessel failure at 270 days of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with a reference vessel diameter (RVD) ≥ 2.5 mm to ≤ 3.75 mm.

Design: The SPIRIT III RCT was a prospective, 2:1 (XIENCE V:TAXUS) randomized, active-controlled, single-blinded, parallel, multicenter, non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V EECSS arm, treatment of a target lesion > 22 mm and ≤ 28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent (see *Section 5.3 Use in Conjunction with Other Procedures*). In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

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

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

All subjects had clinical follow-up at 30, 180, and 270 days and annually from 1 to 5 years. A pre-specified subgroup of 564 subjects had angiographic follow-up at 240 days. Of these 564, 240 subjects had IVUS at baseline and 240 days. Subjects that received a bailout stent also had IVUS at baseline and angiographic and IVUS follow-up at 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age was 63.2 years for the XIENCE V EECSS arm and 62.8 for the TAXUS arm. The XIENCE V EECSS arm had 70.1% (469/669) males and the TAXUS arm had 65.7% (218/332) males. The XIENCE V EECSS arm had 32.3% (215/666) of subjects with prior cardiac interventions and the TAXUS arm had 29.5% (98/332). The XIENCE V EECSS arm had 29.6% (198/669) of subjects with a history of diabetes and the TAXUS arm had 27.9% (92/330). The XIENCE V EECSS arm had 15.4% (103/669) of subjects with a lesion treated in two vessels and TAXUS had 15.4% (51/332). The XIENCE V EECSS arm had 8.1% (54/669) of subjects with planned stent overlap. The XIENCE V EECSS arm had 8.6% (57/666) of subjects with a history of prior CABG while the TAXUS arm had 3.6% (12/332) ($p = 0.0033$). The XIENCE V EECSS arm had 18.7% (123/657) of subjects with a history of unstable angina while the TAXUS arm had 25.1% (82/327) ($p = 0.0243$). The remaining subject baseline clinical features were well-matched between the XIENCE V EECSS arm and the TAXUS arm.

Results: The results are presented in *Table 9.2.1-1*: *SPIRIT III RCT Primary Endpoint Results*, *Table 9.2.1-2: SPIRIT III RCT Clinical Results*, *Table 9.2.1-3: SPIRIT III 8-Month Angiographic and IVUS Results*, *Figure 9.2.1-1: SPIRIT III: Kaplan Meier Time-to-Event Curve for Target Vessel Failure through 5 Years* and *Table 9.2.1-4: SPIRIT III RCT ARC-Defined Definite+Probable Stent Thrombosis through 5 Years*. These analyses are based on the intent-to-treat population.

The co-primary endpoint of in-segment late loss at 240 days was met with measurements of 0.14 ± 0.41 mm (301) for the XIENCE V EECSS arm and 0.28 ± 0.48 mm (134) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a pre-specified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-segment late loss at 240 days ($p = 0.0037$).

The co-primary endpoint of ischemia-driven TVF through 284 days was met with rates of 7.6% (50/660) for the XIENCE V EECSS arm and 9.7% (31/320) for the TAXUS arm ($p < 0.0001$ for non-inferiority).

Table 9.2.1-1: SPIRIT III RCT Primary Endpoint Results

Measurements	XIENCE V (N = 669) (M = 376)	TAXUS (N = 333) (M = 188)	Difference [95% CI]	Non-Inferiority p-value	Superiority p-value
8-Month[1] Late Loss, In-Segment (mm)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	-0.14 [-0.23, -0.05][2]	< 0.0001[3]	0.0037[4]
9-Month[5] Target Vessel Failure[6]	7.2% (47/657)	9.0% (29/321)	-1.88% [-5.58%, 1.82%][2]	< 0.0001[7]	Not Pre-specified

Notes:

- N is the total number of subjects; M is the total number of analysis lesions for the angiographic group.
- One subject in the SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- Analysis results include 9-month events identified at the 9-month follow-up.

[1] 8-month time frame includes follow-up window (240 + 28 days).
[2] By normal approximation.
[3] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.
[4] Two-sided p-value by superiority test using two-sample T-test, to be compared at a 0.05 significance level.
[5] 9-month time frame includes follow-up window (270 + 14 days).
[6] TVF is defined as hierarchical composite of cardiac death, MI, ischemia-driven TLR and ischemia-driven non-TLR TVR.
[7] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

Table 9.2.1-2: SPIRIT III RCT Clinical Results

	Outcomes at 9 Months			Outcomes at 5 Years (latest available follow-up)		
	XIENCE V (N = 669)	**TAXUS (N = 333)**	**Difference [95% CI][1]**	**XIENCE V (N = 669)**	**TAXUS (N = 333)**	**Difference [95% CI][1]**
Composite Efficacy and Safety						
TVF[2]	7.2% (47/657)	9.0% (29/321)	-2.11% [-5.93%, 1.71%]	20.3% (123/605)	26.6% (76/286)	-6.24% [-12.28%, -0.20%]
MACE[3]	4.6% (30/657)	8.1% (26/321)	-3.75% [-7.26%, -0.24%]	14.4% (87/605)	22.0% (63/286)	-7.65% [-13.21%, -2.09%]
Efficacy						
Ischemia-Driven TLR	2.6% (17/657)	5.0% (16/321)	-2.40% [-5.07%, 0.28%]	8.9% (54/605)	12.9% (37/286)	-4.01% [-8.52%, 0.49%]
TLR, CABG	0.2% (1/657)	0.0% (0/321)	0.15% [Assump. not met]	1.0% (6/605)	1.0% (3/286)	-0.06% [Assump. not met]
TLR, PCI	2.4% (16/657)	5.0% (16/321)	-2.55% [-5.21%, 0.11%]	8.3% (50/605)	11.9% (34/286)	-3.62% [-7.97%, 0.72%]
Ischemia-Driven TVR, Non-TL	3.0% (20/657)	4.0% (13/321)	-1.01% [-3.53%, 1.52%]	8.8% (53/605)	11.9% (34/286)	-3.13% [-7.50%, 1.25%]
Non-TLR TVR, CABG	0.5% (3/657)	0.6% (2/321)	-0.17% [Assump. not met]	1.8% (11/605)	2.4% (7/286)	-0.63% [-2.71%, 1.45%]
Non-TLR TVR, PCI	2.6% (17/657)	3.4% (11/321)	-0.84% [-3.17%, 1.49%]	6.9% (42/605)	9.8% (28/286)	-2.85% [-6.84%, 1.15%]
Safety						
All Death	0.9% (6/658)	0.9% (3/322)	-0.02% [Assump. not met]	6.0% (37/621)	10.3% (31/300)	-4.38% [-8.29%,-0.46%]
Cardiac Death	0.5% (3/658)	0.6% (2/322)	-0.17% [Assump. not met]	2.7% (17/621)	4.3% (13/300)	-1.60% [-4.23%,1.04%]
Non-Cardiac Death	0.5% (3/658)	0.3% (1/322)	0.15% [Assump. not met]	3.2% (20/621)	6.0% (18/300)	-2.78% [-5.80%,0.25%]
MI	2.0% (13/657)	2.5% (8/321)	-0.51% [-2.52%, 1.50%]	4.6% (28/605)	7.0% (20/286)	-2.36% [-5.76%, 1.03%]
QMI	0.2% (1/657)	0.0% (0/321)	0.15% [Assump. not met]	1.0% (6/605)	0.7% (2/286)	0.29% [Assump. not met]
NQMI	1.8% (12/657)	2.5% (8/321)	-0.67% [-2.65%, 1.32%]	3.8% (23/605)	6.3% (18/286)	-2.49% [-5.69%,0.71%]
Cardiac Death or MI	2.4% (16/657)	3.1% (10/321)	-0.68% [-2.92%, 1.56%]	7.1% (43/605)	11.2% (32/286)	-4.08% [-8.27%, 0.11%]
Stent Thrombosis – Protocol Defined	0.5% (3/654)	0.0% (0/320)	0.46% [Assump. not met]	1.7% (10/583)	2.2% (6/269)	-0.52% [-2.57%, 1.54%]
Acute (< 1 day)	0.0% (0/669)	0.0% (0/330)	0.00% [Assump. not met]	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (> 30 days)	0.2% (1/653)	0.0% (0/320)	0.15% [Assump. not met]	1.2% (7/582)	2.2% (6/269)	-1.03% [-3.00%, 0.95%]
Stent Thrombosis – ARC Definite	0.8% (5/652)	0.0% (0/319)	0.77% [Assump. not met]	1.2% (7/582)	0.7% (2/268)	0.46% [Assump. not met]

Notes:

- One subject in the SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- 9-month and 5-year time frames include follow-up window (270 +14 days and 1825 + 28 days, respectively).
- "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.
- Cardiac death is defined as the number of patients experiencing cardiac death through the follow-up time point (the number of patients experiencing cardiac death through the follow-up time point + the number of patients followed through the follow-up time point without cardiac death + the number of patients terminated prior to the follow-up time point who did not experience cardiac death but experienced non-cardiac death, MI, ID or non-ID TLR, or ID or non-ID TVR).

[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity, and is meant for descriptive purposes only.
[2] TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.
[3] MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

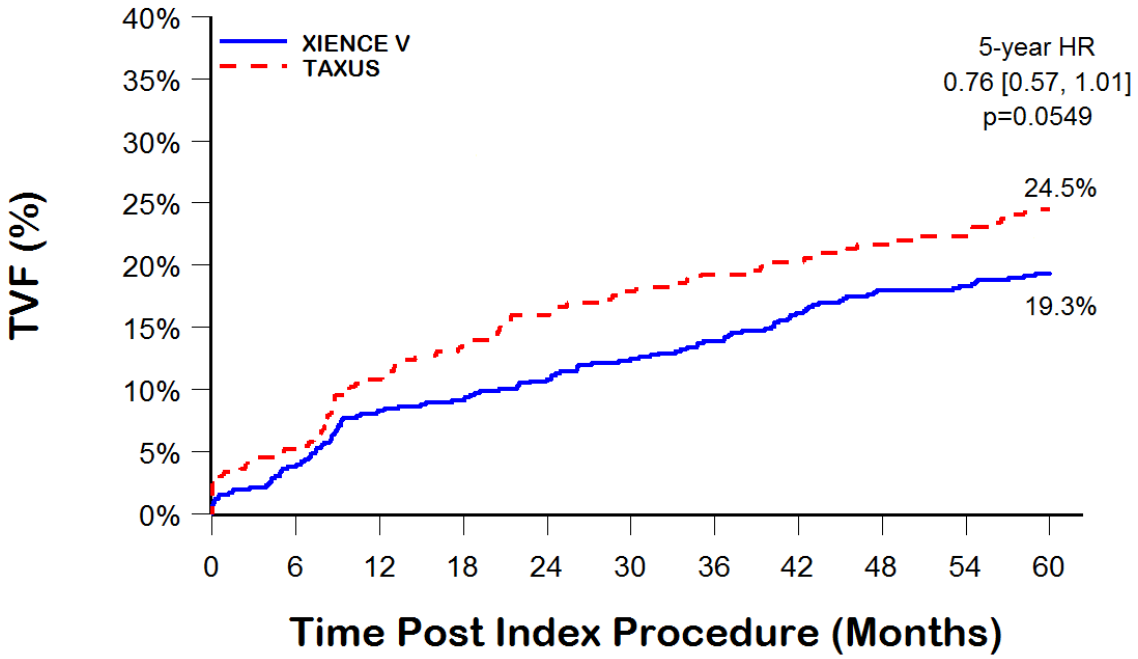
Table 9.2.1-3: SPIRIT III 8-Month Angiographic and IVUS Results

	XIENCE V (N = 376) (M_{ANGIO} = 427) (M_{IVUS} = 181)	TAXUS (N = 188) (M_{ANGIO} = 220) (M_{IVUS} = 93)	Difference [95% CI][1]
Angiographic Results			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD			
Post-Procedure	2.35 ± 0.44 (426)	2.36 ± 0.45 (220)	-0.01 [-0.08, 0.06]
8 Months	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
In-Stent %DS			
Post-Procedure	0.32 ± 8.86 (424)	-0.78 ± 10.65 (220)	1.10 [-0.55, 2.74]
8 Months	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment %DS			
Post-Procedure	13.89 ± 8.04 (425)	13.92 ± 7.20 (220)	-0.03 [-1.26, 1.19]
8 Months	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Late Loss			
In-Stent	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
In-Segment	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04]
Binary Restenosis			
In-Stent	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]
IVUS Results			
Neointimal Volume (mm^3)	10.13 ± 11.46 (101)	20.87 ± 13.51 (41)	-10.74 [-20.92, -0.56]
% Volume Obstruction	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)	-4.30 [-7.72, -0.88]
Incomplete Apposition			
Post-Procedure	34.4% (31/90)	25.6% (11/43)	8.86% [-7.46%, 25.19%]
8 Months	25.6% (23/90)	16.3% (7/43)	9.28% [-4.97%, 23.52%]
Persistent	24.4% (22/90)	14.0% (6/43)	10.49% [-3.15%, 24.13%]
Late Acquired	1.1% (1/90)	2.3% (1/43)	-1.21% [Assump. not met]

Notes:
- N is the total number of subjects; M_{ANGIO} is the total number of lesions in the protocol required angiographic cohort and M_{IVUS} is the total number of lesions in the protocol required IVUS cohort.
- One subject in the SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- 8-month time frame includes follow-up window (240 + 28 days).
- "Assump. not met" means that the assumption of normal approximation was not met due to small sample size or frequency of events.

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

Figure 9.2.1-1: SPIRIT III: Kaplan Meier Time-to-Event Curve for Target Vessel Failure through 5 Years



TVF	Event Free	Event Rate	p-value[1]
XIENCE V	80.7%	19.3%	0.0549
TAXUS	75.5%	24.5%	

Note:
– Time frame includes follow-up window (1825 + 28 days).
[1]p-value based on log rank and not adjusted for multiple comparisons.

Table 9.2.1-4: SPIRIT III RCT ARC-Defined Definite+Probable Stent Thrombosis through 5 Years

	XIENCE V (N = 669)	TAXUS (N = 333)	Difference [95% CI][1]
ARC Definite+Probable Stent Thrombosis (0 days – 5 years)	1.5% (9/582)	1.9% (5/268)	-0.32% [-2.22%, 1.59%]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (31 days – 1 year)	0.5% (3/649)	0.6% (2/317)	-0.17% [Assump. not met]
Very Late (> 1 years)	0.5% (3/580)	1.1% (3/267)	-0.61% [Assump. not met]

Notes:
– One subject in the SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
– Time frame includes follow-up window (1825 + 28 days).
– "Assump. not met" means that assumption of the normal approximation was not met due to small sample size or frequency of events.
[1] Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity, and is meant for descriptive purposes only.

9.2.2 Dual Vessel Treatment in SPIRIT III

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. Subjects requiring both single and dual vessel treatment were included in the SPIRIT III trial; however, there were no pre-specified hypotheses for these patient subgroups.

Table 9.2.2-1 shows the clinical outcomes through 9 months and 5 years in single vessel and dual vessel treated subjects from a post-hoc analysis of SPIRIT III. The number of vessels treated was one of the stratification factors used in the randomization to assure a balance between the XIENCE V and TAXUS treatment arms.

Table 9.2.2-1: Clinical Results in Single and Dual Vessel Treatment through 5 Years (SPIRIT III RCT)

	9 Months				5 Years			
	Single Vessel XIENCE V (N = 566)	**Single Vessel TAXUS (N = 281)**	**Dual Vessel XIENCE V (N = 103)**	**Dual Vessel TAXUS (N = 51)**	**Single Vessel XIENCE V (N = 566)**	**Single Vessel TAXUS (N = 281)**	**Dual Vessel XIENCE V (N = 103)**	**Dual Vessel TAXUS (N = 51)**
TVF	6.3% (35/556)	7.0% (19/271)	11.9% (12/101)	20.0% (10/50)	18.0% (92/510)	22.9% (55/240)	32.6% (31/95)	45.7% (21/46)
Ischemia-Driven TLR	2.3% (13/556)	4.1% (11/271)	4.0% (4/101)	10.0% (5/50)	8.4% (43/510)	11.3% (27/240)	11.6% (11/95)	21.7% (10/46)
Ischemia-Driven TVR, Non-TL	2.7% (15/556)	2.2% (6/271)	5.0% (5/101)	14.0% (7/50)	6.7% (34/510)	8.8% (21/240)	20.0% (19/95)	28.3% (13/46)
All Death	1.1% (6/557)	0.4% (1/271)	0.0% (0/101)	3.9% (2/51)	6.1% (32/523)	9.9% (25/252)	5.1% (5/98)	12.5% (6/48)
Cardiac Death	0.5% (3/557)	0.4% (1/271)	0.0% (0/101)	2.0% (1/51)	2.9% (15/523)	4.0% (10/252)	2.0% (2/98)	6.3% (3/48)
Non-Cardiac Death	0.5% (3/557)	0.0% (0/271)	0.0% (0/101)	2.0% (1/51)	3.3% (17/523)	6.0% (15/252)	3.1% (3/98)	6.3% (3/48)
MI	1.6% (9/556)	1.5% (4/271)	4.0% (4/101)	8.0% (4/50)	3.7% (19/510)	4.6% (11/240)	9.5% (9/95)	19.6% (9/46)
Cardiac Death or MI	2.2% (12/556)	1.8% (5/271)	4.0% (4/101)	10.0% (5/50)	6.5% (33/510)	8.8% (21/240)	10.5% (10/95)	23.9% (11/46)
Stent Thrombosis								
Protocol Defined	0.4% (2/553)	0.0% (0/271)	1.0% (1/101)	0.0% (0/49)	1.2% (6/490)	1.8% (4/226)	4.3% (4/93)	4.7% (2/43)
ARC Definite+Probable	0.7% (4/554)	0.0% (0/271)	2.0% (2/101)	0.0% (0/49)	0.8% (4/488)	1.3% (3/225)	5.3% (5/94)	4.7% (2/43)
ARC Definite	0.4% (2/554)	0.0% (0/271)	2.0% (2/101)	0.0% (0/49)	0.6% (3/488)	0.4% (1/225)	4.3% (4/94)	2.3% (1/43)

Note:
Cardiac death is defined as the number of patients experiencing cardiac death through the follow-up time point / (the number of patients experiencing cardiac death through the follow-up time point + the number of patients followed through the follow-up time point without cardiac death + the number of patients terminated prior to the follow-up time point who did not experience cardiac death but experienced non-cardiac death, MI, ID or non-ID TLR, or ID or non-ID TVR).

9.2.3 SPIRIT III US 4.0 mm Arm

Primary Objective: The objective of the SPIRIT III 4.0 mm arm was to demonstrate the non-inferiority in in-segment late loss at 240 days of the XIENCE V 4.0 mm stent in the treatment of *de novo* lesions with RVD 3.75 to 4.25 mm, compared to the TAXUS arm from the SPIRIT III RCT.

Design: The SPIRIT III 4.0 mm study was a prospective, single-arm, multicenter clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V stent in *de novo* native coronary artery lesions ≤ 28 mm in length with a RVD > 3.75 mm to ≤ 4.25 mm. Seventy-three (73) subjects were enrolled in the SPIRIT III 4.0 mm study arm. For early demonstration of efficacy (in-segment late loss at 240 days), an interim analysis was performed after 69 of the enrolled subjects had completed their scheduled follow-up and after unblinding of the SPIRIT III RCT.

All subjects had clinical follow-up at 30, 180, 240, and 270 days, and annually from 1 to 5 years. In addition, all subjects had angiographic follow-up at 240 days. Intravascular Ultrasound (IVUS) was performed for subjects who received a bailout stent at baseline and 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

Demographics: The mean age in the SPIRIT III 4.0 arm was 61.9 years with 72.5% (50/69) male, 21.7% (15/69) had prior cardiac interventions, and 30.4% (21/69) had a history of diabetes.

Results: The results are presented in *Table 9.2.3-1: SPIRIT III 4.0 mm Primary Endpoint Result, Table 9.2.3-2: SPIRIT III 4.0 mm Clinical Results, Table 9.2.3-3: SPIRIT III 4.0 mm 8-Month Angiographic Results*, and *Table 9.2.3-4: SPIRIT III 4.0 mm ARC-Defined Stent Thrombosis through 5 years*. These analyses were performed on the intent-to-treat population. Although SPIRIT III allowed treatment of two separate epicardial vessels, all subjects in the SPIRIT III 4.0 arm had only one vessel treated. The 5-year follow-up rate for the SPIRIT III 4.0 mm arm was 87.7% (64/73).

The primary endpoint of in-segment late loss at 240 days was met with measurements of 0.17 ± 0.38 mm (49 analysis lesions) for the XIENCE V EECSS 4.0 mm arm and 0.28 ± 0.48 mm (134 analysis lesions) for the TAXUS arm from the SPIRIT III RCT ($p < 0.0001$ for non-inferiority).

Table 9.2.3-1: SPIRIT III 4.0 mm Primary Endpoint Result

Measurements	XIENCE V (M = 69)	TAXUS (M = 188)	Difference [95% CI]	Non-Inferiority p-value
8-Month Late Loss, In-Segment (mm)	0.17 ± 0.38 (49)	0.28 ± 0.48 (134)	-0.11 [-0.24, 0.03][1]	< 0.0001[2]

Notes:
- M is the total number of analysis lesions.
- One subject in the SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- Time frame includes follow-up window (240 + 28 days).

[1] By normal approximation.
[2] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.038 significance level.

Table 9.2.3-2: SPIRIT III 4.0 mm Clinical Results

	Outcomes at 9 Months XIENCE V (N = 73)	Outcomes at 5 Years (Final Follow-up) XIENCE V (N = 73)	Outcomes at 5 Years (Final Follow-up) TAXUS RCT (N = 333)
Composite Efficacy and Safety			
TVF[1]	6.8% (5/73)	11.9% (8/67)	26.6% (76/286)
MACE[2]	6.8% (5/73)	10.4% (7/67)	22.0% (63/286)
Efficacy			
Ischemia-Driven TLR	2.7% (2/73)	4.5% (3/67)	12.9% (37/286)
TLR, CABG	0.0% (0/73)	0.0% (0/67)	1.0% (3/286)
TLR, PCI	2.7% (2/73)	4.5% (3/67)	11.9% (34/286)
Ischemia-Driven TVR, Non-TL	0.0% (0/73)	3.0% (2/67)	11.9% (34/286)
Non-TLR TVR, CABG	0.0% (0/73)	0.0% (0/67)	2.4% (7/286)
Non-TLR TVR, PCI	0.0% (0/73)	3.0% (2/67)	9.8% (28/286)
Safety			
All Death	1.4% (1/73)	8.6% (6/70)	10.3% (31/300)
Cardiac Death	1.4% (1/73)	2.9% (2/70)	4.3% (13/300)
Non-Cardiac Death	0.0% (0/73)	5.7% (4/70)	6.0% (18/300)
MI	4.1% (3/73)	4.5% (3/67)	7.0% (20/286)
QMI	0.0% (0/73)	0.0% (0/67)	0.7% (2/286)
NQMI	4.1% (3/73)	4.5% (3/67)	6.3% (18/286)
Cardiac Death or MI	5.5% (4/73)	7.5% (5/67)	11.2% (32/286)
Stent Thrombosis – Protocol Defined	1.4% (1/72)	3.1% (2/65)	2.2% (6/269)
Acute (≤ 1 day)	1.4% (1/73)	1.4% (1/73)	0.0% (0/330)
Subacute (>1 – 30 days)	0.0% (0/73)	0.0% (0/73)	0.0% (0/330)
Late (> 30 days)	0.0% (0/72)	1.5% (1/65)	2.2% (6/269)
Stent Thrombosis – ARC Definite	0.0% (0/72)	0.0% (0/64)	0.8% (2/268)

Notes:

- 9-month and 5-year time frames include follow-up window (270 +14 days and 1825 + 28 days, respectively).
- Cardiac death is defined as the number of patients experiencing cardiac death through the follow-up time point / (the number of patients experiencing cardiac death through the follow-up time point + the number of patients followed through the follow-up time point without cardiac death + the number of patients terminated prior to the follow-up time point who did not experience cardiac death but experienced non-cardiac death, MI, ID or non-ID TLR, or ID or non-ID TVR).

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

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

Table 9.2.3-3: SPIRIT III 4.0 mm 8-Month Angiographic Results

	XIENCE V (N = 69) (M = 69)
Angiographic Results	
In-Stent MLD	
Post-Procedure	3.46 ± 0.38 (69)
8 Months	3.36 ± 0.46 (49)
In-Segment MLD	
Post-Procedure	3.07 ± 0.43 (69)
8 Months	2.91 ± 0.51 (49)
In-Stent %DS	
Post-Procedure	2.12 ± 10.27 (69)
8 Months	4.78 ± 13.20 (49)
In-Segment %DS	
Post-Procedure	13.42 ± 8.08 (69)
8 Months	17.92 ± 10.83 (49)
Late Loss	
In-Stent	0.12 ± 0.34 (49)
In-Segment	0.17 ± 0.38 (49)
Binary Restenosis	
In-Stent	0.0% (0/49)
In-Segment	2.0% (1/49)

Notes:
- N is the total number of subjects; M is the total number of lesions at baseline.
- 8-month time frame includes follow-up window (240 + 28 days).

Table 9.2.3-4: SPIRIT III 4.0 mm ARC-Defined Stent Thrombosis through 5 Years

	XIENCE V (N = 73)
ARC Definite+Probable Stent Thrombosis (0 days – 5 years)	0.0% (0/64)
Acute (≤ 1 day)	0.0% (0/73)
Subacute (>1 – 30 days)	0.0% (0/73)
Late (31 days – 1 year)	0.0% (0/72)
Very Late (>1 year)	0.0% (0/64)
ARC Definite Stent Thrombosis (0 days – 5 years)	0.0% (0/64)

Note:
- Time frame includes follow-up window (1825 + 28 days).

9.3 SPIRIT IV Clinical Trial

The SPIRIT IV clinical study was designed to confirm the safety and efficacy of the XIENCE V stent when compared to the TAXUS Express stent[13] (TAXUS stent). This randomized controlled trial (RCT) was conducted in the United States (US).

9.3.1 SPIRIT IV Randomized Clinical Trial

Primary Objective: The objective of the SPIRIT IV clinical trial was to determine the safety and effectiveness of the XIENCE V stent for the treatment of subjects with up to three *de novo* coronary artery lesions (maximum of two lesions per epicardial vessel).

Design: The SPIRIT IV clinical trial was a prospective, 2:1 randomized (XIENCE V:TAXUS), active-controlled, single-blinded, multicenter evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to three *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 4.25 mm. Subjects were stratified by diabetes mellitus (diabetic vs. non-diabetic) and lesion characteristics (complex vs. non-complex). Complex lesion characteristics included triple vessel treatment, or dual lesions per vessel treatment, or lesions involving RCA-aorto-ostial locations, or bifurcations lesions. The SPIRIT IV clinical trial was designed to enroll 3,690 subjects at up to 80 sites in the US.

The primary endpoint was target lesion failure (TLF) at 1 year. The major secondary endpoints were ischemia-driven TLR at 1 year and the composite of cardiac death or target vessel MI at 1 year. Formal non-inferiority and superiority testing were planned for the primary and the two major secondary endpoints. To control the familywise Type I error rate, all non-inferiority and superiority hypotheses were tested following a fixed sequence.

The XIENCE V stents used in the SPIRIT IV trial included stents 2.5, 3.0, and 3.5 mm in diameter, and 8, 18 and 28 mm in length. In the XIENCE V EECSS arm, treatment of target lesions > 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 (see *Section 5.3 Use in Conjunction with Other Procedures*). In the TAXUS arm, the treatment strategy for lesions > 22 mm and ≤ 28 mm was recommended to be in accordance to the TAXUS Directions for Use (DFU) at the time of enrollment; these lesions were treated with single 32 mm TAXUS stent or planned overlapping TAXUS stents.

Subjects were evaluated at 30, 180, and 270 days following the index procedure. Follow-up has been performed through 3 years, completing the trial.

According to the guidelines from the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI), following the index procedure, all subjects were to be maintained on 75 mg clopidogrel bisulfate daily for 12 months if subjects were not at high risk for bleeding and ≥ 80 mg of aspirin daily throughout the length of the trial (3 years).

Demographics: The mean age was 63.3 years for both the XIENCE V EECSS arm and the TAXUS arm. The XIENCE V EECSS arm had 67.7% (1665/2458) males and the TAXUS arm had 67.8% (833/1229) males. The XIENCE V EECSS arm had 31.5% (772/2450) of subjects with prior cardiac interventions and the TAXUS arm had 30.7% (376/1224). The XIENCE V EECSS arm had

[13] Of the 1,229 subjects enrolled in the TAXUS arm, 1 subject received one TAXUS Liberté stent.

32.0% (786/2455) of subjects with a history of diabetes and the TAXUS arm had 32.5% (399/1228). The XIENCE V EECSS arm had 24.8% (609/2458) of subjects with two or more lesions treated and TAXUS had 25.3% (311/1229). The XIENCE V EECSS arm had 9.7% (239/2458) of subjects with planned stent overlap. The TAXUS arm had 8.1% (99/1229)[14] of subjects with planned stent overlap and 4.5% (55/1229) of subjects treated with single 32 mm TAXUS stent only. The XIENCE V EECSS arm had 27.7% (669/2416) of subjects with a history of unstable angina while the TAXUS arm had 28.9% (347/1202). The remaining subject baseline clinical features were well-matched between the XIENCE V EECSS arm and the TAXUS arm.

Results: The results are presented in *Table 9.3.1-1: SPIRIT IV Primary and Major Secondary Endpoint Results, Table 9.3.1-2: SPIRIT IV Clinical Results through 3 Years, Figure 9.3.1-1: SPIRIT IV: Kaplan Meier Time-to-Event Curve for TLF through 3 Years, Figure 9.3.1-2: SPIRIT IV: Kaplan Meier Time-to-Event Curve for ID-TLR through 3 Years*, and *Figure 9.3.1-3: SPIRIT IV: Kaplan Meier Time-to-Event Curve for Cardiac Death or Target Vessel MI through 3 Years*. These analyses are based on the intent-to-treat population. At the three-year visit, the follow-up rate for the XIENCE V EECSS arm was 91.8% (2257) and 89.1% (1095) for the TAXUS arm.

Primary Endpoint Analysis (*Table 9.3.1-1*): The primary endpoint was met with TLF rates at 1 year of 4.0% (97/2416) for the XIENCE V EECSS arm and 6.8% (81/1195) for the TAXUS arm ($p < 0.0001$ for non-inferiority). In a pre-specified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent in terms of the primary endpoint of TLF at 1 year ($p_{Sup} = 0.0004$).

Major Secondary Endpoint Analysis (*Table 9.3.1-1*): The major secondary endpoint of ID-TLR was shown to be statistically non-inferior for the XIENCE V stent compared to the TAXUS stent. The ID-TLR rate through 1 year was 2.3% (56/2416) for the XIENCE V EECSS arm and 4.6% (55/1195) for the TAXUS arm ($p < 0.0001$ for non-inferiority). The XIENCE V EECSS arm also showed non-inferiority to the TAXUS arm in terms of the composite endpoint of cardiac death or target vessel MI with rates of 2.2% (53/2416) for the XIENCE V EECSS arm and 3.2% (38/1195) for the TAXUS arm ($p < 0.0001$ for non-inferiority).

In a pre-specified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent in terms of ID-TLR at 1 year ($p_{Sup} = 0.0003$). The rate of composite of cardiac death or target vessel MI was numerically lower in patients treated with the XIENCE V EECSS compared to the TAXUS PECSS ($p_{Sup} = 0.09$).

[14] Includes 6 patients who received planned overlapping TAXUS stents as well as single 32 mm TAXUS stent in two different lesions.

Table 9.3.1-1: SPIRIT IV Primary and Major Secondary Endpoint Results

Primary Endpoint	XIENCE V (N = 2458)	TAXUS (N = 1229)	Difference [Upper 1-Sided 97.5% CL]	Non-Inferiority p-value	Superiority p-value
1 Year TLF	4.0% (97/2416)	6.8% (81/1195)	-2.76% [-1.14%][1]	< 0.0001[2]	0.0004[3]
Major Secondary Endpoints	**XIENCE V (N = 2458)**	**TAXUS (N = 1229)**	**Difference [Upper 1-Sided 95% CL]**	**Non-Inferiority p-value**	**Superiority p-value**
1 Year ID-TLR	2.3% (56/2416)	4.6% (55/1195)	-2.28% [-1.17%][1]	< 0.0001[4]	0.0003[3]
1 Year Cardiac Death or Target Vessel MI	2.2% (53/2416)	3.2% (38/1195)	-0.99% [-0.02%][1]	< 0.0001[4]	0.09[3]

Notes:
- N is the total number of subjects.
- TLF includes cardiac death, target vessel MI (per protocol definition) and ischemia-driven TLR.
- Time frame includes follow-up window (365 + 28 days).

[1] By normal approximation.
[2] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 3.1%, to be compared at a 0.025 significance level.
[3] Two-sided p-value by superiority test using Fisher's exact test, to be compared at a 0.05 significance level.
[4] One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 2.1%, to be compared at a 0.05 significance level.

Table 9.3.1-2: SPIRIT IV Clinical Results through 3 Years

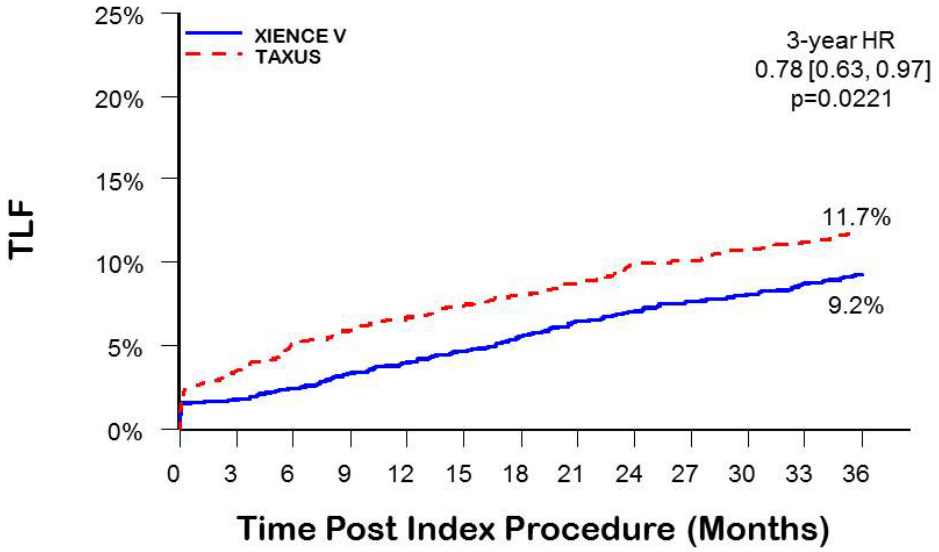
	Outcomes at 1 Year			Outcomes at 3 Years (final follow-up)		
	XIENCE V (N = 2458)	TAXUS (N = 1229)	Difference [95% CI] [1]	XIENCE V (N = 2458)	TAXUS (N = 1229)	Difference [95% CI] [1]
Composite Efficacy and Safety						
TLF	4.0% (97/2416)	6.8% (81/1195)	-2.76% [-4.39%, -1.14%]	9.5% (223/2348)	11.9% (138/1158)	-2.42% [-4.63%, -0.21%]
TVF	5.5% (134/2416)	7.7% (92/1195)	-2.15% [-3.92%, -0.39%]	13.3% (312/2348)	14.5% (168/1158)	-1.22% [-3.67%, 1.23%]
Efficacy						
Ischemia-Driven TLR	2.3% (56/2416)	4.6% (55/1195)	-2.28% [-3.62%, -0.95%]	6.3% (148/2348)	7.9% (92/1158)	-1.64% [-3.48%, 0.20%]
TLR, CABG	0.4% (9/2416)	0.4% (5/1195)	-0.05% [-0.49%, 0.39%]	0.8% (18/2348)	0.9% (10/1158)	-0.10% [-0.74%, 0.54%]
TLR, PCI	2.0% (48/2416)	4.3% (51/1195)	-2.28% [-3.56%, -1.01%]	5.7% (134/2348)	7.5% (87/1158)	-1.81% [-3.59%, -0.02%]
Ischemia-Driven TVR	3.8% (93/2416)	5.7% (68/1195)	-1.84% [-3.36%, -0.32%]	10.1% (238/2348)	10.6% (123/1158)	-0.49% [-2.64%, 1.67%]
Safety						
All Death	1.0% (25/2416)	1.3% (15/1195)	-0.22% [-0.97%, 0.53%]	3.4% (81/2348)	5.2% (60/1158)	-1.73% [-3.21%, -0.26%]
Cardiac Death	0.4% (10/2416)	0.4% (5/1195)	-0.00% [-0.45%, 0.44%]	1.4% (34/2348)	1.9% (22/1158)	-0.45% [-1.37%, 0.47%]
Non-Cardiac Death	0.6% (15/2416)	0.8% (10/1195)	-0.22% [-0.82%, 0.39%]	2.0% (47/2348)	3.3% (38/1158)	-1.28% [-2.45%, -0.11%]
Target Vessel MI	1.8% (44/2416)	2.9% (35/1195)	-1.11% [-2.20%, -0.01%]	2.8% (65/2348)	4.1% (48/1158)	-1.38% [-2.70%, -0.05%]
Cardiac Death or Target Vessel MI	2.2% (53/2416)	3.2% (38/1195)	-0.99% [-2.14%, 0.17%]	4.1% (97/2348)	5.5% (64/1158)	-1.40% [-2.94%, 0.15%]
All MI	1.9% (45/2416)	3.1% (37/1195)	-1.23% [-2.35%, -0.11%]	3.1% (73/2348)	4.7% (55/1158)	-1.64% [-3.05%, -0.23%]
QMI	0.1% (3/2416)	0.4% (5/1195)	-0.29% [Assump. not met]	0.3% (6/2348)	0.9% (11/1158)	-0.69% [-1.29%, -0.10%]
NQMI	1.7% (42/2416)	2.8% (33/1195)	-1.02% [-2.09%, 0.04%]	2.9% (67/2348)	4.0% (46/1158)	-1.12% [-2.43%, 0.19%]
Cardiac Death or MI	2.2% (54/2416)	3.3% (39/1195)	-1.03% [-2.20%, 0.14%]	4.5% (105/2348)	6.0% (70/1158)	-1.57% [-3.18%, 0.03%]
Protocol-Defined Stent Thrombosis (Cumulative)	0.17% (4/2389)	0.85% (10/1181)	-0.68% [Assump. not met]	0.79% (18/2266)	1.99% (22/1104)	-1.20% [-2.10%, -0.30%]
Acute / Subacute (0 – 30 days)	0.12% (3/2451)	0.57% (7/1221)	-0.45% [Assump. not met]	0.12% (3/2451)	0.57% (7/1221)	-0.45% [Assump. not met]
Late (> 30 days)	0.04% (1/2389)	0.34% (4/1181)	-0.30% [Assump. not met]	0.62% (14/2265)	1.45% (16/1103)	-0.83% [-1.61%, -0.06%]
ARC Definite+Probable Stent Thrombosis (Cumulative)	0.29% (7/2391)	1.10% (13/1181)	-0.81% [-1.44%, -0.17%]	0.62% (14/2263)	1.73% (19/1098)	-1.11% [-1.95%, -0.28%]
Early (0 – 30 days)	0.16% (4/2451)	0.74% (9/1221)	-0.57% [Assump. not met]	0.16% (4/2451)	0.74% (9/1221)	-0.57% [Assump. not met]
Late (31 days – 1 year)	0.13% (3/2391)	0.42% (5/1181)	-0.30% [Assump. not met]	0.13% (3/2385)	0.42% (5/1183)	-0.30% [Assump. not met]
Very late (> 1 year)	-	-	-	0.31% (7/2260)	0.55% (6/1095)	-0.24% [-0.73%, 0.26%]
ARC Definite Stent Thrombosis (Cumulative)	0.25% (6/2391)	0.85% (10/1181)	-0.60% [-1.16%, -0.04%]	0.49% (11/2263)	1.28% (14/1098)	-0.79% [-1.51%, -0.07%]

Notes:

- 1-year and 3-year time frames include follow-up window (365 + 28 days and 1095 ± 28 days, respectively).
- TLF is defined as a hierarchical composite of cardiac death, target vessel MI (per protocol definition), and ischemic-driven TLR.
- TVF is defined as a hierarchical composite of cardiac death, all MI (per protocol definition), ischemic-driven TLR and ischemic-driven non-TLR TVR.

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

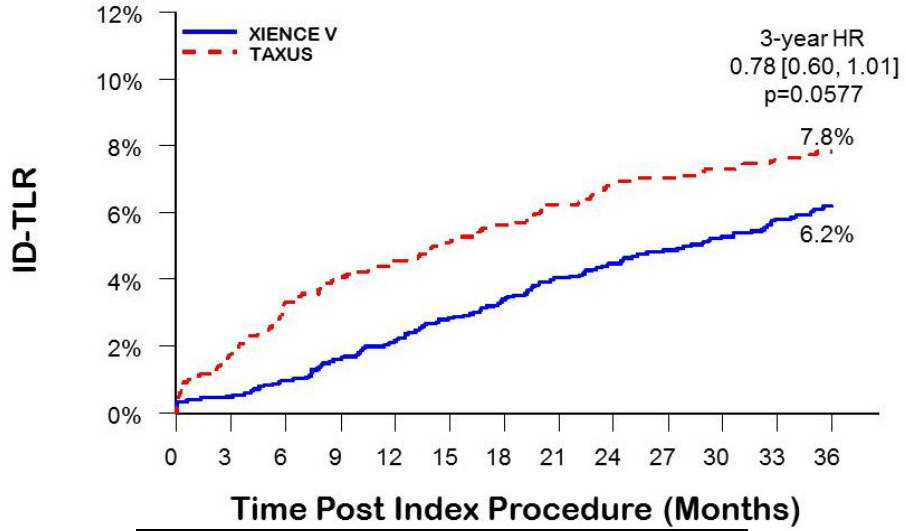
Figure 9.3.1-1: SPIRIT IV: Kaplan Meier Time-to-Event Curve for TLF through 3 Years



TLF	Event Free	Event Rate	p-value[1]
XIENCE V	90.8%	9.2%	0.0221
TAXUS	88.3%	11.7%	

Note:
– Time frame includes follow-up window (1095 + 28 days).
[1]p-value based on log rank and not adjusted for multiple comparisons.

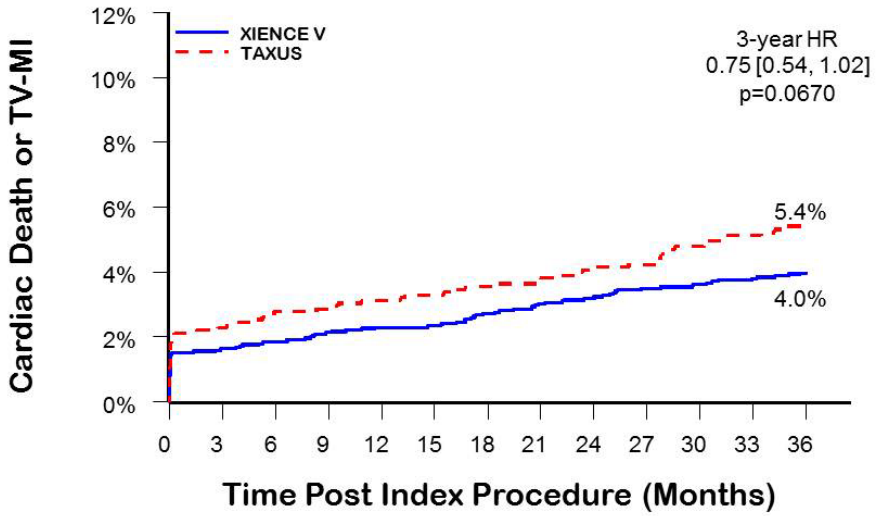
Figure 9.3.1-2: SPIRIT IV: Kaplan Meier Time-to-Event Curve for ID-TLR through 3 Years



ID-TLR	Event Free	Event Rate	p-value[1]
XIENCE V	93.8%	6.2%	0.0577
TAXUS	92.2%	7.8%	

Note:
– Time frame includes follow-up window (1095 + 28 days).
[1]p-value based on log rank and not adjusted for multiple comparisons.

Figure 9.3.1-3: SPIRIT IV: Kaplan Meier Time-to-Event Curve for Cardiac Death or Target Vessel MI through 3 Years



Cardiac Death or TV-MI	Event Free	Event Rate	p-value[1]
XIENCE V	96.0%	4.0%	0.0670
TAXUS	94.6%	5.4%	

Note:
– Time frame includes follow-up window (1095 + 28 days).
[1]p-value based on log rank and not adjusted for multiple comparisons.

9.3.2 Multiple Vessel Treatment in SPIRIT IV

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. The SPIRIT IV trial allowed for up to 3 vessels to be treated. In the XIENCE V EECSS arm, 389 subjects received dual vessel treatment while 19 subjects received triple vessel treatment. In the TAXUS arm, 218 subjects received dual vessel treatment while 5 subjects received triple vessel treatment. There were no pre-specified hypotheses for patients in the single vessel treatment and multiple vessel treatment subgroups.

Table 9.3.2-1 shows the clinical outcomes through 3 years in single- and multiple-vessel treated subjects from a post-hoc analysis of SPIRIT IV.

Table 9.3.2-1: Clinical Results in Single and Multiple Vessel Treatment through 3 Years (SPIRIT IV)

	Outcomes at 1 Year				Outcomes at 3 Years (final follow-up)			
	Single Vessel XIENCE V (N = 2050)	**Single Vessel TAXUS (N = 1006)**	**Multiple Vessel XIENCE V (N = 408)**	**Multiple Vessel TAXUS (N = 223)**	**Single Vessel XIENCE V (N = 2050)**	**Single Vessel TAXUS (N = 1006)**	**Multiple Vessel XIENCE V (N = 408)**	**Multiple Vessel TAXUS (N = 223)**
TLF	3.8% (76/2014)	6.0% (59/983)	5.2% (21/402)	10.4% (22/212)	8.3% (163/1959)	11.0% (105/952)	15.4% (60/389)	16.0% (33/206)
Ischemia-Driven TLR	2.1% (42/2014)	4.0% (39/983)	3.5% (14/402)	7.5% (16/212)	5.3% (104/1959)	7.0% (67/952)	11.3% (44/389)	12.1% (25/206)
Ischemia-Driven TVR, Non-TL	1.9% (38/2014)	2.0% (20/983)	4.0% (16/402)	4.2% (9/212)	4.6% (91/1959)	5.0% (48/952)	10.5% (41/389)	7.3% (15/206)
All Death	0.9% (18/2014)	1.3% (13/983)	1.7% (7/402)	0.9% (2/212)	3.1% (60/1959)	5.6% (53/952)	5.4% (21/389)	3.4% (7/206)
Cardiac Death	0.3% (6/2014)	0.4% (4/983)	1.0% (4/402)	0.5% (1/212)	1.2% (24/1959)	2.0% (19/952)	2.6% (10/389)	1.5% (3/206)
Non-Cardiac Death	0.6% (12/2014)	0.9% (9/983)	0.7% (3/402)	0.5% (1/212)	1.8% (36/1959)	3.6% (34/952)	2.8% (11/389)	1.9% (4/206)
Target Vessel MI	1.8% (37/2014)	2.3% (23/983)	1.7% (7/402)	5.7% (12/212)	2.7% (53/1959)	3.7% (35/952)	3.1% (12/389)	6.3% (13/206)
Cardiac Death or Target Vessel MI	2.1% (43/2014)	2.6% (26/983)	2.5% (10/402)	5.7% (12/212)	3.9% (77/1959)	5.3% (50/952)	5.1% (20/389)	6.8% (14/206)
Stent Thrombosis								
Protocol Defined	0.15% (3/1996)	0.51% (5/971)	0.25% (1/393)	2.38% (5/210)	0.79% (15/1900)	1.88% (17/903)	0.82% (3/366)	2.49% (5/201)
ARC Definite+Probable	0.20% (4/1996)	0.72% (7/971)	0.76% (3/395)	2.86% (6/210)	0.47% (9/1895)	1.45% (13/897)	1.36% (5/368)	2.99% (6/201)
ARC Definite	0.20% (4/1990)	0.51% (5/972)	0.51% (2/395)	2.37% (5/211)	0.47% (9/1895)	1.00% (9/897)	0.54% (2/368)	2.49% (5/201)

Notes:
- 1-year and 3-year time frames include follow-up window (365 + 28 days and 1095 ± 28 days, respectively).
- Multiple vessel subgroup included subjects having two or more vessels treated.
- There were 24 triple vessel treated subjects in SPIRIT IV; of those, 19 were XIENCE V subjects and 5 were TAXUS subjects.

Study Strengths and Limitations: The SPIRIT IV trial was a prospective, randomized, active-controlled, single-blinded, multicenter evaluation of the XIENCE V stent compared to the TAXUS Express stent and was designed to enroll 3,690 subjects in the US. With a large sample size and high data quality, the study provides important safety and effectiveness information on clinical outcomes in a more complex population than those in SPIRIT III. In spite of the large population and less restrictive enrollment criteria however, subgroup analyses from SPIRIT IV are considered exploratory.

9.4 SPIRIT Small Vessel Registry

Objective: The objective of the SPIRIT SV Registry trial was to evaluate the safety and effectiveness of the 2.25 mm XIENCE V EECSS in improving coronary luminal diameter in subjects with ischemic heart disease due to a maximum of two *de novo* native coronary artery lesions in small vessels, each in a different epicardial vessel.

Design: The SPIRIT SV trial enrolled a total of 150 subjects at 33 sites. Additionally, there was an angiographic cohort of 69 subjects who received the 2.25 mm XIENCE V EECSS. Subjects enrolled in the SPIRIT SV trial were allowed to have: 1) one target lesion (treated with one 2.25 mm XIENCE V EECSS), 2) two target lesions (treated with two 2.25 mm XIENCE V EECSS) in separate epicardial vessels, or 3) one target lesion (treated with one 2.25 mm XIENCE V EECSS) and one non-target lesion (treated with commercial sizes of XIENCE V EECSS) in separate epicardial vessels. Planned overlap was allowed for both the target and non-target lesions only with commercial sizes of XIENCE V EECSS. Bailout was allowed with a commercial XIENCE V or 2.25 mm XIENCE V EECSS. The protocol-required RVD for the target lesion was ≥ 2.25 mm to < 2.50 mm and the lesion length was ≤ 28 mm. The 2.25 mm XIENCE V EECSS was available in stent lengths of 8, 18 and 28 mm. The non-target lesion could be treated by the commercial XIENCE V EECSS with a RVD of ≥ 2.5 mm to ≤ 4.25 mm. The commercial XIENCE V EECSS was available in stent diameters of 2.5, 2.75, 3.0, 3.5, 4.0 mm and stent lengths of 8, 12, 15, 18, 23, 28 mm. The primary endpoint was target lesion failure (TLF, defined as the composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization) at 1 year.

Demographics: For the subjects treated with the 2.25 mm XIENCE V EECSS, the mean age was 63 ± 11 years, and the majority of the population was male (61.8%, 89/144). In subjects treated with the 2.25 mm XIENCE V EECSS, 22.9% (32/140) were tobacco users, 81.9% (118/144) were hypertensive requiring medication, 86.5% (122/141) had hypercholesterolemia requiring medication, and 39.2% (56/143) were diabetic. Additionally, 68.8% (99/144) of the subjects had stable angina and 27.1% (39/144) had unstable angina. In subjects treated with the 2.25 mm XIENCE V EECSS, 72.2% (104/144) underwent single vessel treatment, and 27.8% (40/144) underwent dual vessel treatment.

Results: The results are presented in *Table 9.4-1* (Primary Endpoint Results), *Table 9.4-2* (Clinical Results), *Table 9.4-3* (Stent Thrombosis Results), *Table 9.4-4* (Angiographic Results) and *Figure 9.4-1* (Time-to-Event Curve for TLF). These analyses are based on the Full Analysis Set (FAS) population (defined as subjects that received the 2.25 mm XIENCE V EECSS). The primary analysis of the primary endpoint was analyzed in the FAS population. The 1-year TLF rate was 8.1% with an upper limit of the one-sided 95% confidence interval of 13.03%, which met the pre-specified performance goal of 20.4% ($p < 0.0001$). The 3-year follow-up rate for the SPIRIT Small Vessel Registry was 88.2% (127/144).

Table 9.4-1: SPIRIT SV Primary Endpoint Result

Primary Endpoint	2.25 mm XIENCE V (N = 144)	Upper 1-Sided 95% CL	p-value[1]
1-year TLF	8.1% (11/136)	13.03%	< 0.0001

Notes:
- N is the total number of subjects.
- TLF includes cardiac death, target vessel MI (per protocol definition) and clinically indicated TLR.
- Time frame includes follow-up window (365 ± 28 days).

[1] One-sided p-value by testing against the performance goal of 20.4% using exact test at 0.05 significance level.

Table 9.4-2: SPIRIT SV Clinical Endpoint Results through 3 Years

2.25 mm XIENCE V Arm	Per Protocol Definition	
Acute Success (post-index procedure)	**ITT* (N = 149)**	
Clinical Device Success	95.21% (139/146)	
Clinical Procedure Success	97.93% (142/145)	
Clinical Outcomes	**At 1 Year**	**At 3 Years (final follow-up)**
Component Endpoints	FAS (N = 144)	FAS (N = 144)
All Death	1.5% (2/136)	3.8% (5/132)
Cardiac Death	1.5% (2/136)	3.8% (5/132)
Non-Cardiac Death	0.0% (0/136)	0.0% (0/132)
Target Vessel MI	1.5% (2/136)	1.5% (2/132)
Non-Target Vessel MI	0.0% (0/136)	0.0% (0/132)
Clinically Indicated TLR (CI-TLR)	5.1% (7/136)	6.8% (9/132)
Clinically Indicated TVR (CI-TVR)	8.8% (12/136)	12.1% (16/132)
All TLR	6.6% (9/136)	8.3% (11/132)
All TVR	10.3% (14/136)	13.6% (18/132)
All Revascularization	14.7% (20/136)	23.5% (31/132)
Composite Endpoints		
Cardiac Death or MI	2.9% (4/136)	5.3% (7/132)
Cardiac Death or All MI or CI-TLR	8.1% (11/136)	12.1% (16/132)
All Death or All MI or All Revascularization	16.9% (23/136)	26.5% (35/132)
TLF	8.1% (11/136)	12.1% (16/132)

Notes:
- N is the total number of subjects; L is the number of lesions.
- Per protocol MI definition was used for Target Vessel MI, Non-Target Vessel MI, and all composite endpoints. MI per protocol definition is: Q-wave MI: Development of new, pathological Q waves on the ECG, and Non-Q-wave MI: Elevation of CK levels to ≥ two times the upper limit of normal with elevated CK-MB in the absence of new pathological Q waves.
- 1-year and 3-year time frames include follow-up window (365 ± 28 days and 1095 ± 28 days, respectively).
- Non-Target Vessel MI includes MI not attributed to the treated vessel.
- All Revascularization includes TVR and non-TVR, and non-treated vessel revascularization.
- FAS (full analysis set) is defined as subjects that received the 2.25 mm XIENCE V EECSS in the SPIRIT SV trial.
- Clinical Device Success: The successful delivery and deployment of the first study stent intended to be implanted at the intended target lesion (or in an overlapping stent setting, a successful delivery and deployment of the intended first and second investigational stents) and successful withdrawal of the stent delivery system with attainment of final residual stenosis of less than 50% of the target lesion by QCA (or by visual estimation if QCA unavailable). Bailout lesions were included as device success only if the above criteria for clinical device success were met for the bailout stent.
- Clinical Procedure Success: The achievement of a final in-stent diameter stenosis (DS) of < 50% (by QCA) using the assigned device and with any adjunctive devices, without the occurrence of cardiac death, target vessel MI (per protocol definition), or repeat coronary revascularization of the target lesion during the hospital stay (up to 7 days if a subject still is in the hospital). If QCA %DS was not available, procedure success data were considered missing.

*The ITT population provides the most accurate estimate of successful 2.25 mm XIENCE V stent implantation because it includes all subjects, regardless of whether the attempted implantation of 2.25 mm XIENCE V stent was successful.

Table 9.4-3: SPIRIT SV Stent Thrombosis Results through 3 Years

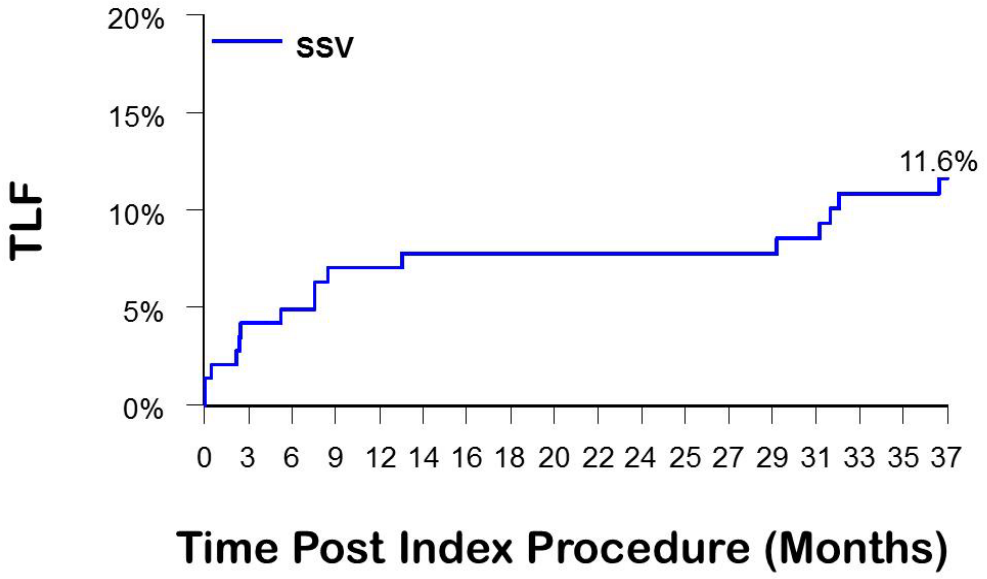
2.25 mm XIENCE V Arm	FAS (N = 144)		
Stent Thrombosis	**Per Protocol Definition**	**Per ARC Definition (Definite+Probable)**	**Per ARC Definition (Definite)**
Acute (≤ 1 day)	0.0% (0/144)	0.0% (0/144)	0.0% (0/144)
Subacute (> 1–30 days)	0.7% (1/142)	0.7% (1/142)	0.0% (0/142)
Acute / Subacute (0–30 days)	0.7% (1/142)	0.7% (1/142)	0.0% (0/142)
Late (Protocol: > 30 days; ARC: 31–393 days)	2.3% (3/129)	0.7% (1/137)	0.7% (1/137)
Very Late (ARC only) (394–1123 days)	-	0.0% (0/128)	0.0% (0/128)
Overall (0–1123 days)	3.1% (4/130)	1.5% (2/130)	0.8% (1/130)

Table 9.4-4: SPIRIT SV 240-Day Angiographic Results (Angiographic Cohort[1])

XIENCE V 2.25 mm Arm	FAS (N = 69) (L = 69)
240-day Late Loss	
In-Stent	0.20 ± 0.40 (52)
In-Segment	0.16 ± 0.41 (52)
Proximal	0.21 ± 0.35 (34)
Distal	0.00 ± 0.28 (45)
240-day %DS	
In-Stent	12.86 ± 19.58 (52)
In-Segment	20.85 ± 22.53 (52)
Proximal	14.31 ± 13.16 (37)
Distal	10.40 ± 8.45 (46)
240-day ABR	
In-Stent	3.8% (2/52)
In-Segment	9.6% (5/52)
Proximal	2.7% (1/37)
Distal	0.0% (0/46)

Notes:
N is the total number of subjects. L is the total number of lesions.
240-day angiographic data is available for 52 subjects.
[1] Per protocol defined qualifying angiogram with follow-up window extended to 268 days.

Figure 9.4-1: SPIRIT SV: Kaplan Meier Time-to-Event Curve for TLF through 3 Years



TLF	Event Free	Event Rate
XIENCE V 2.25 mm Arm	88.4%	11.6%

Note:
– Time frame includes follow-up window (1095 + 28 days).

Study Strengths and Limitations: The SPIRIT SV study was a prospective, open-label, multicenter registry. All event adjudications were performed by an independent Clinical Event Committee (CEC) with 100% site-reported adjudicable events being source-verified. The study provides important information on clinical outcomes and demonstrates the safety and effectiveness of the 2.25 mm XIENCE V stent in patients with small vessels. The study is limited by being a small registry with no head-to-head comparison with other DES platforms. In addition, due to the small population size, subgroup analysis can at best be considered exploratory.

9.5 Pooled Analysis of the SPIRIT II-III-IV Clinical Trials

A subject-level pooled analysis of three randomized, single-blinded, controlled trials was conducted to provide an assessment of safety outcomes with increased precision and to better estimate the incidence of low frequency events in specific subgroups. Definitive proof of the presence or absence of any differences between such subgroups requires prospectively powered assessment in dedicated clinical trials.

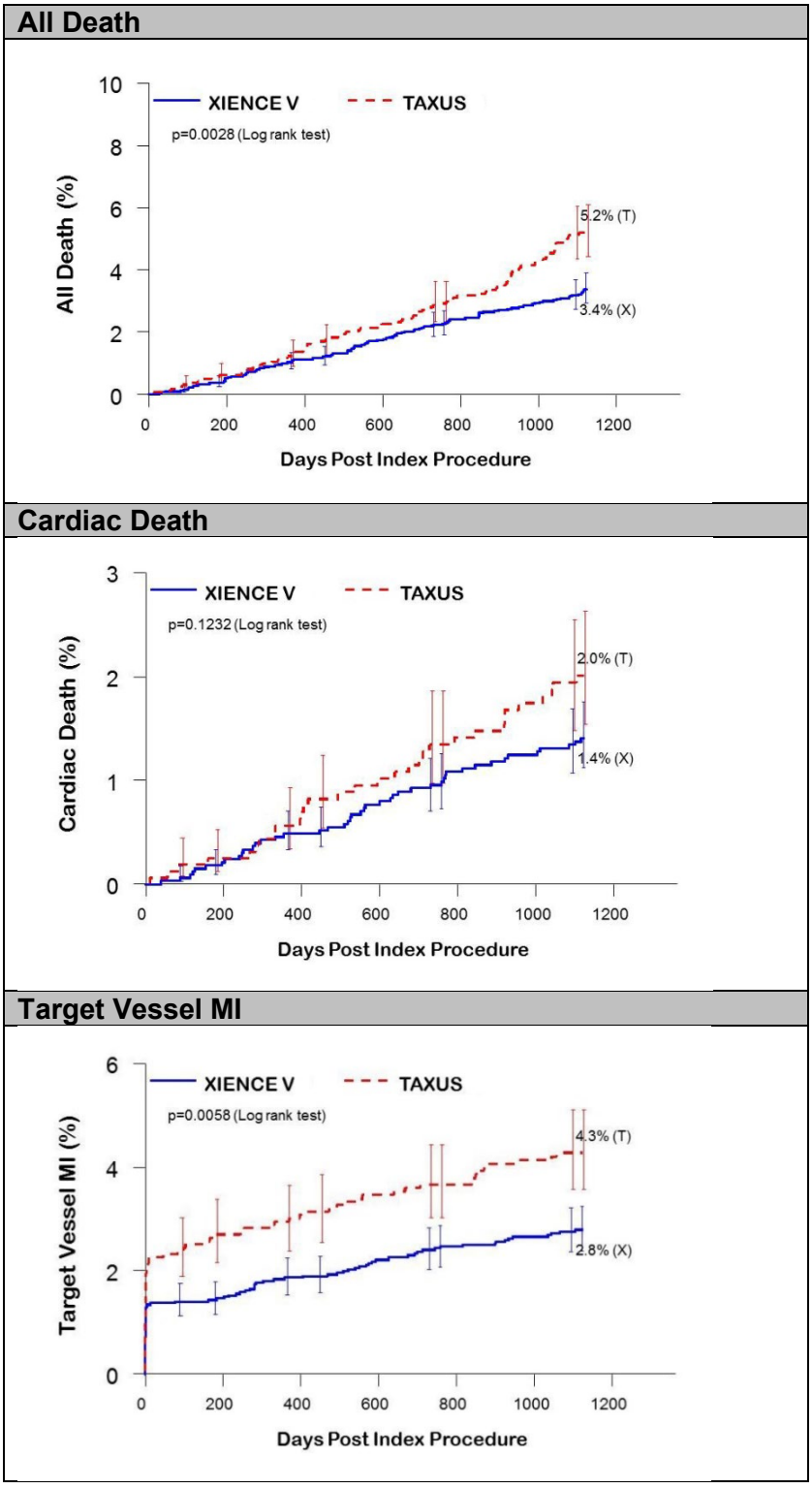
Data from the SPIRIT II, SPIRIT III randomized control trial (RCT) arm, and SPIRIT IV clinical trials were pooled to compare the XIENCE V stent to the TAXUS stent in 4989 subjects (with 6233 lesions) through 3 years (1123 days) of follow-up. Although SPIRIT IV permitted the enrollment of somewhat more complex patients, the three studies have subjects with generally similar baseline and angiographic characteristics and share key elements of study design, allowing pooling of the data for the purposes of these safety analyses.

Table 9.5-1: Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Clinical Results through 3 Years

Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	1 Year		3 Years	
	XIENCE V (N = 3350) [95% CI] [1]	TAXUS (N = 1639)[2] [95% CI] [1]	XIENCE V (N = 3350) [95% CI] [1]	TAXUS (N = 1639)[2] [95% CI] [1]
TLF	4.3% (143/3295) [3.67%, 5.09%]	7.5% (119/1592) [6.23%, 8.88%]	9.3% (295/3184) [8.28%, 10.33%]	12.7% (196/1541) [11.10%, 14.49%]
Ischemia-Driven TLR	2.7% (88/3295) [2.15%, 3.28%]	4.9% (78/1592) [3.89%, 6.08%]	6.1% (195/3184) [5.32%, 7.01%]	8.3% (128/1541) [6.98%, 9.80%]
TLR, CABG	0.3% (11/3295) [0.17%, 0.60%]	0.3% (5/1592) [0.10%, 0.73%]	0.7% (23/3184) [0.46%, 1.08%]	0.8% (13/1541) [0.45%, 1.44%]
TLR, PCI	2.4% (78/3295) [1.88%, 2.95%]	4.6% (74/1592) [3.67%, 5.80%]	5.6% (178/3184) [4.82%, 6.45%]	7.8% (120/1541) [6.50%, 9.24%]
Ischemia-Driven TVR	4.3% (143/3295) [3.67%, 5.09%]	6.3% (100/1592) [5.14%, 7.59%]	10.2% (326/3184) [9.21%, 11.34%]	11.5% (177/1541) [9.94%, 13.18%]
All Death	1.1% (36/3295) [0.77%, 1.51%]	1.4% (22/1592) [0.87%, 2.08%]	3.4% (109/3184) [2.82%, 4.11%]	5.3% (81/1541) [4.20%, 6.49%]
Cardiac Death	0.5% (15/3295) [0.26%, 0.75%]	0.6% (9/1592) [0.26%, 1.07%]	1.4% (45/3184) [1.03%, 1.89%]	2.0% (31/1541) [1.37%, 2.84%]
Non-Cardiac Death	0.6% (21/3295) [0.39%, 0.97%]	0.8% (13/1592) [0.44%, 1.39%]	2.0% (64/3184) [1.55%, 2.56%]	3.2% (50/1541) [2.42%, 4.26%]
Target Vessel MI	1.8% (60/3295) [1.39%, 2.34%]	3.1% (49/1592) [2.29%, 4.05%]	2.9% (91/3184) [2.31%, 3.50%]	4.4% (68/1541) [3.44%, 5.56%]
Cardiac Death or Target Vessel MI	2.2% (73/3295) [1.74%, 2.78%]	3.4% (54/1592) [2.56%, 4.40%]	4.1% (132/3184) [3.48%, 4.90%]	5.8% (90/1541) [4.72%, 7.13%]
All MI	2.0% (65/3295) [1.53%, 2.51%]	3.3% (53/1592) [2.50%, 4.33%]	3.3% (106/3184) [2.73%, 4.01%]	5.2% (80/1541) [4.14%, 6.42%]
QMI	0.2% (5/3295) [0.05%, 0.35%]	0.4% (6/1592) [0.14%, 0.82%]	0.3% (11/3184) [0.17%, 0.62%]	0.8% (13/1541) [0.45%, 1.44%]
NQMI	1.8% (60/3295) [1.39%, 2.34%]	3.0% (48/1592) [2.23%, 3.98%]	3.0% (95/3184) [2.42%, 3.64%]	4.5% (69/1541) [3.50%, 5.63%]
Cardiac Death or All MI	2.4% (78/3295) [1.88%, 2.95%]	3.6% (57/1592) [2.72%, 4.61%]	4.6% (147/3184) [3.91%, 5.40%]	6.6% (101/1541) [5.37%, 7.91%]
Protocol-Defined Stent Thrombosis (Cumulative)	0.3% (10/3258) [0.15%, 0.56%]	0.8% (13/1574) [0.44%, 1.41%]	0.9% (28/3071) [0.61%, 1.32%]	2.0% (30/1471) [1.38%, 2.90%]
Acute / Subacute (0 – 30 days)	0.2% (6/3341) [0.07%, 0.39%]	0.4% (7/1628) [0.17%, 0.88%]	0.2% (7/3341) [0.08%, 0.43%]	0.4% (7/1628) [0.17%, 0.88%]
Late (> 30 days)	0.1% (4/3257) [0.03%, 0.31%]	0.4% (7/1574) [0.18%, 0.91%]	0.7% (21/3069) [0.42%, 1.04%]	1.6% (24/1470) [1.05%, 2.42%]
ARC Definite+Probable Stent Thrombosis (Cumulative)	0.4% (13/3261) [0.21%, 0.68%]	1.0% (16/1574) [0.58%, 1.65%]	0.8% (24/3069) [0.50%, 1.16%]	1.8% (26/1463) [1.16%, 2.59%]
Acute / Subacute (0 – 30 days)	0.2% (7/3341) [0.08%, 0.43%]	0.6% (10/1628) [0.29%, 1.13%]	0.2% (7/3341) [0.08%, 0.43%]	0.6% (10/1628) [0.29%, 1.13%]
Late (31 days – 1 year)	0.2% (6/3260) [0.07%, 0.40%]	0.5% (8/1574) [0.22%, 1.00%]	0.2% (6/3254) [0.07%, 0.40%]	0.5% (8/1577) [0.22%, 1.00%]
Very late (> 1 year)	-	-	0.4% (11/3064) [0.18%, 0.64%]	0.7% (10/1458) [0.33%, 1.26%]
ARC-Definite Stent Thrombosis (Cumulative)	0.3% (11/3261) [0.17%, 0.60%]	0.8% (12/1574) [0.39%, 1.33%]	0.6% (18/3069) [0.35%, 0.93%]	1.2% (18/1463) [0.73%, 1.94%]
Bleeding Complications	3.1% (102/3261) [2.56%, 3.78%]	3.3% (52/1573) [2.48%, 4.31%]	5.8% (180/3086) [5.03%, 6.72%]	6.6% (97/1474) [5.37%, 7.97%]

Notes:
– 1-year and 3-year time frames include follow-up window (365 + 28 days and 1095 ± 28 days, respectively).
[1] By Clopper-Pearson Exact Confidence Interval.
[2] In the pooled TAXUS stent arm, there were 18 subjects who received at least one TAXUS Liberté stent.

Figure 9.5-1: Kaplan Meier Time-to-Event Curves through 3 Years (Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV)



Note: p-value based on log rank and not adjusted for multiple comparisons

9.6 Gender-Based Analysis of the SPIRIT Family of Clinical Trials

9.6.1 Background

Cardiovascular disease is the leading cause of death for both women and men in the US and coronary artery disease (CAD) is a major cause of morbidity and mortality in women. It is estimated that the prevalence of CAD in the United States is 9.1% (9,200,000) in males and 7.0% (8,400,000) in females for adults at least 20 years old according to the American Heart Association 2010 Update.[15] However, it is estimated that only 36% of annual PCIs are performed in women.[16] In PCI clinical trials, women represent only 25 – 35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in these trials may be partly attributable to gender differences in symptoms and pathophysiology,[17] which may lead to under-diagnosis and under-referral of female patients with CAD. Women tend to have worse clinical outcomes compared to men, most likely due to their higher baseline risk profile and more complex angiographic characteristics.[18, 19, 20]

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15 Lloyd-Jones D, Adams R, Carnethon M, De Simone G, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; 121:e46-215

16 Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; 119(3):e21-181.

17 Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: Gender Differences in Traditional and Novel Risk Factors, Symptom Evaluation, and Gender-Optimized Diagnostic Strategies. J Am Coll Cardiol 2006 47: S4-20.

18 Mahoney EM, Jurkovitz CT, Chu H, Becker ER, Culler S, Kosinski AS, et al. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *Jama* 2002; 288(15):1851-8.

19 Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009; 157(1):141-8.

20 Vaina S, Voudris V, Morice M-C, de Bruyne B, Colombo A, Macaya C, Richardt, G, Fajadet, J et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularization in patients with multivessel coronary artery disease: Insights from ARTS I and ARTS II. *EuroInterv*. 2009; 4(4):492-501.

9.6.2 Gender-Based Analysis of the SPIRIT PRIME Clinical Trial

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

In the Core Size Registry, 119/401 (29.7%) subjects were female and 282/401 (70.3%) were male. In the Long Lesion Registry, 39/104 (37.5%) subjects were female and 65/104 (62.5%) were male. In comparison, the prevalence of CAD is estimated at 9.2 million in males and 8.4 million in females for adults age 20 and older in the United States (i.e., the CAD population is estimated to be 52.2% males and 47.7% females). The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology, which may lead to under-diagnosis and under-referral of female patients with CAD. The gender proportions enrolled in this trial are similar to other drug-eluting stent trials.[21, 22]

Table 9.6.2-1 presents the baseline demographics, risk factors, and angiographic characteristics by gender for subjects in the Core Size Registry. As is consistent with previous literature, female patients at baseline were numerically older and had a higher BMI. Additionally, more females than males had hypertension requiring medication and diabetes mellitus. *Table 9.6.2-2* presents the baseline demographics, risk factors, and angiographic characteristics by gender for subjects in the Long Lesion Registry.

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[21] Lansky AJ, Costa RA, Mooney M, et al. Gender-Based Outcomes After Paclitaxel-Eluting Stent Implantation in Patients With Coronary Artery Disease. J Am Coll Cardiol 2005 45: 1180-5.

[22] Solinas E, Nikolsky E, Lansky AJ, et al. Gender-Specific Outcomes After Sirolimus-Eluting Stent Implantation. J Am Coll Cardiol 2007;50:2111–6.

Table 9.6.2-1: Demographics, Risk Factors, and Baseline Angiographic Characteristics for SPIRIT PRIME Core Size Registry Subjects*

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

*Subjects with Cardiac Enzyme Data in Window

[1] From T-test

[2] From Fisher's exact test

Notes:

- All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.
- N is the total number of subjects.
- M is the total number of target lesions.
- This table contains only subjects with post-index procedure cardiac enzyme data in window (between 8 hours post-index procedure and hospital discharge).

Table 9.6.2-2: Demographics, Risk Factors, and Baseline Angiographic Characteristics for SPIRIT PRIME Long Lesion Registry Subjects*

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

*Subjects with Cardiac Enzyme Data in Window

[1] From T-test

[2] From Fisher's exact test

Notes:

- All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.
- N is the total number of subjects.
- M is the total number of target lesions.
- This table contains only subjects with post-index procedure cardiac enzyme data in window (between 8 hours post-index procedure and hospital discharge).

A post-hoc analysis was conducted on the composite primary safety and effectiveness endpoint of TLF, per protocol and per ARC, to assess for heterogeneity of treatment effect across sex / gender (using Fisher's Exact Test). *Table 9.6.2-3* and *Table 9.6.2-4* present the 3-year clinical results for the Core Size Registry and Long Lesion Registry, respectively. Due to the modest sample size (Core Size Registry 282 males vs. 119 females and Long Lesion Registry 65 males vs. 39 females), these analyses and interpretation are limited.

Table 9.6.2-3: Clinical Results for All Female and All Male Subgroups in the SPIRIT PRIME Core Size Registry through 3 Years*

SPIRIT PRIME	Male (N = 282)	Female (N = 119)	Total (N = 401)	p-value[1]
All Death	4.0% (11/274)	0.9% (1/116)	3.1% (12/390)	0.1192
Cardiac Death	1.1% (3/274)	0.0% (0/116)	0.8% (3/390)	0.5578
Non-Cardiac Death	2.6% (7/274)	0.0% (0/116)	1.8% (7/390)	0.1091
Target Vessel MI per Protocol	2.9% (8/274)	1.7% (2/116)	2.6% (10/390)	0.7297
Cardiac Death or Target Vessel MI per Protocol	4.0% (11/274)	1.7% (2/116)	3.3% (13/390)	0.3599
Target Vessel MI per ARC	5.5% (15/274)	7.8% (9/116)	6.2% (24/390)	0.4891
Cardiac Death or Target Vessel MI per ARC	6.6% (18/274)	7.8% (9/116)	6.9% (27/390)	0.6666
Major Bleeding Complication	4.5% (12/265)	1.7% (2/115)	3.7% (14/380)	0.2439
Stent Thrombosis				
Protocol defined	1.5% (4/263)	0.0% (0/115)	1.1% (4/378)	0.3185
ARC definite + probable	1.1% (3/265)	0.0% (0/115)	0.8% (3/380)	0.5566
TLF				
per Protocol	9.1% (25/274)	6.9% (8/116)	8.5% (33/390)	0.5540
per ARC	10.2% (28/274)	12.1% (14/116)	10.8% (42/390)	0.5948
Ischemia-Driven TLR	5.5% (15/274)	5.2% (6/116)	5.4% (21/390)	1.0000
Ischemia-Driven TVR, Non-TL	5.8% (16/274)	6.0% (7/116)	5.9% (23/390)	1.0000

*Subjects with Cardiac Enzyme Data in Window

[1] From Fisher's exact test

Notes:

- All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.
- Subjects are only counted once for each type of event in each time period.
- N is the total number of subjects.
- This table contains only subjects with post-index procedure cardiac enzyme data in window (between 8 hours post-index procedure and hospital discharge).

Table 9.6.2-4: Clinical Results for All Female and All Male Subgroups in the SPIRIT PRIME Long Lesion Registry through 3 Years[1]*

SPIRIT PRIME	Male (N = 65)	Female (N = 39)	Total (N = 104)	p-value[1]
All Death	3.1% (2/65)	2.6% (1/39)	2.9% (3/104)	1.0000
Cardiac Death	0.0% (0/65)	0.0% (0/39)	0.0% (0/104)	NA
Non-Cardiac Death	3.1% (2/65)	2.6% (1/39)	2.9% (3/104)	1.0000
Target Vessel MI per Protocol	4.6% (3/65)	5.1% (2/39)	4.8% (5/104)	1.0000
Cardiac Death or Target Vessel MI per Protocol	4.6% (3/65)	5.1% (2/39)	4.8% (5/104)	1.0000
Target Vessel MI per ARC	13.8% (9/65)	5.1% (2/39)	10.6% (11/104)	0.2024
Cardiac Death or Target Vessel MI per ARC	13.8% (9/65)	5.1% (2/39)	10.6% (11/104)	0.2024
Major Bleeding Complication	3.2% (2/62)	2.7% (1/37)	3.0% (3/99)	1.0000
Stent Thrombosis				
Protocol defined	0.0% (0/62)	0.0% (0/37)	0.0% (0/99)	NA
ARC definite + probable	0.0% (0/62)	0.0% (0/37)	0.0% (0/99)	NA
TLF				
per Protocol	10.8% (7/65)	7.7% (3/39)	9.6% (10/104)	0.7397
per ARC	18.5% (12/65)	7.7% (3/39)	14.4% (15/104)	0.1585
Ischemia-Driven TLR	6.2% (4/65)	2.6% (1/39)	4.8% (5/104)	0.6480
Ischemia-Driven TVR, Non-TL	7.7% (5/65)	2.6% (1/39)	5.8% (6/104)	0.4063

*Subjects with Cardiac Enzyme Data in Window

[1] From Fisher's exact test

Notes:

- All p-values displayed are two-tailed and not from formal hypothesis testing and are displayed for descriptive purposes only.
- Subjects are only counted once for each type of event in each time period.
- N is the total number of subjects.
- This table contains only subjects with post-index procedure cardiac enzyme data in window (between 8 hours post-index procedure and hospital discharge).

9.6.3 Gender-Based Analysis in the SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Clinical Trials

To evaluate gender-specific clinical outcomes with the XIENCE V stent, Abbott Vascular conducted a pooled analysis of SPIRIT II, SPIRIT III RCT, and SPIRIT IV. The pooled SPIRIT trial data were assessed for differences between males and females in baseline characteristics and study outcomes, as well as for any interaction between treatment and gender. Results suggest that the general conclusions of safety and effectiveness of the XIENCE V stent can be generalized for males and females.

In the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV intent-to-treat population, 1584 subjects were female (32%) and 3404 subjects were male (68%). The gender proportions enrolled in this trial are similar to other drug-eluting stent trials.[23, 24]

Of the 1584 female subjects in the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population, 1058 were XIENCE V subjects and 526 were TAXUS subjects.

Table 9.6.3-1 describes the demographics, risk factors, and baseline angiographic characteristics of all female and all male subgroups of the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population.

Table 9.6.3-1: Demographics, Risk Factors, and Baseline Angiographic Characteristics for the All-Female and All-Male Subgroups (Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Population)

Subject Characteristics	All Females (N = 1584; 32%) (M = 1901)	All Males (N = 3404; 68%) (M = 4332)	p-value[1]
Baseline Demographics, Mean ± SD (n)			
Age (year)	65.7 ± 10.5 (1584)	62.0 ± 10.2 (3404)	< 0.0001
Baseline Risk Factors, % (No./total)			
All Diabetes	35.9% (569/1583)	28.7% (975/3398)	< 0.0001
Diabetes Treated with Insulin	12.1% (192/1583)	6.5% (222/3398)	< 0.0001
Current Tobacco Use	21.7% (337/1550)	23.2% (772/3321)	0.2555
Hypertension Requiring Medication	80.7% (1278/1584)	73.9% (2511/3398)	< 0.0001
Hypercholesterolemia Requiring Medication	73.2% (1143/1562)	75.9% (2537/3341)	0.0399
Stable Angina	57.2% (889/1554)	57.7% (1933/3348)	0.7327
Unstable Angina	29.1% (452/1554)	25.5% (854/3348)	0.0092
Prior MI	15.8% (245/1551)	23.6% (783/3316)	< 0.0001
Target Vessel, % (No./total)			
LAD	43.1% (820/1901)	39.6% (1712/4327)	0.0085
Circumflex or Ramus	21.9% (416/1901)	26.8% (1159/4327)	< 0.0001
RCA	35.0% (665/1901)	33.6% (1454/4327)	0.2959
LMCA	0.0% (0/1901)	0.0% (2/4327)	1.0000
Pre-Procedure QCA Analysis, Mean ± SD (m)			
Lesion Length (mm)	14.22 ± 6.25 (1888)	14.79 ± 6.51 (4293)	0.0012
Pre-Procedure RVD (mm)	2.66 ± 0.44 (1894)	2.79 ± 0.48 (4303)	< 0.0001
Pre-Procedure MLD (mm)	0.79 ± 0.38 (1899)	0.78 ± 0.40 (4310)	0.2207
Pre-Procedure Percent Diameter Stenosis (%DS)	69.92 ± 12.84 (1899)	71.58 ± 13.05 (4310)	< 0.0001

N is the total number of subjects; M is the total number of lesions analyzed.

[1]p-values are displayed for descriptive purposes only.

[23] Lansky AJ, Costa RA, Mooney M, et al. Gender-Based Outcomes After Paclitaxel-Eluting Stent Implantation in Patients With Coronary Artery Disease. J Am Coll Cardiol 2005 45: 1180-5.

[24] Solinas E, Nikolsky E, Lansky AJ, et al. Gender-Specific Outcomes After Sirolimus-Eluting Stent Implantation. J Am Coll Cardiol 2007;50:2111–6.

Table 9.6.3-1 shows that females in the SPIRIT family of trials were older and had higher rates of diabetes, hypertension, and unstable angina compared with males. The generally higher clinical risk profile in females is consistent with gender differences in baseline demographics reported from other PCI studies.[25, 26, 27, 28, 29, 30, 31]

Table 9.6.3-2 presents key clinical outcomes through 3 years in female and male subjects from the SPIRIT IV trial and the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population. In post-hoc analyses of the pooled SPIRIT II, SPIRIT III RCT and SPIRIT IV population, rates of death, target vessel MI and stent thrombosis through 3 years were comparable between females and males. At 3 years, post-hoc analyses of the SPIRIT IV trial suggest that females treated with XIENCE V stents (despite generally increased clinical risk factors at baseline) had numerically similar adverse event rates compared to males treated with XIENCE V stents. Comparisons of study outcomes in patients receiving the XIENCE V stent versus the TAXUS stent were consistent within each gender subgroup. Based on the interaction p-value calculated from Wald Chi-square statistics of logistic regression analysis, no significant treatment-by-gender interaction effect was observed at a 0.15 significance level. These analyses suggest that the conclusions regarding safety and effectiveness of the XIENCE V stent are generalizable to both males and females. However, it should be noted that there were no pre-specified hypotheses for the use of the XIENCE V stent in females.

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26 Abbott JD, Vlachos HA, Selzer F, Sharaf BL, Holper E, Glaser R et al. Gender-based outcomes in percutaneous coronary intervention with drug-eluting stents (from the National Heart, Lung, and Blood Institute Dynamic Registry). *Am J Cardiol* 2007; 99(5):626-31.

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29 Blomkalns AI, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005; 45(6):832-7.

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31 Lansky AJ, Costa RA, Mooney M, Midei MG, Lui HK, Strickland W, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. *J Am Coll Cardiol* 2005; 45 (8):1180-5.

Table 9.6.3-2: Clinical Results in XIENCE V Females, XIENCE V Males and All Subjects through 3 Years (SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Population)

Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	1 Year				3 Years			
	XIENCE V		All Subjects		XIENCE V		All Subjects	
	Females (N = 1058)	Males (N = 2292)	XIENCE V (N = 3350)	TAXUS (N = 1639)	Females (N = 1057)	Males (N = 2293)	XIENCE V (N = 3350)	TAXUS (N = 1639)
All Death	1.2% (12/1038)	1.1% (24/2257)	1.1% (36/3295)	1.4% (22/1592)	3.0% (30/993)	3.6% (79/2191)	3.4% (109/3184)	5.3% (81/1541)
Cardiac Death	0.5% (5/1038)	0.4% (10/2257)	0.5% (15/3295)	0.6% (9/1592)	1.2% (12/993)	1.5% (33/2191)	1.4% (45/3184)	2.0% (31/1541)
Non-Cardiac Death	0.7% (7/1038)	0.6% (14/2257)	0.6% (21/3295)	0.8% (13/1592)	1.8% (18/993)	2.1% (46/2191)	2.0% (64/3184)	3.2% (50/1541)
Target Vessel MI	1.9% (20/1038)	1.8% (40/2257)	1.8% (60/3295)	3.1% (49/1592)	2.7% (27/993)	2.9% (64/2191)	2.9% (91/3184)	4.4% (68/1541)
Cardiac Death or Target Vessel MI	2.4% (25/1038)	2.1% (48/2257)	2.2% (73/3295)	3.4% (54/1592)	3.9% (39/993)	4.2% (93/2191)	4.1% (132/3184)	5.8% (90/1541)
Bleeding Complication	4.5% (46/1029)	2.5% (56/2232)	3.1% (102/3261)	3.3% (52/1573)	8.3% (80/967)	4.7% (100/2119)	5.8% (180/3086)	6.6% (97/1474)
Stent Thrombosis								
Protocol Defined	0.4% (4/1028)	0.3% (6/2230)	0.3% (10/3258)	0.8% (13/1574)	0.7% (7/963)	1.0% (21/2108)	0.9% (28/3071)	2.0% (30/1471)
ARC Definite+Probable	0.4% (4/1028)	0.4% (9/2233)	0.4% (13/3261)	1.0% (16/1574)	0.5% (5/961)	0.9% (19/2108)	0.8% (24/3069)	1.8% (26/1463)
ARC Definite	0.4% (4/1026)	0.3% (7/2229)	0.3% (11/3255)	0.8% (12/1577)	0.4% (4/961)	0.7% (14/2108)	0.6% (18/3069)	1.2% (18/1463)
TLF	4.0% (31/777)	4.0% (66/1639)	4.0% (97/2416)	6.8% (81/1195)	9.3% (69/745)	9.6% (154/1603)	9.5% (223/2348)	11.9% (138/1158)
Ischemia-Driven TLR	2.2% (17/777)	2.4% (39/1639)	2.3% (56/2416)	4.6% (55/1195)	5.8% (43/745)	6.6% (105/1603)	6.3% (148/2348)	7.9% (92/1158)
Ischemia-Driven TVR, Non-TL	2.7% (21/777)	2.0% (33/1639)	2.2% (54/2416)	2.4% (29/1195)	5.6% (42/745)	5.6% (90/1603)	5.6% (132/2348)	5.4% (63/1158)

Notes:
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- 1-year and 3-year time frames include follow-up window (365 + 28 days and 1095 ± 28 days, respectively).
- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI (per protocol definition), and ischemia-driven TLR.

9.7 XIENCE V USA Post-Approval Study

Objective: The objectives of the XIENCE V USA post-approval study were: (1) to evaluate the continued safety and effectiveness of the XIENCE V EECSS during commercial use in real-world settings; (2) to support the Food and Drug Administration's (FDA) dual antiplatelet therapy (DAPT) initiative.

Design: The XIENCE V USA study was a prospective, multicenter, FDA-mandated post-approval study with 3 cohorts: phase I (from index procedure to 1 year), long-term follow-up cohort of phase II (from 1 year to 4 years), and AV-DAPT cohort of phase II (from 1 year to 33 months). Patients were considered as enrolled upon signing the Institutional Review Board (IRB)-approved Informed Consent Form (ICF) and only XIENCE V EECSS was (were) implanted during the index procedure. There were no angiographic inclusion and exclusion criteria for this study. A total of 8,040 patients were consecutively enrolled from 191 sites in United States from two enrollment phases (5,042 patients from the first enrollment phase and 2,998 patients from the second enrollment phase). Phase I cohort consisted of all the 8,040 enrolled patients. Clinical follow-up occurred at 14, 30, 180 days, and 1 year. The long-term follow-up cohort of phase II consisted of 4,663 patients from the first enrollment phase who were not transferred to the HCRI-DAPT study (IDE#G080186) and remained in the study beyond 1 year. Clinical follow-up occurred at 2, 3, and 4 years. For phase I and the long-term follow-up cohort, the primary endpoint was the annual rate of ARC-defined stent thrombosis (definite and probable), and the co-primary endpoint was the annual composite rate of cardiac death or any MI. For phase I, the primary hypothesis for the co-primary endpoint of cardiac death or MI from 0-1 year is based on a comparison of the near on-label patients from the second enrollment stage of XIENCE V USA who had cardiac markers drawn between 12 – 24 hours post procedure to the population of SPIRIT III and SPIRIT III-like patients in SPIRIT IV treated with XIENCE V EECSS (with a non-inferiority margin of 3%). For the long-term follow-up cohort, the four yearly annual rates of ARC-defined definite and probable stent thrombosis will be simultaneously evaluated against a performance goal of 1.5%. The AV-DAPT cohort of phase II consisted of 868 patients from the second enrollment phase who were eligible and got randomized at 12 months post-index procedure to either DAPT or placebo for an additional 18 months thienopyridine treatment (from 12 to 30 months). Clinical follow-up and endpoints for the AV-DAPT cohort are the same as the HCRI-DAPT study (IDE#G080186). All clinical endpoint events were adjudicated by an independent CEC.

Results: Phase I of the study has been completed in the entire population. A total of 8,040 patients with 11,137 lesions were treated with a total of 12,873 XIENCE V stents during the index procedure. There were 39% near on-label patients and 61% non-near on-label patients. The non-near on-label cohort includes patients with any of the following: baseline lesion length > 28 mm, reference vessel diameter < 2.5 mm or > 4.25 mm, restenosis, chronic total occlusion, graft lesion, bifurcation with side branch ≥ 2 mm, ostial, left main, more than 2 lesions stented in the same vessel, more than 2 vessels treated, acute MI, renal insufficiency, ejection fraction < 30%, or staged procedure. Patients who do not meet the above criteria are classified as the "near on-label" cohort. Baseline characteristics (*Table 9.7-1*) and key endpoint results through 4 years were summarized below (*Table 9.7-2* and *Table 9.7-3*). The 4-year follow-up rate for the XIENCE V USA clinical trial was 87.7% (4,405/5,020).

The 1-year primary endpoint of ARC definite and probable ST rate was 0.81%. The 1-year co-primary endpoint of the composite cardiac death or MI rate was 7.2%. The primary analysis for the co-primary endpoint was summarized in *Table 9.7-2*. The difference in cardiac death or MI rate between XIENCE V USA and SPIRIT study was 0.01% with the 95% upper confidence limit being 1.74%, which was less than the quasi non-inferiority margin of 3% (P_{NI} = 0.0022).

Table 9.7-1: XIENCE V USA Baseline Characteristics

Analysis population: 8,040 patients; 11,137 lesions; 12,873 stents			
Patient Demographics		**Procedural Characteristics**	
Male	69.6% (5599/8040)	Vessels Treated	
Age (year)	64.58 ± 10.82 (8040)	1	86.3% (6564/7609)
All Diabetes Mellitus	35.8% (2856/7969)	2	13.1% (998/7609)
Oral Hypoglycemics Treated	23.6% (1879/7969)	≥ 3	0.6% (47/7609)
Insulin Treated	12.3% (979/7969)	Target Vessels	
Multivessel Disease	39.8% (3202/8040)	RCA	32.8% (3656/11136)
Prior MI	29.7% (2212/7440)	LAD	37.5% (4173/11136)
Prior PCI	39.1% (3065/7836)	LCX	23.5% (2617/11136)
Prior CABG	16.4% (1289/7836)	LMCA	1.6% (182/11136)
Unstable Angina	28.7% (2188/7612)	Graft	4.6% (508/11136)
AMI	14.7% (1054/7146)	Lesions Treated	
Renal Insufficiency	10.5% (840/8015)	1	70.0% (5627/8040)
Lesion Characteristics		2	23.2% (1868/8040)
Reference Vessel Diameter (mm)	3.02 ± 0.53 (10707)	≥ 3	6.8% (545/8040)
Lesion Length (mm)	15.8 ± 9.4 (10642)	Stenting	
Lesion Type		Direct stenting (per lesion)	36.8% (4096/11126)
A	17.7% (1643/9273)	Stents implanted per patient	1.6 ± 0.9 (8040)
B1	32.4% (3002/9273)	Patients with > 1 stent	40.8% (3280/8040)
B2	25.8% (2390/9273)	Stent length per patient (mm)	29.2 ± 19.1 (8039)
C	24.1% (2238/9273)	Stent length per lesion (mm)	21.2 ± 11.3 (11093)
Restenosis Lesion	8.7% (972/11134)		
Bifurcation Lesion	9.7% (1084/11120)		
Ostial Lesion	11.2% (1176/10456)		
Patient Categorization			
Near On-label	**39.0% (3132/8040)**		
Non-Near On-label[1]	**61.0% (4908/8040)**		
Lesion length > 28 mm	12.5% (613/4908)	> 2 lesions in same vessel	4.6% (227/4908)
Reference vessel diameter < 2.5 mm	5.3% (258/4908)	> 2 vessels treated	1.0% (47/4908)
Reference vessel diameter > 4.25 mm	2.0% (97/4908)	AMI	21.5% (1054/4908)
Chronic total occlusion	3.7% (184/4908)	Renal insufficiency	17.1% (840/4908)
Graft lesion	8.8% (431/4908)	LVEF < 30%	4.1% (200/4908)
Bifurcation with side branch ≥ 2 mm	15.2% (746/4908)	With staged procedure	8.9% (439/4908)
Ostial lesion	22.5% (1103/4908)		
Left main	3.6% (179/4908)		
Restenosis lesion	17.3% (847/4908)		

Note: Numbers presented here are % (n/N) or mean ± SD.

[1] A patient can be counted in more than 1 category of the non-near on-label criteria.

Table 9.7-2: XIENCE V USA Primary Analysis of the 1-Year Co-Primary Endpoint

	XIENCE V USA (N = 997)	SPIRIT III and IV (N = 2720)	Difference (Upper One-Sided 95% CI)	Non-inferiority p-value
1 Year Cardiac Death and MI	6.2% (55/881)	6.2% (166/2663)	0.01% (1.74%)	0.0022

Notes:

- N is the total number of patients.
- The 1-year window is through 407 days (or randomization date if occurred within 407 days for the second enrollment phase) for XIENCE V USA, and 393 days for SPIRIT III and IV.
- The XIENCE V USA arm includes near on-label patients from the second enrollment phase who had cardiac enzyme collected between 12 and 24 hours post-index procedure.
- The SPIRIT study arm includes XIENCE V patients in SPIRIT III and SPIRIT III-like XIENCE V patients in SPIRIT IV.
- One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 3% at 0.05 significance level.

Table 9.7-3: XIENCE V USA Clinical Outcomes at 1 and 4 Years

	XIENCE V USA Overall Population at 1 Year (N = 8040)	XIENCE V USA Long-Term Follow-up Cohort at 4 Years (N = 5020)
COMPOSITE EFFICACY & SAFETY		
TLF (WHO MI Definition)	6.9% (514/7491)	16.5% (747/4518)
TLF (ARC)	9.4% (707/7522)	19.3% (875/4530)
EFFICACY (Non-Hierarchical Subject Counts)		
Clinically indicated TLR	4.4% (330/7522)	10.4% (473/4530)
Clinically indicated TLR, CABG	0.8% (57/7522)	2.0% (91/4530)
Clinically indicated TLR, PCI	4.0% (301/7522)	8.9% (402/4530)
Clinically indicated TVR, Non-TLR	2.1% (161/7522)	6.1% (277/4530)
SAFETY (Non-Hierarchical Subject Counts)		
All Death	2.6% (194/7522)	10.9% (494/4530)
Cardiac Death	1.4% (108/7522)	5.4% (244/4530)
Vascular Death	0.2% (12/7522)	0.7% (32/4530)
Non-Cardiovascular Death	1.0% (74/7522)	4.8% (218/4530)
Target Vessel MI (WHO)	1.9% (140/7491)	3.5% (157/4518)
Target Vessel MI (ARC)	5.5% (415/7522)	8.7% (396/4530)
All MI (WHO)	2.2% (162/7491)	4.8% (215/4518)
QMI	0.5% (39/7491)	1.5% (68/4518)
NQMI	1.7% (126/7491)	3.4% (152/4518)
All MI (ARC)	6.3% (475/7522)	11.3% (511/4530)
QMI	0.5% (39/7522)	1.5% (68/4530)
NQMI	5.9% (442/7522)	10.1% (457/4530)
COMPOSITE SAFETY		
Cardiac Death or Target Vessel MI (WHO)	3.1% (231/7491)	8.0% (361/4518)
Cardiac Death or Target Vessel MI (ARC)	6.5% (491/7522)	12.6% (571/4530)
Cardiac Death or MI (WHO)	3.3% (250/7491)	9.1% (412/4518)
Cardiac Death or MI (ARC)	7.2% (545/7522)	14.9% (676/4530)
STENT THROMBOSIS (ARC-Defined Definite / Probable)		
Cumulative through 1 year	0.81% (60/7380)	-
Acute / Subacute (0 – 30 days)	0.40% (32/7951)	-
Late (31 – 365 days)	0.37% (27/7364)	-
Very Late (366 – 1502 days)	-	0.55% (22/4032)
Cumulative through 4 years	-	1.56% (64/4093)
STENT THROMBOSIS (ARC-Defined Definite)		
Cumulative through 1 year	0.54% (40/7380)	-
Acute / Subacute (0 – 30 days)	0.23% (18/7951)	-
Late (31 – 365 days)	0.29% (21/7364)	-
Very Late (366 – 1502 days)	-	0.42% (17/4032)
Cumulative through 4 years	-	1.05% (43/4093)

Notes:
- N is the total number of patients.
- The 1-year window is through 407 days (or randomization date if occurred within 407 days for the second enrollment phase of XIENCE V USA). The 4-year window is through 1502 days.
- Per ARC definition was used for MI and MI related endpoints.
- TLF is defined as hierarchical composite of cardiac death, target vessel MI (per ARC definition), and clinically indicated TLR.

Study Strengths and Limitations: The XIENCE V USA study was a prospective, open-label, multicenter, post-approval study. All event adjudications were performed by an independent event committee with 100% site-reported adjudicable events being source-verified. With a large sample size and high data quality, the study provides important information on the clinical outcomes in a real-world population beyond those from selected patients in randomized pre-approval studies. However, the study is limited by being observational in nature, and therefore a head-to-head comparison with other DES platforms was not possible. In addition, the monitoring level is less rigorous than a randomized pivotal trial. However, the consistent results between XIENCE V USA near on-label population and the XIENCE V EECSS arm in SPIRIT III and IV trials suggests that the quality measures taken in XIENCE V USA study as described above produced high quality data. Therefore, this study affords a reliable benchmark for understanding the safety of XIENCE V EECSS in the context of real-world clinical practice.

9.7.1 Analysis of Patients with 4.0 mm Stent

There were 186 near on-label patients with at least one XIENCE V 4.0 mm stent implanted during the index procedure. A pre-specified descriptive comparison of 1-year TLR is summarized in *Table 9.7.1-1*.

Table 9.7.1-1: XIENCE V USA Patients with 4.0 mm Stent

	XIENCE V USA (N = 186)	SPIRIT III and IV (N = 74)
1-Year TLR	3.4% (6/177)	2.7% (2/74)

Notes:
- N is the total number of patients.
- The 1-year window is through 407 days (or randomization date if occurred within 407 days for the second enrollment phase) for XIENCE V USA, and 393 days for SPIRIT III and IV.
- The XIENCE V USA arm includes near on-label patients who had at least a 4.0 mm XIENCE V stent implanted during the index procedure.
- The SPIRIT study arm includes XIENCE V patients in SPIRIT III 4.0 mm registry and SPIRIT III-like XIENCE V patients in SPIRIT IV who were treated with at least a 4.0 mm XIENCE V stent.

9.7.2 Analysis of Patients Treated with Direct Stenting

There were two pre-specified hypothesis tests on direct stenting. The results of both tests were summarized in *Table 9.7.2-1*. One-year TLF rate of XIENCE V USA patients who had a single lesion treated with direct stenting in real-world settings was non-inferior to the event rate of SPIRIT III-like XIENCE V patients in SPIRIT IV who had a single lesion treated with pre-dilatation (P_{NI} = 0.0119). In XIENCE V USA, one-year TLF rate in patients who had a single lesion treated with direct stenting was non-inferior to the event rate of those who had a single lesion treated with pre-dilatation (P_{NI} < 0.0001).

In these two analyses, there was, as expected, some degree of selection bias with lesions undergoing direct-stenting displaying lower complexity than lesions undergoing pre-dilation. For hypothesis 1, there were more patients who had prior cardiac intervention and history of MI in XIENCE V USA direct stenting group, but there were more B2/C lesions and more multiple stents implanted in the SPIRIT IV pre-dilatation group. The propensity score (PS) approach was utilized to address this selection bias. A logistic regression was fit to obtain the PS for direct stenting, which was defined as the probability of having direct stenting given specific values for the following variables: age, sex, current smoker, diabetes treated, hypertension requiring medication, lipid disorder requiring medication, prior CABG, prior PCI, CCS III or IV stable angina, prior MI, prior brachytherapy, multivessel disease, LAD, heavy calcification, baseline DS%, TIMI, lesion length ≥ 22mm, B2/C lesion, and multiple stents per lesion. Then patients were divided into 5 strata with approximately equal size based on the rank of their PS. A stratified non-inferiority test was finally performed. For hypothesis 2, the XIENCE V USA direct stenting group had less B2/C lesion, less bifurcations, and fewer patients with multiple stents implanted than the pre-dilatation group. For hypothesis 2, the propensity analysis method was the same as hypothesis 1, except that some additional variables were added such as AMI, renal insufficiency, left ventricular ejection fraction (LVEF) < 30%, left main, graft, restenotic lesion, bifurcation, ostial lesion, and history of stroke, which were not included in the propensity model of hypothesis 1 because these patients were either excluded in SPIRIT IV or data were not collected in SPIRIT IV. The propensity analysis results for both hypothesis 1 and hypothesis 2 indicated that adjustment for baseline differences in lesion characteristics did not change the findings of non-inferiority of direct stenting to pre-dilation in either analysis *(Table 9.7.2-1*).

Table 9.7.2-1: XIENCE V USA Direct Stenting Results

Analysis 1	XIENCE V USA Direct Stenting (N = 506)	SPIRIT IV Pre-dilatation (N = 1726)	Difference (Upper One-Sided 95% CI)	Non-inferiority p-value
1-Year TLF	7.7% (34/440)	7.4% (124/1687)	0.38% (3.01%)	0.0119
1-Year TLF (Propensity Score Analysis)	7.7% (34/440)	7.4% (124/1687)	-0.09% (2.70%)	0.0079
Hierarchical TLF Components				
Cardiac Death	0.7% (3/440)	0.4% (6/1687)	NA	NA
Target Vessel MI	4.5% (20/440)	5.7% (97/1687)	NA	NA
Clinically indicated TLR	2.5% (11/440)	1.2% (21/1687)	NA	NA
1-Year Stent Thrombosis (ARC definite / probable)	0.23% (1/430)	0.18% (3/1675)	NA	NA
1-Year Stent Thrombosis (ARC definite)	0.23% (1/430)	0.18% (3/1675)	NA	NA
Analysis 2	**XIENCE V USA Direct Stenting (N = 1947)**	**XIENCE V USA Pre-dilatation (N = 3405)**	**Difference (Upper One-Sided 95% CI)**	**Non-inferiority p-value**
1-Year TLF	6.8% (124/1817)	7.9% (252/3182)	-1.10% (0.23%)	< 0.0001
1-Year TLF (Propensity Score Analysis)	6.8% (124/1817)	7.9% (252/3182)	-0.60% (0.75%)	0.0008
Hierarchical TLF Components				
Cardiac Death	1.3% (24/1817)	1.3% (40/3182)	NA	NA
Target Vessel MI	3.3% (60/1817)	4.5% (142/3182)	NA	NA
Clinically indicated TLR	2.2% (40/1817)	2.2% (70/3182)	NA	NA
1-Year Stent Thrombosis (ARC definite / probable)	0.56% (10/1786)	0.51% (16/3118)	NA	NA
1-Year Stent Thrombosis (ARC definite)	0.28% (5/1786)	0.35% (11/3118)	NA	NA

Notes:

- N is the total number of patients.
- The 1-year window is through 407 days (or randomization date if occurred within 407 days for the second enrollment phase) for XIENCE V USA, and 393 days for SPIRIT IV study.
- In Analysis 1, the XIENCE V USA direct stenting arm included patients from the second enrollment phases who had cardiac enzyme collected between 12 and 24 hours post-procedure and only 1 lesion treated during index procedure and the lesion was treated with direct stenting. Patients with staged procedure (s) were excluded. The SPIRIT IV pre-dilatation arm included SPIRIT III-like XIENCE V patients in SPIRIT IV who had only 1 lesion treated. All SPIRIT IV patients were considered to have pre-dilatation done for lesions treated during index procedure per protocol requirement. One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 4% at 0.05 significance level.
- In Analysis 2, the XIENCE V USA direct stenting arm included all patients who had only 1 lesion treated and the lesion was treated with direct stenting from both enrollment phases of XIENCE V USA. The XIENCE V USA pre-dilatation arm included all patients who had only 1 lesion treated and the lesion was treated with pre-dilatation from both enrollment phases of XIENCE V USA. Patients with staged procedure(s) were excluded. One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 2% at 0.05 significance level.
- TLF included cardiac death, target vessel MI (per ARC definition) and clinically indicated TLR. In SPIRIT IV, ischemic-driven TLR was used rather than clinically indicated. The two definitions are similar but differ in regards to clinically indicated TLR requiring that there is ≥ 50% diameter stenosis and the presence of clinical symptoms. Ischemic-driven TLR does not always require angiographic evidence of ≥ 50% diameter stenosis; revascularization due to a positive functional ischemia study alone qualifies as ischemic-driven.

9.7.3 Pre-specified XIENCE V USA Subgroup Analysis

Elderly (age ≥ 65 years), female, insulin-treated diabetic, acute MI (STEMI and NSTEM combined) patients and patients with multivessel disease and two vessels stented are at increased risk for cardiovascular morbidity and mortality. In addition, patients with complex lesion characteristics, such as long lesions (≥ 20 mm), bifurcation lesions, ostial lesions and in-stent restenotic lesion are also associated with worse clinical outcomes. In XIENCE V USA, the above-mentioned subgroups were pre-specified for descriptive analysis to assess the safety and effectiveness of those high-risk patients. There were no pre-specified hypotheses for those subgroups.

The pre-specified XIENCE V USA subgroup 4-year clinical outcomes were summarized in *Table 9.7.3-1*.

Table 9.7.3-1: XIENCE V USA Subgroup Clinical Outcomes through 4 Years

	XV USA Overall (N = 5020)	Near On-Label (N = 1871)	Age ≥ 65 (N = 2495)	Female (N = 1564)	Insulin-Treated Diabetics (N = 593)	Acute MI (STEMI/ NSTEMI) (N = 667)	Multivessel Disease (N = 2050)	Two Vessels Treated (N = 620)	Long Lesions (≥ 20mm) (N = 860)	Bifurcation Lesions (N = 261)	Ostial Lesions (N = 366)	ISR (N = 257)
COMPOSITE EFFICACY AND SAFETY												
ARC-Defined Device Oriented Endpoint	19.7% (893/4530)	13.4% (228/1704)	20.3% (475/2339)	21.7% (305/1406)	37.3% (198/531)	22.2% (129/581)	25.1% (471/1875)	26.2% (148/565)	18.3% (142/776)	12.6% (28/222)	23.9% (77/322)	27.6% (64/232)
TLF	19.3% (875/4530)	13.0% (222/1704)	20.0% (468/2339)	21.1% (297/1406)	37.1% (197/531)	21.9% (127/581)	24.7% (463/1875)	25.3% (143/565)	18.2% (141/776)	12.2% (27/222)	23.9% (77/322)	27.2% (63/232)
SAFETY												
Cardiac Death or Target Vessel MI	12.6% (571/4530)	8.3% (142/1704)	14.5% (338/2339)	14.0% (197/1406)	26.9% (143/531)	15.8% (92/581)	15.8% (296/1875)	16.5% (93/565)	12.1% (94/776)	6.8% (15/222)	14.6% (47/322)	14.7% (34/232)
Cardiac Death or MI	14.9% (676/4530)	10.3% (176/1704)	16.2% (380/2339)	16.1% (227/1406)	30.1% (160/531)	20.1% (117/581)	18.6% (348/1875)	18.2% (103/565)	14.3% (111/776)	8.1% (18/222)	18.0% (58/322)	17.7% (41/232)
All Death	10.9% (494/4530)	7.8% (133/1704)	15.0% (352/2339)	11.7% (164/1406)	22.0% (117/531)	14.1% (82/581)	12.3% (230/1875)	11.5% (65/565)	12.0% (93/776)	6.3% (14/222)	13.7% (44/322)	9.9% (23/232)
Cardiac Death	5.4% (244/4530)	3.3% (57/1704)	6.7% (157/2339)	5.4% (76/1406)	14.1% (75/531)	6.7% (39/581)	6.6% (123/1875)	6.4% (36/565)	5.0% (39/776)	1.8% (4/222)	6.2% (20/322)	4.7% (11/232)
All MI	11.3% (511/4530)	8.0% (137/1704)	11.6% (272/2339)	12.5% (176/1406)	20.9% (111/531)	15.3% (89/581)	14.3% (268/1875)	14.3% (81/565)	10.8% (84/776)	6.3% (14/222)	13.0% (42/322)	15.1% (35/232)
QMI	1.5% (68/4530)	1.1% (18/1704)	1.1% (26/2339)	1.5% (21/1406)	2.3% (12/531)	3.6% (21/581)	1.8% (34/1875)	2.5% (14/565)	1.4% (11/776)	0.5% (1/222)	0.6% (2/322)	0.9% (2/232)
NQMI	10.1% (457/4530)	7.1% (121/1704)	10.7% (251/2339)	11.2% (158/1406)	19.0% (101/531)	12.7% (74/581)	12.9% (242/1875)	12.6% (71/565)	9.8% (76/776)	5.9% (13/222)	12.4% (40/322)	14.7% (34/232)
Target Vessel MI	8.7% (396/4530)	5.9% (101/1704)	9.5% (222/2339)	10.2% (143/1406)	17.3% (92/531)	10.7% (62/581)	11.3% (212/1875)	12.4% (70/565)	8.2% (64/776)	5.0% (11/222)	9.6% (31/322)	11.6% (27/232)
Efficacy												
TLR	10.9% (495/4530)	7.1% (121/1704)	9.5% (222/2339)	11.9% (167/1406)	20.0% (106/531)	11.2% (65/581)	14.5% (271/1875)	15.6% (88/565)	10.1% (78/776)	7.2% (16/222)	13.7% (44/322)	20.3% (47/232)
Stent Thrombosis												
ARC Definite / Probable	1.56% (64/4093)	0.70% (11/1577)	1.60% (33/2058)	1.53% (19/1244)	3.39% (15/443)	2.57% (13/506)	2.27% (38/1674)	2.34% (12/513)	1.45% (10/688)	0.98% (2/205)	1.04% (3/288)	2.86% (6/210)
ARC Definite	1.05% (43/4093)	0.25% (4/1577)	0.92% (19/2058)	1.05% (13/1244)	2.03% (9/443)	2.17% (11/506)	1.43% (24/1674)	1.17% (6/513)	1.02% (7/688)	0.98% (2/205)	0.69% (2/288)	2.38% (5/210)

Notes:

- N is the total number of patients.
- The 4-year window is through 1502 days.
- Per ARC definition was used for MI and MI-related endpoints.
- ARC-defined device oriented endpoint is defined as hierarchical composite of cardiac death, target vessel MI (per ARC definition), and TLR.
- TLF included cardiac death, target vessel MI (per ARC definition) and clinically indicated TLR. Near on-label patients are those who are not defined as non-near on-label. The non-near on-label cohort includes patients with any of the following: baseline lesion length >28 mm, reference vessel diameter < 2.5 mm or > 4.25 mm, restenosis, chronic total occlusion, graft lesion, bifurcation with side branch ≥ 2 mm, ostial, left main, more than 2 lesions stented in the same vessel, more than 2 vessels treated, acute MI, renal insufficiency, ejection fraction < 30%, or staged procedure.
- For long lesion (≥ 20 mm), bifurcation, ostial and ISR subgroups, only patients with single-lesion treated during the index procedure and without any staged procedures were included in the analysis.

9.8 EXPERT CTO Clinical Trial

The EXPERT CTO clinical trial was designed to demonstrate the safety and effectiveness of the XIENCE Family of Stents in the treatment of chronic total occlusions (CTO). The trial, conducted in the United States, consists of a single arm, and one-year results are presented here.

Primary Objective: The objective of the EXPERT CTO clinical trial is to evaluate the safety and effectiveness of the XIENCE Family of Stents in improving coronary luminal diameter in subjects with symptomatic heart disease due to CTO.

Design: The EXPERT CTO clinical trial is a prospective, non-randomized, open-label, multicenter single-arm study evaluating stent diameters of 2.25 – 4.0 mm with stent lengths 8 – 38 mm in 222 subjects at 20 sites in the United States. Each subject was to receive treatment of one *de novo* native coronary CTO lesion. However, treatment of non-CTO lesions distal to the target lesion (non-target lesions in the target vessel) which was not identified on the pre-procedural angiogram prior to CTO recanalization but were identified only after successful CTO recanalization, was allowed using XIENCE stents. Treatment of one lesion in a non-target vessel was also allowed during the index procedure.

The primary endpoint is Major Adverse Cardiac Events (MACE) at one year, a composite endpoint of death, myocardial infarction (MI), and clinically driven Target Lesion Revascularization (TLR). The primary endpoint rate of MACE at 1 year was compared to a pre-specified Performance Goal (PG). The PG of 24.4% for the EXPERT CTO trial was developed utilizing historical clinical trial data. First, the average 1-year MACE rate per ARC MI definition was weighted by sample size and adjusted for MI definition if necessary. The adjustment was derived from Abbott Vascular historical trials to account for difference in the primary endpoint between ARC and protocol MI definitions. The weighted average event rate after the above adjustment was 14.4%. The final performance goal was set at 24.4% after adding a delta of 10% to account for variability and uncertainty. Analyses of the primary endpoint were conducted on both the Intent-To-Treat (ITT) population and Per Protocol (PP) population.

Demographics: The mean age was 61.65 ± 10.43 years, 81.1% (180/222) were male, 18.9% (42/222) were female and 80.2% (178/222) were white. Regarding medical risk factors, 26.0% (54/208) were tobacco users, 91.9% (203/221) were hypertensive, and 96.8% (215/222) were dyslipidemic. There were 43.4% (96/221) of subjects who had a prior percutaneous cardiac intervention, 29.0% (61/210) who had a prior MI, and 9.9% (22/222) who had prior coronary artery bypass graft surgery. Furthermore, the population consisted of 40.1% (89/222) diabetics, of which 68.5% (61/89) were diabetics requiring oral medication, 30.3% (27/89) were diabetics requiring insulin, and 28.1% (25/89) were diabetics controlled by diet.

Results: The primary endpoint results are presented in *Table 9.8-1*. These analyses are based on the ITT and PP populations. The ITT population is defined as all enrolled patients for whom recanalization and pre-dilatation of the target lesion are completed and the study stent(s) (XIENCE V and / or XIENCE PRIME) is inserted into the coronary guiding catheter. The PP population is defined as all ITT patients for the stent-related analysis in whom at least one study stent is implanted with both procedure success and available follow-up data but without major protocol deviations due to inappropriate enrollment.

The observed MACE rate at one year was 18.5% (39/211) in the ITT population and 8.2% (15/183) in the PP population. Both the ITT and PP populations met the primary endpoint with MACE rates significantly lower than the pre-specified PG (24.4%) ($p = 0.0248$ and $p < 0.0001$, respectively).

Secondary endpoints results at 1, 2, 3 and 4 years are presented in *Table 9.8-2*. The 4-year follow-up rate for the EXPERT CTO clinical trial was 86.0% (191/222).

Table 9.8-1: EXPERT CTO Primary Endpoint Results

Primary Endpoint Analysis	MACE	Upper One-Sided 95% CL[4]	Performance Goal	p-value[4]
ITT Set[1] (N = 222) Exact Rate[3]	18.5% (39/211)	23.4%	24.4%	0.0248
PP Set[2] (N = 183) Exact Rate[3]	8.2% (15/183)	12.3%	24.4%	< 0.0001

[1] ITT subjects include all subjects who met the study entry criteria, signed the written informed consent, were enrolled in the trial, and whose target lesion was successfully crossed and pre-dilated.

[2] The per-protocol population is defined as all ITT subjects in whom at least one study stent was implanted, met procedure success, had available follow-up data (i.e., a MACE event within 360 days or follow up of at least 330 days), and did not have major protocol deviations due to inappropriate enrollment.

[3] The numerator includes subjects who have MACE events before or on day 360, and the denominator includes subjects who had available follow-up data (i.e., a MACE event within 360 days or follow up of at least 330 days).

[4] p-value and upper one-sided 95% CI were calculated using exact binomial method.

Table 9.8-2: EXPERT CTO Secondary Endpoint Results to 4 Years (ITT Population)

	1 Year (N = 222)	2 Years (N = 222)	3 Years (N = 222)	4 Years (N = 222)
Composite Safety and Effectiveness				
TLF (per ARC)	15.8% (33/209)	19.5% (39/200)	21.8% (42/193)	24.1% (45/187)
TLF (per protocol)	9.1% (19/209)	13.1% (26/199)	15.1% (29/192)	17.2% (32/186)
Safety				
All Death	1.9% (4/210)	5.4% (11/202)	8.2% (16/195)	10.5% (20/191)
Cardiac Death	1.0% (2/208)	2.6% (5/196)	4.3% (8/188)	5.5% (10/181)
Non-Cardiac Death	1.0% (2/208)	3.0% (6/197)	4.3% (8/187)	5.5% (10/182)
Target Vessel MI (per ARC)	12.0% (25/209)	13.7% (27/197)	14.9% (28/188)	15.5% (28/181)
Target Vessel QMI (per ARC)	1.0% (2/208)	1.0% (2/193)	1.1% (2/182)	1.1% (2/174)
Target Vessel NQMI (per ARC)	11.1% (23/207)	12.8% (25/195)	13.5% (25/185)	14.0% (25/178)
All MI (per ARC)	13.9% (29/209)	15.7% (31/197)	18.1% (34/188)	20.3% (37/182)
QMI (per ARC)	1.0% (2/208)	1.0% (2/193)	1.1% (2/182)	1.1% (2/174)
NQMI (per ARC)	13.0% (27/207)	14.9% (29/195)	16.2% (30/185)	18.4% (33/179)
Target Vessel MI (per protocol)	3.4% (7/208)	3.6% (7/194)	3.8% (7/183)	4.0% (7/176)
Target Vessel QMI (per protocol)	1.0% (2/208)	1.0% (2/193)	1.1% (2/182)	1.1% (2/174)
Target Vessel NQMI (per protocol)	2.4% (5/206)	2.6% (5/192)	2.8% (5/181)	2.9% (5/174)
All MI (per protocol)	3.4% (7/208)	3.6% (7/194)	3.8% (7/183)	5.7% (10/176)
QMI (per protocol)	1.0% (2/208)	1.0% (2/193)	1.1% (2/182)	1.1% (2/174)
NQMI (per protocol)	2.4% (5/206)	2.6% (5/192)	2.8% (5/181)	4.6% (8/174)
Effectiveness				
Clinically driven TLR	6.3% (13/207)	9.3% (18/194)	10.3% (19/185)	11.3% (20/177)
Clinically driven TLR, CABG	0.5% (1/206)	2.1% (4/192)	2.2% (4/181)	2.3% (4/173)
Clinically driven TLR, PCI	5.8% (12/207)	7.8% (15/193)	8.7% (16/184)	9.7% (17/176)
Clinically driven TVR	7.2% (15/207)	10.8% (21/194)	11.9% (22/185)	13.6% (24/177)
Stent Thrombosis				
ARC Definite+Probable Stent Thrombosis				
Acute (0 – 1 day)	0.0% (0/222)	NA	NA	NA
Subacute (2 – 30 days)	0.9% (2/218)	NA	NA	NA
Late (31 days – 1 year)	0.5% (1/206)	NA	NA	NA
Cumulative	1.4% (3/207)	1.6% (3/192)	1.6% (3/182)	1.7% (3/174)
ARC Definite Stent Thrombosis (cumulative)	1.0% (2/207)	1.0% (2/192)	1.1% (2/182)	1.1% (2/174)

Notes:
- ITT subjects include all subjects who met the study entry criteria, signed the written informed consent, were enrolled in the trial, and whose target lesion was successfully crossed and predilated.
- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI, and clinically driven TLR.
- ARC: Academic Research Consortium
- NA: Not applicable

Study Strengths and Limitations: The EXPERT CTO study was a prospective, open-label, multicenter study. All event adjudications were performed by an independent Clinical Event Committee (CEC) with 100% site-reported adjudicable events being source-verified. This study provides important information on clinical outcomes in patients with chronic total occlusions treated with the XIENCE Family of Stents. The study is limited by being a small study with no head-to-head comparison with other DES platforms. In addition, due to the small population size, subgroup analysis can at best be considered exploratory.

9.8.1 Gender-Based Analysis of the EXPERT CTO Clinical Trial

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

In the EXPERT CTO study, 81.1% (180/222) were male and 18.9% (42/222) were female. In comparison, the prevalence of CAD is estimated at 9.2 million in males and 8.4 million in females for adults age 20 and older the United States (i.e., the CAD population is estimated to be 52.2% males and 47.7% females). The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology, which may lead to under-diagnosis and under-referral of female patients with CAD. The gender proportions enrolled in this trial are similar to other CTO drug-eluting stent trials.[32, 33, 34]

Table 9.8.1-1 presents the baseline demographics, risk factors, and angiographic characteristics by gender for subjects in the EXPERT CTO trial. As is consistent with previous literature, female patients at baseline were numerically older. More females than males were diabetic.

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[32] Kandzari DE, Rao SV, Moses JW, et al. Clinical and angiographic outcomes with sirolimus-eluting stents in total coronary occlusions: the ACROSS/TOSCA-4 (Approaches to Chronic Occlusions With Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4) trial. J Am Coll Cardiol Intv 2009;2:97-106.

[33] Valenti R, Vergara R, Migliorini A, et al. Predictors of reocclusion after successful drug-eluting stent-supported percutaneous coronary intervention of chronic total occlusion. J Am Coll Cardiol 2013;61:545-550.

[34] Wohrle J, Rottbauer W, Imhof A. Everolimus-eluting stents for treatment of chronic total coronary occlusions. Clin Res in Cardiol 2011;101:23-28.

Table 9.8.1-1: Demographics, Risk Factors, and Baseline Angiographic Characteristics for EXPERT CTO

Subject / Lesion Characteristics	Male (N = 180) (L = 180)	Female (N = 42) (L = 42)	Difference [95% CI]	p-value
Baseline Demographics, Mean ± SD (n)				
Age (year)	61.08±10.46 (180)	64.12±10.09 (42)	-3.04[-6.45,0.37]	0.089
Baseline Risk Factors, % (No./total)				
All Diabetes	38.3% (69/180)	47.6% (20/42)	-9.3%[-26.0%,7.4%]	0.297
Diabetes Treated with Insulin	29.0% (20/69)	35.0% (7/20)	-6.0%[-29.5%,17.5%]	0.593
Current Tobacco Use	28.9% (48/166)	14.3% (6/42)	14.6%[2.0%,27.3%]	0.222
Hypertension	91.6% (164/179)	92.9% (39/42)	-1.2%[-10.0%,7.5%]	1.000
Dyslipidemia	96.1% (173/180)	100.0% (42/42)	-3.9%[-6.7%,-1.1%]	0.352
Congestive Heart Failure	13.3% (24/180)	7.1% (3/42)	6.2%[-3.0%,15.4%]	0.430
Prior PCI	44.1% (79/179)	40.5% (17/42)	3.7%[-12.9%,20.2%]	0.731
Prior MI	30.0% (51/170)	25.0% (10/40)	5.0%[-10.1%,20.1%]	0.569
Target Vessel, % (No./total)				
LAD	30.6% (55/180)	33.3% (14/42)	-2.8%[-18.5%,13.0%]	0.715
Circumflex or Ramus	17.8% (32/180)	7.1% (3/42)	10.6%[1.1%,20.2%]	0.103
RCA	51.7% (93/180)	59.5% (25/42)	-7.9%[-24.4%,8.7%]	0.394
LMCA	0.0% (0/180)	0.0% (0/42)	0.0%[0.0%,0.0%]	--
Pre-Procedure QCA Analysis, Mean ± SD (m)				
Lesion Length (mm)	35.92±19.20 (180)	36.68±15.19 (42)	-0.76[-6.14,4.62]	0.811
Pre-Procedure RVD (mm)	2.69±0.43 (180)	2.52±0.43 (42)	0.17[0.02,0.31]	0.022
Pre-Procedure MLD (mm)	0.01±0.06 (180)	0.00±0.00 (42)	0.01[0.00,0.02]	0.026
Pre-Procedure Percent Diameter Stenosis (%DS)	99.62±2.36 (180)	100.00±0.00 (42)	-0.38[-0.72,-0.04]	0.032

A post-hoc analysis was conducted on the composite primary safety and effectiveness endpoint of MACE, per ARC and per protocol, to assess for heterogeneity of treatment effect across sex / gender (*Table 9.8.1-2*). Due to the modest sample size (180 males vs. 42 females), these analyses and interpretation are limited.

Table 9.8.1-2: Clinical Results for All Female and All Male Subgroups in the EXPERT CTO Study through 1 Year

EXPERT CTO	Male (N = 180)	Female (N = 42)	Difference [95% CI]	p-value
All Death	1.2% (2/171)	5.1% (2/39)	-4.0%[-11.1%,3.1%]	0.158
Cardiac Death	0.6% (1/170)	2.6% (1/38)	-2.0%[-7.3%,3.2%]	0.333
Non-Cardiac Death	0.6% (1/170)	2.6% (1/38)	-2.0%[-7.3%,3.2%]	0.333
Target Vessel MI per ARC	11.1% (19/171)	15.8% (6/38)	-4.7%[-17.2%,7.8%]	0.413
Target Vessel MI per Protocol	3.5% (6/171)	2.7% (1/37)	0.8%[-5.1%,6.7%]	1.000
Clinically Driven TLR	6.5% (11/170)	5.4% (2/37)	1.1%[-7.1%,9.2%]	1.000
Clinically Driven TVR, Non-TL	1.2% (2/169)	0.0% (0/37)	1.2%[-0.4%,2.8%]	1.000
Stent Thrombosis				
ARC definite + probable	1.2% (2/170)	2.7% (1/37)	-1.5%[-7.0%,3.9%]	0.448
MACE				
per ARC MI definition	16.9% (29/172)	25.6% (10/39)	-8.8%[-23.6%,6.0%]	0.252
per Protocol MI definition	9.3% (16/172)	12.8% (5/39)	-3.5%[-14.9%,7.8%]	0.553

9.9 Analysis of Diabetic Patients

9.9.1 Analysis of Diabetic Subjects in SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Trials

Diabetic subjects with CAD comprise an important subject subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic subjects were included in the SPIRIT family of trials, there were no pre-specified hypotheses for the use of the XIENCE V stent in diabetic individuals.

Tables 9.9.1-1 and *9.9.1-2* show the clinical outcomes through 3 years in subjects from a post-hoc analysis of the SPIRIT IV and the pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV population. History of diabetes was one of the stratification factors used in randomization to assure a balance between the XIENCE V EECSS and TAXUS treatment arms for each individual trial. In XIENCE V patients, there were numerically higher event rates in diabetics compared with non-diabetics. Given the potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

In the XIENCE V stent patients group, there were numerically higher event rates in diabetics compared with non-diabetics. Given the potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

Table 9.9.1-1: Clinical Results in Diabetics and Non-Diabetics through 3 Years (SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT and SPIRIT IV Population)

	1 Year				3 Years			
SPIRIT IV	**Non-Diabetics**		**All Diabetics**		**Non-Diabetics**		**All Diabetics**	
	XIENCE V (N = 1669)	**TAXUS (N = 829)**	**XIENCE V (N = 786)**	**TAXUS (N = 399)**	**XIENCE V (N = 1669)**	**TAXUS (N = 829)**	**XIENCE V (N = 786)**	**TAXUS (N = 399)**
TLF	3.1% (52/1652)	6.7% (55/815)	5.9% (45/761)	6.9% (26/379)	8.2% (132/1610)	11.4% (90/790)	12.4% (91/735)	13.1% (48/367)
Ischemia-Driven TLR	1.8% (29/1652)	4.5% (37/815)	3.5% (27/761)	4.7% (18/379)	5.7% (91/1610)	8.1% (64/790)	7.8% (57/735)	7.6% (28/367)
Ischemia-Driven TVR, Non-TL	1.5% (24/1652)	2.2% (18/815)	3.9% (30/761)	2.9% (11/379)	4.8% (77/1610)	4.9% (39/790)	7.5% (55/735)	6.5% (24/367)
Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	**Non-Diabetics**		**All Diabetics**		**Non-Diabetics**		**All Diabetics**	
	XIENCE V (N = 2312)	**TAXUS (N = 1125)**	**XIENCE V (N = 1035)**	**TAXUS (N = 509)**	**XIENCE V (N = 2312)**	**TAXUS (N = 1125)**	**XIENCE V (N = 1035)**	**TAXUS (N = 509)**
TLF	3.2% (74/2284)	8.0% (89/1106)	6.8% (69/1008)	6.2% (30/482)	8.0% (177/2211)	12.7% (137/1075)	12.2% (118/970)	12.8% (59/462)
Ischemia-Driven TLR	2.0% (45/2284)	5.3% (59/1106)	4.3% (43/1008)	3.9% (19/482)	5.7% (125/2211)	8.7% (94/1075)	7.2% (70/970)	7.4% (34/462)
Ischemia-Driven TVR, Non-TL	1.9% (43/2284)	3.5% (39/1106)	3.8% (38/1008)	2.9% (14/482)	5.2% (114/2211)	5.6% (60/1075)	6.9% (67/970)	7.1% (33/462)
All Death	0.8% (19/2284)	1.7% (19/1106)	1.7% (17/1008)	0.6% (3/482)	2.5% (56/2211)	5.5% (59/1075)	5.5% (53/970)	4.8% (22/462)
Cardiac Death	0.2% (5/2284)	0.7% (8/1106)	1.0% (10/1008)	0.2% (1/482)	0.8% (18/2211)	1.7% (18/1075)	2.8% (27/970)	2.8% (13/462)
Non-Cardiac Death	0.6% (14/2284)	1.0% (11/1106)	0.7% (7/1008)	0.4% (2/482)	1.7% (38/2211)	3.8% (41/1075)	2.7% (26/970)	1.9% (9/462)
Target Vessel MI	1.3% (30/2284)	3.0% (33/1106)	3.0% (30/1008)	3.3% (16/482)	2.1% (47/2211)	4.1% (44/1075)	4.5% (44/970)	5.2% (24/462)
Cardiac Death or Target Vessel MI	1.5% (35/2284)	3.3% (37/1106)	3.8% (38/1008)	3.5% (17/482)	2.9% (65/2211)	5.3% (57/1075)	6.9% (67/970)	7.1% (33/462)
Stent Thrombosis								
Protocol Defined	0.1% (3/2265)	0.7% (8/1091)	0.7% (7/990)	1.0% (5/479)	0.5% (11/2150)	1.6% (16/1018)	1.9% (17/918)	3.1% (14/449)
ARC Definite+Probable	0.1% (3/2265)	0.9% (10/1091)	1.0% (10/993)	1.3% (6/479)	0.4% (8/2148)	1.7% (17/1017)	1.7% (16/918)	2.0% (9/442)
ARC Definite	0.1% (3/2265)	0.5% (6/1091)	0.8% (8/993)	1.3% (6/479)	0.3% (7/2148)	1.1% (11/1017)	1.2% (11/918)	1.6% (7/442)

Notes:

- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- 1-year and 3-year time frames include follow-up window (365 + 28 days and 1095 + 28 days, respectively).

Table 9.9.1-2: Clinical Results in Diabetics through 3 Years (SPIRIT IV and Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV Population – XIENCE V Subjects)

	1 Year				3 Years			
SPIRIT IV	**Non-Diabetics (N = 1669)**	**All Diabetics (N = 786)**	**Insulin-Dependent Diabetics (N = 209)**	**Non-Insulin-Dependent Diabetics (N = 577)**	**Non-Diabetics (N = 1669)**	**All Diabetics (N = 786)**	**Insulin-Dependent Diabetics (N = 209)**	**Non-Insulin-Dependent Diabetics (N = 577)**
TLF	3.1% (52/1652)	5.9% (45/761)	7.0% (14/199)	5.5% (31/562)	8.2% (132/1610)	12.4% (91/735)	17.3% (33/191)	10.7% (58/544)
Ischemia-Driven TLR	1.8% (29/1652)	3.5% (27/761)	5.0% (10/199)	3.0% (17/562)	5.7% (91/1610)	7.8% (57/735)	13.1% (25/191)	5.9% (32/544)
Ischemia-Driven TVR, Non-TL	1.5% (24/1652)	3.9% (30/761)	6.5% (13/199)	3.0% (17/562)	4.8% (77/1610)	7.5% (55/735)	11.0% (21/191)	6.3% (34/544)
Pooled SPIRIT II, SPIRIT III RCT, and SPIRIT IV	**Non-Diabetics (N = 2312)**	**All Diabetics (N = 1035)**	**Insulin-Dependent Diabetics (N = 272)**	**Non-Insulin-Dependent Diabetics (N = 763)**	**Non-Diabetics (N = 2312)**	**All Diabetics (N = 1035)**	**Insulin-Dependent Diabetics (N = 272)**	**Non-Insulin-Dependent Diabetics (N = 763)**
TLF	3.2% (74/2284)	6.8% (69/1008)	8.8% (23/262)	6.2% (46/746)	8.0% (177/2211)	12.2% (118/970)	16.3% (41/252)	10.7% (77/718)
Ischemia-Driven TLR	2.0% (45/2284)	4.3% (43/1008)	6.1% (16/262)	3.6% (27/746)	5.7% (125/2211)	7.2% (70/970)	11.9% (30/252)	5.6% (40/718)
Ischemia-Driven TVR, Non-TL	1.9% (43/2284)	3.8% (38/1008)	5.3% (14/262)	3.2% (24/746)	5.2% (114/2211)	6.9% (67/970)	8.7% (22/252)	6.3% (45/718)
All Death	0.8% (19/2284)	1.7% (17/1008)	2.3% (6/262)	1.5% (11/746)	2.5% (56/2211)	5.5% (53/970)	6.0% (15/252)	5.3% (38/718)
Cardiac Death	0.2% (5/2284)	1.0% (10/1008)	1.1% (3/262)	0.9% (7/746)	0.8% (18/2211)	2.8% (27/970)	3.2% (8/252)	2.6% (19/718)
Non-Cardiac Death	0.6% (14/2284)	0.7% (7/1008)	1.1% (3/262)	0.5% (4/746)	1.7% (38/2211)	2.7% (26/970)	2.8% (7/252)	2.6% (19/718)
Target Vessel MI	1.3% (30/2284)	3.0% (30/1008)	4.6% (12/262)	2.4% (18/746)	2.1% (47/2211)	4.5% (44/970)	6.0% (15/252)	4.0% (29/718)
Cardiac Death or Target Vessel MI	1.5% (35/2284)	3.8% (38/1008)	5.0% (13/262)	3.4% (25/746)	2.9% (65/2211)	6.9% (67/970)	7.9% (20/252)	6.5% (47/718)
Stent Thrombosis								
Protocol Defined	0.1% (3/2265)	0.7% (7/990)	0.8% (2/256)	0.7% (5/734)	0.5% (11/2150)	1.9% (17/918)	2.5% (6/238)	1.6% (11/680)
ARC Definite+Probable	0.1% (3/2265)	1.0% (10/993)	1.2% (3/257)	1.0% (7/736)	0.4% (8/2148)	1.7% (16/918)	2.1% (5/237)	1.6% (11/681)
ARC Definite	0.1% (3/2265)	0.8% (8/993)	0.8% (2/257)	0.8% (6/736)	0.3% (7/2148)	1.2% (11/918)	1.3% (3/237)	1.2% (8/681)

Notes:

- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject are excluded from all data analyses.
- 1-year and 3-year time frames include follow-up window (365 + 28 days and 1095 ± 28 days, respectively).

9.9.2 Bayesian Analysis of Diabetic Patients Treated with XIENCE Stents

A Statistical Analysis Plan (SAP) was developed with a pre-specified hypothesis to evaluate the safety and effectiveness of the XIENCE Family of Everolimus Eluting Coronary Stent Systems (XIENCE stent, including XIENCE V, XIENCE PRIME, XIENCE Xpedition™ and XIENCE Skypoint stents) to treat *de novo* native coronary artery lesions in diabetic patients with CAD. This section provides an overview of the SAP and the results supporting the use of the XIENCE stent in patients with diabetes mellitus (DM).

Primary Objective: To evaluate the safety and effectiveness of the XIENCE stent for the treatment of *de novo* lesions in native coronary arteries in diabetic patients.

Population: The analysis population consists of diabetic patients from the following trial / registry databases:

- SPIRIT IV
- SPIRIT PRIME (including Core Size Registry and Long Lesion Registry)
- XIENCE V USA First Enrollment Phase
- XIENCE V USA Second Enrollment Phase
- External databases: Cleveland Clinic and Wake Forest Baptist Medical Center databases

A total of 1239 patients were included in the DM analysis. The contributions of patients from each trial / registry database were: SPIRIT IV (N = 451); SPIRIT PRIME (N = 121); XIENCE V USA First Enrollment Phase (N = 185); XIENCE V USA Second Enrollment Phase (N = 192); and the pooled external databases from Cleveland Clinic and Wake Forest (N = 290).

Design: A Bayesian hierarchical modeling approach was utilized to analyze the primary endpoint of Target Vessel Failure (TVF) at 12 months, defined as a composite of cardiac death, Target-Vessel Myocardial Infarction (TVMI), and Ischemia-Driven Target Vessel Revascularization (ID-TVR), which was tested against a pre-specified performance goal of 14.8% (expected rate 8.6% plus a delta of 6.2%).

Results from the six data sources were used in the analysis. Data from the four historical Abbott Vascular (AV) sponsored trial databases (SPIRIT IV, SPIRIT PRIME, XIENCE V USA first enrollment phase, and XIENCE V USA second enrollment phase) were considered as prior information. The two external XIENCE databases (Cleveland Clinic and Wake Forest) were pooled as current data and served as the basis for statistical inference.

Patients were included in the analysis if they have diabetes mellitus (based on medical history) and had at least one XIENCE stent implanted for the treatment of up to two *de novo* lesions (each located in a different epicardial vessel) < 32 mm in length in native coronary arteries with an RVD between 2.25 and 4.25 mm. The other clinical and lesion criteria of the diabetic analysis population are consistent with the enrollment criteria of the SPIRIT III US Pivotal Clinical Trial.

Demographics and Lesion Characteristics: The mean age of the diabetic population was 63 years from the pooled historical AV trials (SPIRIT IV, SPIRIT PRIME, XIENCE V USA first enrollment phase and second enrollment phase) and 65 years from the pooled two external databases (Wake Forest and Cleveland Clinic). There were 62.8% males from the pooled AV trials and 64.1% from the pooled external databases. Insulin treated diabetic patients comprised

of 25.9% and 35.5% of the overall diabetic analysis population from the pooled AV trials and pooled external databases, respectively. A total of 26.6% of patients presented with unstable angina from the pooled AV trials and 57.6% from the pooled external databases. There were 23.8% and 35.9% patients who had prior MI, 34.2% and 44.8% who had prior PCI, and 10.5% and 24.5% who had prior CABG from the pooled AV trials and pooled external databases, respectively. The mean lesion length was 13.5 mm for the pooled AV trials, and 16.3 mm for the pooled external databases. There were 12.0% type C lesions in the pooled AV trials and 25.5% in the pooled external databases. There were 2.6% (32/1239) patients treated with 33 or 38 mm stents in this pooled dataset (2.5% from the pooled AV trials, and 2.8% from the pooled external databases). Compared to the pooled AV trials, patient and lesion characteristics in the two external databases were generally more complex, likely due to their non-trial real-world settings.

Primary Endpoint Results: The primary endpoint of TVF rate at 1-year was evaluated in diabetic patients from the six trial / registry databases using a Bayesian statistical model. The posterior mean of 1-year TVF rate was 8.04%. The posterior probability of a 1-year TVF rate < 14.8% (performance goal) is > 0.999 (*Table 9.9.2-1*), which exceeds the pre-specified success criteria (> 0.975). Therefore, the XIENCE stent met the pre-specified success criteria for the primary endpoint of 1-year TVF.

Table 9.9.2-1: The XIENCE Diabetic Bayesian Analysis Primary Endpoint

Primary Endpoint	TVF Rate [95% Central Posterior Interval]*	Bayesian Posterior Probability (TVF < 14.8%)
1-year TVF	8.04% [5.23%, 11.52%]	> 0.999

* The posterior mean is the Bayesian posterior average; the 95% central posterior interval is the symmetric 95% Bayesian credible interval, similar to the 95% confidence interval.

Notes:

- The 1-year window is through 393 days (365 + 28 days).
- TVF is defined as hierarchical composite of cardiac death, target vessel MI, and ischemia-driven TVR. For the primary composite endpoint of TVF, an adjustment factor of 0.826 was applied to one of the external databases to calculate the TVF rate based on the composite rate of all death/all MI/all TVR as the specifics of these events were not available from that database.

1-Year Clinical Outcomes: The 1-year clinical outcomes of the XIENCE diabetic population from each of the AV trials (SPIRIT IV, SPIRIT PRIME and XIENCE V USA) and the pooled two external databases are presented in *Table 9.9.2-2*.

Table 9.9.2-2: One-Year Clinical Outcomes of the XIENCE Diabetic Population

	SPIRIT IV (N = 451)	SPIRIT PRIME (N = 121)	XV USA 5K (N = 185)	XV USA 3K (N = 192)	Pooled External (N = 290)
TVF	7.9% (34/433)	11.8% (14/119)	7.3% (13/178)	3.6% (6/169)	8.0% (21/261)
TLF	5.5% (24/433)	5.9% (7/119)	6.7% (12/178)	2.4% (4/169)	2.4% (3/126)
Cardiac death or TVMI	3.0% (13/433)	2.5% (3/119)	3.4% (6/178)	0.6% (1/169)	0.8% (1/126)
ID-TVR	5.5% (24/433)	9.2% (11/119)	5.1% (9/178)	3.0% (5/169)	6.3% (8/126)
ID-TLR	3.2% (14/433)	3.4% (4/119)	3.9% (7/178)	1.8% (3/169)	2.4% (3/126)
Death	1.4% (6/433)	0.0% (0/119)	2.2% (4/178)	1.2% (2/169)	3.1% (8/261)
Cardiac death	0.9% (4/433)	0.0% (0/119)	1.1% (2/178)	0.6% (1/169)	0.0% (0/126)
TVMI	2.3% (10/433)	2.5% (3/119)	2.2% (4/178)	0.0% (0/169)	0.8% (1/126)
ST (ARC def / prob)	0.9% (4/431)	0.0% (0/119)	0.0% (0/175)	0.6% (1/169)	0.8% (2/261)

Notes:

- Numbers presented in this table are % (n/N).
- The 1-year window is through 393 days (365 + 28 days).
- XV USA 5K refers to the first enrollment phase of 5,000 patients in the XIENCE V USA study; XV USA 3K refers to the second enrollment phase of 3,000 patients in the XIENCE V USA study; pooled external refers to the pooled analysis of the two external databases (Cleveland Clinic and Wake Forest).
- TVF is defined as hierarchical composite of cardiac death, target vessel MI, and ischemia-driven TVR; TLF is defined as hierarchical composite of cardiac death, target vessel MI, and ischemia-driven TLR. ID-TLR= ischemia driven target lesion revascularization; ID-TVR=ischemia driven target vessel revascularization; TVMI=target vessel myocardial infarction; ST (ARC def/prob) = definite or probable stent thrombosis defined per the ARC definition.
- MI from the historical AV trials was defined per protocol and was categorized as Q-wave (development of new, pathological Q waves on the ECG) or non-Q-wave (elevation of CK levels to greater than two times the upper limit of normal and elevated CK-MB in the absence of new pathological Q waves). For the two external databases, MI was defined based on Universal MI definition per the National Cardiovascular Data Registry (NCDR) requirement.
- For the primary composite endpoint of TVF, an adjustment factor of 0.826 was applied to one of the two external databases in order to calculate the TVF rate based on the composite rate of all death/all MI/all TVR, as the specifics of these events were not available from that database.
- For other endpoints (TLF, cardiac death or TVMI, ID-TLR, ID-TVR, cardiac death and TVMI), only one of the external databases was included in the analysis, as the specific event information was not available in the other external database.

9.10 Clinical Data on Multiple Stent Use

The XIENCE Skypoint EECSS is the newest member of the XIENCE™ Family of Stents. The XIENCE Skypoint EECSS is based on the predicate XIENCE Sierra™, XIENCE Alpine™, XIENCE Xpedition, XIENCE PRIME and XIENCE V EECSS. Therefore, the extensive body of XIENCE PRIME and XIENCE V EECSS clinical data is supportive of the performance of the XIENCE Skypoint EECSS.

In the SPIRIT II, SPIRIT III, and SPIRIT IV clinical trials, lesions > 22 mm in length and ≤ 28 mm in length were treated with planned overlapping XIENCE V stents in the XIENCE V EECSS arm, or a single 32 mm TAXUS stent or planned overlapping TAXUS stents in the TAXUS arm.

In the SPIRIT IV clinical trial, there were 239 patients in the planned overlapping XIENCE V stent subgroup, 55 patients in the single 32 mm TAXUS stent subgroup, and 99 patients in the planned overlapping TAXUS subgroup (with 6 patients in the TAXUS arm receiving both single 32 mm and overlapping TAXUS stents). At two years, the Target Lesion Failure (TLF) rate was 11.9% in the planned overlapping XIENCE V stent subgroup, 11.3% in the single 32 mm TAXUS stent subgroup, and 12.9% in the planned overlapping TAXUS stent subgroup.

In the pooled SPIRIT II, SPIRIT III, and SPIRIT IV analysis, there were a total of 317 patients in the planned overlapping XIENCE V stent subgroup, 86 patients in the single 32 mm TAXUS stent subgroup, and 113 patients in the planned overlapping TAXUS stent subgroup. At two years, the TLF rate was 11.7% in the planned overlapping XIENCE V stent subgroup, 12.2% in the single 32 mm TAXUS stent subgroup, and 12.1% in the planned overlapping TAXUS stent subgroup. At two years, the all-cause mortality rate was 3.2% in the planned overlapping XIENCE V stent subgroup, 4.9% in the single 32 mm TAXUS stent subgroup, and 1.9% in the planned overlapping TAXUS stent subgroup. The cardiac death rate was 1.0% in the planned overlapping XIENCE V stent subgroup, 1.2% in the single 32 mm TAXUS stent subgroup, and 0.9% in the planned overlapping TAXUS stent subgroup. At two years, the rate of target vessel MI was 3.2% in the planned overlapping XIENCE V stent subgroup, 7.3% in the single 32 mm TAXUS stent subgroup, and 3.7% in the planned overlapping TAXUS stent subgroup. The Academic Research Consortium (ARC)-defined definite plus probable stent thrombosis rate at two years was 0.7% in the planned overlapping XIENCE V stent subgroup, 1.3% in the single 32 mm TAXUS stent subgroup, and 1.9% in the planned overlapping TAXUS stent subgroup.

In XIENCE V USA, there was no angiographic restriction for patient enrollment. Stent implantation was done per site's standard care. There were 8040 patients with a total of 11,137 lesions treated during the index procedure. The mean lesion length was 15.8 mm, with 29% of those ≥ 20 mm in length based on visual estimation. Approximately 40.8% of patients had 2 or more stents implanted during the index procedure with a total of 12,873 XIENCE V stents implanted. The mean stent length was 29.2 mm per patient and 21.2 mm per lesion. Stent overlaps occurred in 14.5% of the lesions treated during the index procedure.

In XIENCE V USA, there were 1301 (16.7%) patients with 1577 lesions (14.5%) where stent overlapping during the index procedure was reported, including situations where an implanted XIENCE V stent overlaps with a previously implanted stent prior to the index procedure. At 1 year, the composite of cardiac death or target vessel MI rate (defined by ARC) was 9.8%, the ARC definite and probable ST rate was 1.40%, TLF (composite of cardiac death, target vessel MI [per ARC] and clinically indicated TLR) was 13.1%.

9.11 XIENCE Short DAPT Program

The short DAPT program was designed to evaluate the safety of shorter DAPT duration in patients at high bleeding risk (HBR) undergoing PCI with the XIENCE Family of Stents, and provides data to support indication for HBR patients. The XIENCE 90 trial, which was conducted in the United States, evaluated the safety of 3-month DAPT post-PCI, while the combined population from the XIENCE 28 USA (conducted in United States and Canada) and the XIENCE 28 Global (conducted in Europe and Asia) trials assessed the safety of 1-month DAPT. Both XIENCE 28 trials had similar designs, and analysis of the combined population from the two XIENCE 28 trials was pre-specified in the statistical analysis plan (SAP) of the XIENCE 28 USA trial.

In all three short DAPT trials, subjects were considered HBR if at least one of the following criteria was fulfilled at the time of registration and in the opinion of the referring physician, the risk of major bleeding with > 3-month (XIENCE 90) or > 1-month (XIENCE 28 USA and XIENCE 28 Global) DAPT outweighed the benefit:

a) ≥ 75 years of age.
b) Clinical indication for chronic (at least 6 months) or lifelong anticoagulation therapy.
c) History of major bleeding which required medical attention within 12 months of the index procedure.
d) History of stroke (ischemic or hemorrhagic).
e) Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent).
f) Systemic conditions associated with an increased bleeding risk (e.g., hematological disorders, including a history of or current thrombocytopenia defined as a platelet count <100,000/mm^3, or any known coagulation disorder associated with increased bleeding risk).
g) Anemia with hemoglobin < 11g/dl.

For both XIENCE 90 and XIENCE 28 analyses, the results were compared to XIENCE V USA historical control, a US post-approval study to evaluate the safety of XIENCE V EECSS in an “all-comer” population under a real-world setting, for the primary and secondary endpoints.

9.11.1 XIENCE 90 Clinical Trial

Primary Objective: To show non-inferiority of the primary endpoint of all death or all MI (modified ARC) from 3 to 12 months following XIENCE stents implantation in HBR subjects treated with 3-month DAPT compared to a historical control after propensity score (PS) adjustment.

Secondary Objectives:

- To show superiority of the major secondary endpoint of major bleeding (Bleeding Academic Research Consortium [BARC] type 2–5) from 3 to 12 months following XIENCE stent implantation in HBR subjects treated with 3-month DAPT compared to a historical control after PS adjustment.
- To evaluate stent thrombosis (ARC definite / probable) from 3 to 12 months following XIENCE stent implantation in HBR subjects treated with 3-month DAPT against a performance goal (PG).

Design: XIENCE 90 was a prospective, single-arm, multicenter, open-label trial to evaluate the safety of 3-month DAPT in subjects at high risk of bleeding undergoing PCI with the approved XIENCE Family of Stents.

For the primary endpoint of all death or all MI and the secondary endpoint of BARC 2–5, the primary analysis population for the XIENCE 90 study was the 3-month clear subjects, and these subjects were compared with the 3-month clear population of the historical control of non-complex HBR subjects treated with standard DAPT duration of up to 12 months from the XIENCE V USA study. For the powered secondary endpoint of stent thrombosis, XIENCE 90 3-month clear subjects were evaluated against a performance goal. The derivation of the performance goal was based on the pooled (from bare metal stents and drug coated stents arms) 1-year rate of ST (2.1%) from the LEADERS FREE trial[35]. This rate was discounted by approximately 40% to account for the censoring of events in the first 3 months post-PCI in XIENCE 90.

The study population consisted of non-complex HBR subjects with up to three native coronary artery lesions (a maximum of two lesions per epicardial vessel) with reference vessel diameter between 2.25 mm and 4.25 mm. The subjects were treated with XIENCE stents per standard of care in accordance to the XIENCE Family of Stents IFU. Eligibility of P2Y12 receptor inhibitor discontinuation was assessed at 3-month follow-up. Subjects who were free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, or stent thrombosis (ARC definite / probable) within 3 months (prior to 3-month visit but at least 90 days) after stenting and have been compliant with 3-month DAPT without interruption of either aspirin and / or P2Y12 receptor inhibitor for > 7 consecutive days were considered as “3-month clear,” and were to discontinue P2Y12 receptor inhibitor and continue with aspirin monotherapy after the 3-month follow-up. All registered subjects were followed at 3, 6, and 12 months post-index procedure.

Demographics and Lesion Characteristics: The primary analysis population included a total of 1,693 patients with 2,078 lesions that were treated with a total of 2,119 XIENCE stents during the index procedure. Baseline characteristics (*Table 9.11.1-1*) and HBR criteria met (*Table 9.11.1-2*) are summarized below.

[35] Urban P, Meredith IT, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med*. 2015;373:2038-47.

Table 9.11.1-1: XIENCE 90 Baseline Characteristics for 3-Month Clear Population

Analysis population: 1,693 patients; 2,078 lesions; 2,119 stents			
Patient Demographics		**Procedural Characteristics**	
Age, years (Mean ± SD)	75.25 ± 9.29 (1693)	**Target lesion location**	
Gender (Female)	35.2% (596/1693)	LAD	43.2% (898/2078)
Race (White)	88.4% (1496/1693)	LCX	24.7% (513/2078)
Current / Recent Smoker	11.6% (197/1693)	RCA	32.0% (665/2078)
Hypertension	89.5% (1516/1693)	LMCA	0.1% (2/2078)
Dyslipidemia	82.8% (1401/1693)	**Number of lesions treated**	
Diabetes	39.2% (663/1692)	1 lesion treated	80.2% (1358/1693)
CKD (eGFR < 60 mL/min)	40.2% (677/1682)	2 lesions treated	16.9% (286/1693)
Prior MI	15.8% (264/1669)	≥ 3 lesions treated	2.9% (49/1693)
Prior CABG	12.1% (205/1693)	**Number of vessels treated**	
ACS	34.7% (588/1693)	1 vessel treated	89.7% (1518/1693)
NSTEMI	7.1% (120/1693)	2 vessels treated	10.0% (170/1693)
Unstable angina	28.7% (486/1693)	3 vessels treated	0.3% (5/1693)
PARIS score	6.0 ± 2.3 (1693)	**Number of stents per patient**	
PRECISE-DAPT score	26.1 ± 11.5 (1606)	1 stent per subject	79.1% (1339/1693)
Lesion Characteristics		2 stents per subject	17.1% (289/1693)
Mean RVD (pre-procedure) (mm)	2.99 ± 0.49 (2078)	≥ 3 stents per subject	3.8% (65/1693)
Mean lesion length (mm)	16.0 ± 7.1 (2078)	**Stent Type**	
% DS (pre-procedure)	83.7 ± 10.3 (2078)	XIENCE Sierra	66.4%(1406/2119)
B2/C lesion	32.1% (667/2078)	XIENCE Alpine	33.6% (711/2119)
Thrombus	0.1% (2/2078)	Stents Other than XIENCE	0.1% (2/2119)
Bifurcation	6.6% (138/2078)	–	–

Note: Numbers presented here are % (n/N) or mean ± SD (N).

Table 9.11.1-2: XIENCE 90 HBR Criteria for All Registered Subjects and 3-Month Clear Population

	XIENCE 90 All Registered (N = 2047)	XIENCE 90 3-Month Clear (N = 1693)
HBR criteria met ≥ 75 years of age	65.6% (1342/2047)	66.5% (1125/1693)
≥ 75 years of age only (and no other criteria met)	35.5% (727/2047)	36.5% (618/1693)
Clinical indication for chronic or lifelong anticoagulation therapy	40.8% (836/2047)	41.6% (705/1693)
History of major bleeding which required medical attention within 12 months of the index procedure	2.9% (60/2047)	2.9% (49/1693)
History of stroke (ischemic or hemorrhagic)	11.3% (232/2047)	10.7% (181/1693)
Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent)	8.0% (164/2047)	7.7% (131/1693)
Systemic conditions associated with an increased bleeding risk	3.0% (61/2047)	2.8% (48/1693)
Anemia with hemoglobin < 11g/dl	16.2% (332/2047)	15.0% (254/1693)
Number of HBR criteria met Mean ± SD (N)	1.5 ± 0.7 (2047)	1.5 ± 0.7 (1693)
One criterion met	61.7% (1262/2047)	61.9% (1048/1693)
≥ 2 criteria met	38.3% (784/2047)	38.1% (645/1693)
≥ 3 criteria met	8.2% (167/2047)	7.9% (133/1693)

Note: Numbers presented here are % (n/N) or mean ± SD (N).

Results: The primary endpoint was met demonstrating that the XIENCE Family of Stents is safe in HBR patients treated with 3-month (as short as 90 days) DAPT post-PCI. Based on the number of patients and observed rates in each stratum, the results show a non-inferiority p-value of 0.0063, meeting the pre-specified significance level of 0.025. The 3–12 months Propensity Score (PS) stratified mean rate for all death / all MI in 3-month clear patients was 5.4% for both XIENCE 90 and XIENCE V USA historical control (*Table 9.11.1-3*). This demonstrated that the 3-12 months composite rate of all death / all MI for the 3-month DAPT regimen is non-inferior to the 12-month DAPT regimen recommended in the historical control.

The PS stratification method was also used to compare the XIENCE 90 trial arm to historical control for the secondary endpoint of BARC 2–5 bleeding. Based on the number of patients and observed rates in each stratum, the results show a superiority p-value of 0.0687, which did not meet the pre-specified significance level of 0.025. Although the significance level was not met, the 3–12 months PS stratified mean rate of BARC 2–5 bleeding in 3-month clear patients was numerically lower in XIENCE 90 as compared to the historical control (5.1% vs. 7.0%; *Table 9.11.1-3*). Even though it was not pre-specified, the PS stratification methodology was used to provide a comparison of BARC 3–5[36] bleeding rates between XIENCE 90 and XIENCE V USA historical control. The observed 3–12 months BARC 3–5 bleeding rate was 2.2% in XIENCE 90 subjects as compared to 6.3% in XIENCE V USA subjects (*Table 9.11.1-4*). An observed 65% reduction in BARC 3-5 bleeding with 3-month DAPT as compared to 12-month

[36] Mehran R, Rao SV, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736-47, ibid.

DAPT suggests that severe bleeding may be less with the shorter duration of DAPT. The stent thrombosis rate for XIENCE 90 trial arm is 0.2%, which was significantly lower than the pre-specified performance goal of 1.2% (p-value < 0.0001; *Table 9.11.1-5*).

Clinical outcomes for other secondary endpoints, without PS stratification adjustment, are summarized in *Table 9.11.1-6*.

Table 9.11.1-3: XIENCE 90 Primary and Powered Secondary Endpoint Results – All Death / All MI and BARC 2–5 Bleeding from 3–12 Months in 3-Month Clear Subjects

	XIENCE 90 (N = 1693)	XIENCE V USA (N = 1280)	Difference [95% CI]	p-value*
All death / All MI	5.4%	5.4%	0.15% [-1.93%, 2.23%]	0.0063**
BARC 2–5 bleeding	5.1%	7.0%	-1.72% [-4.00%, 0.55%]	0.0687***

*Stratified Farrington-Manning method is carried out using PS stratified data in each imputed dataset, and Rubin's combination rule is applied to integrate the final test results from each imputed dataset.
**The test is carried out with a non-inferiority margin of 2.8% against a one-sided significance level of 0.025.
***The superiority test is carried out against a one-sided significance level of 0.025.

Notes:
- Subjects are only counted once for each type of event in each time period.
- Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators.
- Subjects who are lost to follow-up without any DMR event (death, MI [modified ARC], revascularization) are excluded.
- Subjects who are lost to follow-up without any bleeding event (BARC 1–5) are excluded.

Table 9.11.1-4: XIENCE 90 PS Stratified Analysis of BARC 3–5 Bleeding from 3–12 Months in 3-Month Clear Patients

	XIENCE 90 (N = 1693)	XV USA (N = 1280)
BARC 3–5 bleeding (PS stratified mean rate)	2.2%	6.3%

Notes:
- Subjects are only counted once for each type of event in each time period.
- Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators.
- Subjects who are lost to follow-up without any bleeding event (BARC 1-5) are excluded.
- Not pre-specified PS stratified analysis.

Table 9.11.1-5: XIENCE 90 Powered Secondary Endpoint Result – Stent Thrombosis from 3–12 Months in 3-Month Clear Subjects

	XIENCE 90 (N = 1693)	Upper Limit of Two-Sided 95% Confidence Interval	PG	p-value
Stent Thrombosis (ARC definite / probable)	0.2% (4/1635)	0.63%	1.2%	< 0.0001

Notes:
- Subjects are only counted once for each type of event in each time period.
- Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators.
- Subjects who are lost to follow-up without any Stent Thrombosis event are excluded.

Table 9.11.1-6: XIENCE 90 Secondary Endpoint Results 3–12 Months in 3-Month Clear Subjects (Not Propensity Score Stratified)

	XIENCE 90 (N = 1693)	XIENCE V USA (N = 1280)
Safety		
All Death / All MI (modified ARC)	5.5% (92/1672)	4.4% (55/1246)
All Death	3.2% (54/1672)	2.6% (32/1246)
Cardiac Death	1.7% (29/1672)	1.2% (15/1246)
Vascular Death	0.1% (2/1672)	0.2% (3/1246)
Non-cardiovascular Death	1.4% (23/1672)	1.1% (14/1246)
All MI (modified ARC)	2.9% (48/1672)	2.2% (28/1246)
Target Vessel MI (TV-MI, modified ARC)	2.4% (40/1672)	2.1% (26/1246)
Cardiac Death / All MI (modified ARC)	4.0% (67/1672)	3.1% (39/1246)
Major Bleeding (BARC 2–5)	5.8% (95/1629)	5.2% (63/1217)
Major Bleeding (BARC 3–5)	2.5% (41/1629)	4.4% (53/1217)
All Stroke	1.3% (21/1624)	0.6% (2/355)
Ischemic Stroke	1.2% (19/1624)	0.6% (2/355)
Hemorrhagic Stroke	0.1% (2/1624)	NA
Effectiveness		
Clinically indicated Target Lesion Revascularization (CI-TLR)	1.0% (16/1672)	1.4% (18/1246)
Clinically indicated Target Vessel Revascularization (CI-TVR)	1.6% (26/1672)	2.9% (36/1246)
Safety and Effectiveness		
Target Lesion Failure (TLF)	3.9% (66/1672)	4.1% (51/1246)
Target Vessel Failure (TVF)	4.2% (70/1672)	5.0% (62/1246)
Stent Thrombosis (ARC definite / probable)	0.2% (4/1635)	0.3% (4/1225)

Notes:

- Subjects are only counted once for each type of event in each time period.
- Hemorrhagic and Ischemic Strokes not collected for XIENCE V USA Phase I; Hemorrhagic Strokes not collected for XIENCE V USA Phase II.
- Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators.
- Subjects who are lost to follow-up without any DMR event (death, MI [modified ARC], revascularization) are excluded; for Stent Thrombosis, Major Bleeding, and Stroke, subjects who are lost to follow-up without a related event (Stent Thrombosis, BARC [1–5], or Stroke, respectively) are excluded.

9.11.2 Pooled Analysis of XIENCE 28 USA and XIENCE 28 Global Clinical Trials

Primary Objective: To show non-inferiority of the primary endpoint of all death or all MI (modified ARC) from 1 to 6 months following XIENCE stent implantation in HBR subjects treated with 1-month DAPT compared to a historical control after PS adjustment.

Secondary Objective: To show superiority of the major secondary endpoint of major bleeding (Bleeding Academic Research Consortium [BARC] type 2–5) from 1 to 6 months following XIENCE stent implantation in HBR subjects treated with 1-month DAPT compared to a historical control (XIENCE V USA) after PS adjustment.

Design: As pre-specified in the XIENCE 28 USA SAP, the XIENCE 28 analysis was conducted on the combined populations from XIENCE 28 USA and XIENCE 28 Global trials. Both trials were prospective, single-arm, multicenter, open-label trials to evaluate the safety of 1-month (as short as 28 days) DAPT in subjects at high risk of bleeding undergoing PCI with the approved XIENCE Family of Stents.

The study population consists of non-complex HBR subjects with up to three native coronary artery lesions (a maximum of two lesions per epicardial vessel) with reference vessel diameter between 2.25 mm and 4.25 mm. The subjects were treated with XIENCE stents per standard of care in accordance to the XIENCE Family of Stents IFU. Eligibility of P2Y12 receptor inhibitor discontinuation was assessed at 1-month follow-up. Subjects who are free from myocardial infarction (modified ARC), repeat coronary revascularization, stroke, and stent thrombosis (ARC definite / probable), within 1 month (prior to 1-month visit but at least 28 days) after stenting AND have been compliant with 1-month DAPT without interruption of either aspirin and / or P2Y12 receptor inhibitor for > 7 consecutive days, are considered "1-month clear," and discontinued P2Y12 receptor inhibitor as early as at 28 days and continue with aspirin monotherapy through 12-month follow-up. All registered subjects were followed at 1, 3, 6, and 12 months post-index procedure.

The primary analysis population for the XIENCE 28 analysis is the 1-month clear subjects. As pre-specified in the XIENCE 28 USA SAP, the analysis was conducted using the combined patient populations from XIENCE 28 Global and XIENCE 28 USA, and compared with the 1-month clear population in the historical control of non-complex HBR subjects treated with standard DAPT duration of up to 12 months from the XIENCE V USA Study.

Demographics and Lesion Characteristics: The primary analysis population included a total of 1,392 patients with 1,700 lesions that were treated with a total of 1,734 XIENCE stents during the index procedure. Baseline characteristics (*Table 9.11.2-1*), HBR criteria met (*Table 9.11.2-2*) and key endpoint results 1 through 6 months are summarized below.

Table 9.11.2-1: XIENCE 28 Baseline Characteristics for 1-Month Clear Population

Analysis population: 1,392 patients; 1,700 lesions; 1,734 stents			
Patient Demographics		**Procedural Characteristics**	
Age, years (Mean ± SD)	75.97 ± 8.37 (1392)	**Target lesion location**	
Gender (Female)	32.5% (453/1392)	LAD	45.9% (781/1700)
Race (White)	58.0% (807/1392)	LCX	24.1% (409/1700)
Current / Recent Smoker	14.7% (205/1392)	RCA	29.9% (509/1700)
Hypertension	84.7% (1179/1392)	LMCA	0.1% (1/1700)
Dyslipidemia	67.5% (939/1392)	**Number of lesions treated**	
Diabetes	37.0% (512/1382)	1 lesion treated	80.3% (1118/1392)
CKD (eGFR < 60 mL/min)	47.4% (631/1330)	2 lesions treated	17.2% (240/1392)
Prior MI	16.4% (227/1382)	≥ 3 lesions treated	2.4% (34/1392)
Prior CABG	8.0% (112/1392)	**Number of vessels treated**	
ACS	34.1% (475/1392)	1 vessel treated	88.2% (1228/1392)
NSTEMI	17.6% (245/1392)	2 vessels treated	11.6% (162/1392)
Unstable Angina	16.5% (230/1392)	3 vessels treated	0.1% (2/1392)
PARIS Score	6.1 ± 2.3 (1392)	**Number of stents per patient**	
PRECISE-DAPT Score	27.7 ± 11.3 (1295)	1 stent per subject	78.7% (1093/1389)
Lesion Characteristics		2 stents per subject	17.9% (249/1389)
Mean RVD (pre-procedure) (mm)	2.99 ± 0.50 (1700)	≥ 3 stents per subject	3.4% (47/1389)
Mean Lesion Length (mm)	18.01 ± 8.43 (1700)	**Stent Type**	
% DS (pre-procedure)	82.47 ± 10.80 (1699)	XIENCE Alpine	29.9% (518/1734)
B2/C Lesion	33.9% (576/1697)	XIENCE Xpedition	7.9% (137/1734)
Thrombus	3.6% (61/1700)	XIENCE Sierra	62.2% (1079/1734)
Bifurcation	9.8% (167/1700)		

Note: Numbers presented here are % (n/N) or mean ± SD (N).

Table 9.11.2-2: XIENCE 28 HBR Criteria for All Registered Subjects and 1-Month Clear Population

	XIENCE 28 All Registered (N = 1605)	XIENCE 28 1-Month Clear (N = 1392)
HBR Criteria Met ≥ 75 Years of Age	69.3% (1112/1605)	68.2% (950/1392)
≥ 75 Years of Age only (and No Other Criteria Met)	35.1% (563/1605)	35.1% (488/1392)
Clinical Indication for Chronic or Lifelong Anticoagulation Therapy	43.9% (704/1605)	44.3% (617/1392)
History of Major Bleeding which Required Medical Attention within 12 Months of the Index Procedure	3.6% (57/1605)	3.3% (46/1392)
History of Stroke (Ischemic or Hemorrhagic)	10.8% (174/1605)	10.4% (145/1392)
Renal Insufficiency (Creatinine ≥ 2.0 mg/dl) or Failure (Dialysis Dependent)	8.6% (138/1605)	8.3% (116/1392)
Systemic Conditions Associated with an Increased Bleeding Risk	3.9% (63/1605)	4.0% (55/1392)
Anemia with Hemoglobin < 11 g/dl	15.2% (244/1605)	14.4% (201/1392)
Number of HBR criteria met Mean ± SD (N)	1.6 ± 0.8 (1603)	1.5 ± 0.7 (1391)
One criterion met	57.8% (927/1603)	58.7% (816/1391)
≥ 2 criteria met	42.0% (674/1603)	41.3% (575/1391)
≥ 3 criteria met	10.7% (172/1603)	9.3% (129/1391)

Note: Numbers presented here are % (n/N) or mean ± SD (N).

Results: The primary endpoint was met demonstrating that XIENCE stents are safe in HBR patients treated with 1-month (as short as 28 days) DAPT post-PCI. Based on the number of patients and observed rates in each stratum, the results show a non-inferiority p-value of 0.0005, meeting the pre-specified significance level of 0.025. The 1–6 months PS stratified mean rate for all death / all MI in 1-month clear patients was 3.5% in XIENCE 28 vs. 4.3% in XIENCE V USA historical control (*Table 9.11.2-3*). This demonstrated that the 1-6 months composite rate of all death / all MI for the 1-month DAPT regimen is non-inferior to 6-months DAPT regimen.

The PS stratification method was also used to compare the XIENCE 28 patient population to historical control for the endpoint of BARC 2–5 bleeding. Based on the number of patients and observed rates in each stratum, the results show a superiority p-value of 0.1888, which did not meet the pre-specified significance level of 0.025. Although the significance level was not met, the 1–6 months PS stratified mean rate of BARC 2–5 bleeding in 1-month clear patients was numerically lower in XIENCE 28 as compared to the historical control (4.9% vs. 5.9%; *Table 9.11.2-3*). Although not pre-specified, the PS stratification methodology was used to provide a comparison of BARC 3–5 bleeding rates between XIENCE 28 and XIENCE V USA. The observed 1–6 months BARC 3–5 bleeding rate was 2.2% in XIENCE 28 subjects as compared to 4.5% in XIENCE V USA subjects (*Table 9.11.2-4*). An observed 51% reduction in BARC 3-5 bleeding with 1-month DAPT as compared to 6-month DAPT suggests that severe bleeding may be less with the shorter duration of DAPT.

Clinical outcomes for other secondary endpoints, without PS stratification adjustment, are summarized in *Table 9.11.2-5*.

Table 9.11.2-3: XIENCE 28 Primary and Powered Secondary Endpoint Results – All Death / All MI and BARC 2–5 Bleeding from 1–6 Months in 1-Month Clear Subjects

	XIENCE 28 (N = 1392)	XIENCE V USA (N = 1411)	Difference [95% CI]	p-value
All death / All MI	3.5%	4.3%	-0.97% [-3.02%, 1.09%]	*0.0005
BARC 2–5 bleeding	4.9%	5.9%	-1.07% [-3.45%, 1.31%]	**0.1888

Notes:
- Stratified Farrington-Manning method is carried out using PS stratified data in each imputed dataset, and Rubin's combination rule is applied to integrate the final test results from each imputed dataset.
- *Denominator includes subjects with the DMR (Death, ARC MI and Revascularization) or subjects without the DMR who had 6 months visit or had 180 days in the study (i.e., without early termination).
- *Non-Inferiority margin and one-sided significant level are 2.5% and 0.025, respectively.
- **Denominator includes subjects with any BARC bleeding or subjects who had 6 months visit or had 180 days in the study (i.e., without early termination).
- **Superiority one-sided significant is 0.025.

Table 9.11.2-4: XIENCE 28 PS Stratified Analysis of BARC 3–5 Bleeding from 1–6 Months in 1-Month Clear Patients

	XIENCE 28 (N = 1392)	XV USA (N = 1411)
BARC 3–5 bleeding (PS stratified mean rate)	2.2%	4.5%

Notes:
- Denominator includes subjects with any BARC bleeding or subjects who had 6 months visit or had 180 days in the study (i.e., without early termination).
- Not pre-specified PS stratified analysis.

Table 9.11.2-5: XIENCE 28 Secondary Endpoint Results 1–6 Months in 1-Month Clear Subjects (Not Propensity Score Stratified)

	XIENCE 28 (N = 1392)	XIENCE V USA (N = 1411)
Safety		
All Death / All MI (modified ARC)	3.3% (46/1380)	3.2% (45/1399)
All Death	1.7% (23/1380)	1.9% (27/1399)
Cardiac Death	0.9% (12/1380)	1.1% (15/1399)
Vascular Death	0.1% (2/1380)	0.3% (4/1399)
Non-cardiovascular Death	0.7% (9/1380)	0.6% (8/1399)
All MI (modified ARC)	1.7% (24/1380)	1.8% (25/1399)
Target Vessel MI (TV-MI, modified ARC)	1.5% (21/1380)	1.4% (19/1399)
Cardiac Death/All MI (modified ARC)	2.5% (35/1380)	2.4% (34/1399)
Major Bleeding (BARC 2–5)	5.3% (72/1362)	4.3% (60/1380)
Major Bleeding (BARC 3–5)	2.4% (33/1362)	3.6% (49/1380)
All Stroke	0.3% (4/1357)	0.2% (3/1373)
Ischemic Stroke	0.2% (3/1357)	0.2% (3/1373)
Hemorrhagic Stroke	0.1% (1/1357)	0.0% (0/1373)
Effectiveness		
Clinically indicated Target Lesion Revascularization (CI-TLR)	0.7% (10/1380)	1.4% (20/1399)
Clinically indicated Target Vessel Revascularization (CI-TVR)	0.1% (14/1380)	1.7% (24/1399)
Safety and Effectiveness		
Target Lesion Failure (TLF)	2.5% (35/1380)	3.2% (45/1399)
Target Vessel Failure (TVF)	2.8% (38/1380)	3.3% (46/1399)
Stent Thrombosis (ARC definite / probable)	0.3% (4/1361)	0.3% (4/1387)

Notes:
- Subjects are only counted once for each type of event in each time period.
- Subjects who are on or beyond the target day of follow-up visit (i.e., 30 days and 180 days) at the time of data extraction are included in the denominators.

9.12 SPIRIT 48 Clinical Trial

9.12.1 Overview of SPIRIT 48 Clinical Study

Objectives

The objective of the SPIRIT 48 study was to evaluate the safety and effectiveness of 48 mm stent length of the XIENCE Skypoint stent system in improving coronary artery luminal diameter in subjects with coronary artery disease (CAD) due to *de novo* native coronary artery long lesions.

Study Design

The SPIRIT 48 study was a prospective, single-arm, open-label, multi-center clinical investigation in 107 subjects at 25 global sites to evaluate the safety and effectiveness of 48 mm stent length of XIENCE Skypoint in the treatment of *de novo* native coronary artery long lesions. This study registered subjects with a maximum of two *de novo* coronary artery lesions, of which, only one target lesion was allowed and required to be treated by 48 mm stent length of XIENCE Skypoint. The other lesion, if any, was required to be a non-target lesion in a separate epicardial coronary vessel and treated by stents other than 48 mm stent length of XIENCE Skypoint.

Subjects enrolled in this study received 48 mm stent length of XIENCE Skypoint for the treatment of a single *de novo* coronary artery lesion, with visually estimated lesion length of > 32 mm and ≤ 44 mm, visually estimated reference vessel diameter of ≥ 2.5 mm and ≤ 4.25 mm, and visually estimated diameter stenosis of > 50% and < 100% with a thrombolysis in myocardial infarction (TIMI) flow of ≥ 1.

The primary endpoint of the SPIRIT 48 clinical trial was target lesion failure (TLF), defined as a composite of cardiac death, target vessel myocardial infarction (TV-MI) per Society for Cardiovascular Angiography and Interventions (SCAI) definition, and clinically indicated target lesion revascularization (CI-TLR) at 1 year. In addition, the study is evaluating TLF in hospital, at 30 days, 180 days, and 2 years as descriptive secondary endpoints.

The study mandates each subject to be followed for a two-year period, with hospital or office follow-up visits at 30 days, 6 months, 1 year and 2 years.

The SPIRIT 48 study completed the 1-year primary endpoint follow-up and is currently ongoing through the 2-year follow-up.

Enrollment, Demographics, and Baseline Lesion Characteristics

SPIRIT 48 registered 107 subjects at 25 sites globally. Of the 107 registered subjects, 105 subjects had the study device successfully deployed; hence the full analysis set (FAS) population comprised of 105 subjects, in whom endpoint analyses was carried out.

In the FAS population, 102 subjects completed their 1-year follow-up visit, with a theoretical follow-up rate of 98.1%.

The mean age of subjects was 67.3 years (range 35-91), with 72.4% (76/105) male subjects and 27.6% (29/105) female subjects. For subjects enrolled in the trial, the mean body-mass index (BMI) was 28.97 ± 6.88 kg/m^2, and 71.4% (75/105) of subjects had BMI ≥ 25 kg/m^2.

Risk factors in the subjects were:

- Hypertension in 82.9% (87/105) of subjects, including hypertension requiring medication in 92% (80/87) of subjects
- Dyslipidemia in 88.6% (93/105) of subjects, including dyslipidemia requiring medication in 84.9% (79/93) of subjects
- Diabetes mellitus in 34.3% (36/105) of subjects, including type II diabetes in 91.7% (33/36) of subjects
- Furthermore, 66% (68/103) of subjects had coronary artery disease (CAD), with
    - 35.3% (24/68) having single-vessel disease
    - 36.8% (25/68) having two-vessel disease
    - 72.4% (76/105) subjects presenting with stable angina

Procedurally, radial access was used for 68.6% (72/105) of subjects. The mean number of target lesions treated in 105 subjects was 1, while the mean number of non-target lesions treated in 24 subjects was 1.1. The mean procedure duration was 48.2 ± 26.4 minutes. Out of 132 lesions treated, 94.7% (125/132) used pre-dilatation and 93.9% (124/132) used post-dilatation.

Based on angiographic core lab target lesion analyses:

- Mean lesion length was 35.19 ± 8.03 mm
- Mean pre-procedure reference vessel diameter was 2.75 ± 0.46 mm
- Mean pre-procedure minimum lumen diameter was 1.03 ± 0.44 mm
- Mean pre-procedure percent diameter stenosis was 62.85% ± 13.06%

9.12.2 SPIRIT 48 Results

The analyses are all based on the FAS population and the results are presented as below:

Table 9.12.2-1: SPIRIT 48 Primary Endpoint Results
Table 9.12.2-2: SPIRIT 48 Event rates through 1 Year
Table 9.12.2-3: SPIRIT 48 Secondary and Other Clinical Endpoint Results through 1 Year
Table 9.12.2-4: SPIRIT 48 ARC-Defined Stent Thrombosis through 1 Year

Primary Endpoint (1-Year TLF)

The primary endpoint of TLF at 1 year in the FAS population was met, with a Kaplan-Meier estimate of 5.7% (using the Com-Nougue method), and the upper limit for the one-sided 95% confidence limit of 9.5%, which was significantly lower than the pre-specified performance goal of 20% (p-value < 0.0001). Please refer to **Table 9.12.2-1** and **Table 9.12.2-2** for event rates for TLF and the individual components of TLF at 1 year.

Table 9.12.2-1: SPIRIT 48 Primary Endpoint Results

XIENCE Skypoint 48 (N = 105)				
Primary Endpoint	**Estimate (SE)**	**Upper Limit for the One-Sided 95% Confidence Limit**	**Performance Goal**	**p-value[1]**
Kaplan-Meier Estimate 1-Year TLF	5.7% (2.3%)	9.5%	20%	<0.0001

[1] p-value calculated from Z test using Kaplan Meier survival estimate together with Greenwood method estimated variance, against pre-specified performance goal of 20% at one-sided significance level of 5%.
Note: The primary endpoint is defined as a composite Cardiac Death, TV-MI per SCAI definition, CI-TLR at 1 year.
Note: Subjects who have not experienced any TLF event and die due to non-cardiac cause within 1 year, will be censored at the date of death. Subjects who have not experienced any TLF event, and withdrew prior to 1 year, will be censored on the date of withdrawal. Subjects who are not withdrawn, and who have not experienced a primary endpoint event will be censored on the latest information available.
Note: The analysis was based on the data extraction of October 12, 2022.

Table 9.12.2-2: SPIRIT 48 Event Rates through 1 Year

365 days After Index Procedure (days)				
	TLF	**Cardiac Death**	**TV-MI**	**CI-TLR**
% Survived	94.3%	99.0%	95.2%	99.0%
% Event Rate	5.7%	1.0%	4.8%	1.0%
% Standard Error	2.3%	1.0%	2.1%	0.9%

Note: Includes only each subject's first occurrences of Target Lesion Failure (TLF) (Per SCAI Definition), Target Vessel MI (per SCAI Definition), and CI-TLR.
Note: Subjects who have experienced cardiac death likely related to COVID-19 (relatedness adjudicated as "likely related" to COVID-19 by CEC) will be censored.
Note: Subjects without events will be censored at their last known event-free time point.

Secondary and Other Clinical Endpoints

The descriptive secondary endpoint of TLF (per SCAI definition), and other clinical endpoints, including composites (all death, all MI, and all revascularization, DMR; and cardiac death / MI), and individual endpoints (all death, all MI, TLF, TLR, and TVR), in the FAS population at 1 year of follow-up are presented in **Table 9.12.2-3**.

Table 9.12.2-3: Secondary and Other Clinical Endpoints (Full Analysis Set)

Secondary and Other Clinical Endpoints	Outcomes at 1 Year (N = 105)
TLF (MI per SCAI definition)	5.8% (6/104)
DMR (MI per SCAI definition)	5.8% (6/104)
Cardiac Death/All MI per SCAI definition	5.8% (6/104)
All Death (per ARC definition)	1.0% (1/104)
Cardiac Death	1.0% (1/104)
Vascular Death	0.0% (0/104)
Non-cardiovascular Death	0.0% (0/104)
Clinically Indicated TVR	1.0% (1/104)
CABG	0.0% (0/104)
PCI	1.0% (1/104)
Clinically Indicated TLR	1.0% (1/104)
CABG	0.0% (0/104)
PCI	1.0% (1/104)
All MI (Periprocedural SCAI/Spontaneous ARC 1)	4.8% (5/104)
Periprocedural MI (SCAI)	3.8% (4/104)
Spontaneous MI (ARC 1)	1.0% (1/104)
Q-wave MI	1.9% (2/104)
Non-Q-wave MI	2.9% (3/104)
Target Vessel MI	4.8% (5/104)
Q-wave MI	1.9% (2/104)
Non-Q-wave MI	2.9% (3/104)
Any Revascularization	1.0% (1/104)
All Target Vessel Revascularization (including TLR)	1.0% (1/104)
Clinically Indicated TVR	1.0% (1/104)
CABG	0.0% (0/104)
PCI	1.0% (1/104)
All Target Lesion Revascularization	1.0% (1/104)
Clinically Indicated TLR	1.0% (1/104)
CABG	0.0% (0/104)
PCI	1.0% (1/104)

Note: Subjects are only counted once for each type of event in each time period.
Note: Denominators exclude subjects who are truly lost-to-follow-up, defined as subjects who are terminated through a given time point without any DMR events (all death, all MI regardless of MI definition, all revascularization), respectively.
Note: N is the total number of subjects.
Note: 95% confidence interval is calculated using Clopper-Pearson exact confidence interval.

Stent Thrombosis

Stent thrombosis (ST) was evaluated as acute (≤ 1 day), subacute (> 1 to 30 days), acute / subacute (0 to 30 days), and late (31 to 365 days), and cumulative through 1 year (0 to 365 days) time points. In the FAS population, the rate of definite acute / subacute ST was 1.0% (1/105), and the 1-year cumulative rate for definite ST was 1.0% (1/104), as shown in **Table 9.12.2-4**.

Table 9.12.2-4: SPIRIT 48 ARC-Defined Stent Thrombosis through 1 Year

ARC-defined Stent Thrombosis	Event Rates (N = 105)
Acute / Subacute Stent Thrombosis (0 to 30 Days)	
Definite	1.0% (1/105)
Probable	0.0% (0/105)
Definite / Probable	1.0% (1/105)
Late Stent Thrombosis (31 to 365 Days)	
Definite	0.0% (0/104)
Probable	0.0% (0/104)
Definite / Probable	0.0% (0/104)
Cumulative Stent Thrombosis through 1 Year (0 – 365 days)	
Definite	1.0% (1/104)
Probable	0.0% (0/104)
Definite / Probable	1.0% (1/104)

Note: Subjects are only counted once for each type of event.
Note: Denominator excludes subjects who are truly lost-to-follow-up, defined as subjects who are terminated through a given timepoint without any Stent Thrombosis event.
Note: N is the total number of subjects.

Subgroup Analyses

While subgroup analyses were performed primarily to examine the consistency of data, these analyses were not powered to evaluate differences in different subgroups.

Analyses were carried out in 3 pre-specified subgroups: age, gender, and race; and in addition, in subjects with / without diabetes mellitus.

1. Age-Based Analysis: All observed TLF events (8.8%) were seen in subjects ≥ 65 years old, whereas subjects < 65 years of age had no events.
2. Gender-Based Analysis: Female subjects had numerically higher TLF event rates (6.9%) when compared to male subjects (5.3%).
3. Race-Based Analysis: Non-white subjects had numerically higher event rates (7.7%) when compared to white subjects (4.8%).

Diabetes-based Subgroup Analyses: In the FAS population in SPIRIT 48, there were 36 subjects with diabetes mellitus (mean age: 67.8 ± 10.1) and 69 subjects without diabetes (mean age: 67.1 ± 11.3). Patients with diabetes had a higher incidence of moderate or severe lesion calcification; 65.7% (23/35) of subjects with diabetes had lesion calcification, when compared to 37.7% (26/69) of subjects without diabetes. All other baseline parameters, including target lesion characteristics, were comparable in the two groups. Of the 36 subjects with diabetes enrolled in the study, one had a primary endpoint event, with an event rate of 2.8%. In comparison, five non-diabetic subjects had primary endpoint events, with an event rate of 7.3%.

Conclusions

In spite of the COVID-19 pandemic, during which a majority of the data in this study were collected, robust and high-quality data were obtained. All event adjudications were performed by an independent Clinical Event Committee (CEC). Data obtained in this study are consistent with data from previous studies on the XIENCE Family of Stents. Importantly, these data support the safety and effectiveness of XIENCE Skypoint 48.

10.0 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the XIENCE Skypoint™ EECSS. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy. The XIENCE™ Family of Stents has demonstrated low stent thrombosis rate from 1–6 months in HBR patients with 1-month (as short as 28 days) DAPT duration and from 3–12 months in HBR patients with 3-month DAPT post-PCI.

Antiplatelet drugs should be used in combination with the XIENCE Skypoint stent, per the guidelines from the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI). Physicians should use information from the XIENCE family of clinical trials, including the XIENCE Short DAPT program, coupled with current drug eluting stent (DES) literature and the specific needs of individual patients to determine the specific antiplatelet / anticoagulation regimen to be used for their patients in general practice. See also *Section 5.6 Use in Special Populations.*

Pre-morbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

It is very important that the patient comply with the post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, MI, or death. In HBR patients, in whom ischemic and bleeding risks must be weighed, DAPT discontinuation after 3-months or 1-month (as short as 28 days) post-PCI did not show any increase in ischemic risks. Prior to PCI, if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, should a surgical or dental procedure be recommended, requiring suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy. Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

11.0 PATIENT COUNSELING AND PATIENT INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with an everolimus eluting stent
- Discuss the risks of early discontinuation of the antiplatelet therapy
- Discuss the risks of late stent thrombosis with DES use in higher risk patient subgroups
- Discuss the risk / benefit issues for this particular patient
- Discuss alternation to current lifestyle immediately following the procedure and over the long term

The following patient materials are provided for this product:

- A Patient Information Guide, including information on CAD, the implant procedure and the XIENCE Skypoint™ EECSS (provided to physician, online at: vascular.eIFU.abbott, or by calling customer service 1-800-227-9902).
- A Stent Implant Card, including both patient information and stent implant information (provided in package).

12.0 HOW SUPPLIED

Sterile − This device is sterilized with ethylene oxide gas and is non-pyrogenic. It is intended for single use only. Do not resterilize. Do not use if the package is opened or damaged.

Contents − One (1) XIENCE Skypoint™ EECSS; one (1) stent implant card.

Storage − Store in a dry, dark, cool place. Protect from light. Do not remove from carton until ready for use. Store at 25°C (77°F); excursions permitted between 15 − 30°C (59 − 86°F).

13.0 CLINICIAN USE INFORMATION

13.1 Inspection Prior to Use

- Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
- Do not use after the “Use by” date.
- Tear open the foil pouch and remove the inner pouch.

Note: The outside of the inner pouch is NOT sterile. Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.

- Prior to using the XIENCE Skypoint™ EECSS, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not use if any defects are noted. However, **do not manipulate, touch, or handle the stent**, which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.

Note: At any time during use of the XIENCE Skypoint EECSS, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

13.2 Materials Required

- Appropriate arterial sheath
- Appropriate guiding catheter(s). See *Table 1.1-1: XIENCE Skypoint EECSS Product Description*
- 2 – 3 syringes (10 – 20 cc)
- 1,000 u/500 cc heparinized normal saline (HepNS)
- Rotating hemostatic valve with appropriate minimum inner diameter (0.096” [2.44 mm])
- 0.014” (0.36 mm) x 175 cm (minimum length) guide wire
- Torque device
- Guide wire introducer
- Contrast diluted 1:1 with heparinized normal saline
- Inflation device
- Appropriately sized pre-dilatation angioplasty balloon
- Appropriately sized post-dilatation noncompliant angioplasty balloon
- Three-way stopcock
- Appropriate anticoagulation and antiplatelet drugs

13.3 Preparation

13.3.1 Packaging Removal

Note: The foil pouch is not a sterile barrier. The inner header bag (pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Rapid Exchange (RX) system, do not bend or kink the hypotube during removal.
2. Remove the product mandrel and protective stent sheath by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent sheath removal, do not use this product, and replace with another. Follow the product returns procedure for the unused device.

13.3.2 Guide Wire Lumen Flush

1. Flush the guide wire lumen with HepNS until fluid exits the guide wire exit notch.

Note: Avoid manipulation of the stent while flushing the guide wire lumen, as this may disrupt the placement of the stent on the balloon.

13.3.3 Delivery System Preparation

1. Prepare an inflation device / syringe with diluted contrast medium.
2. Attach an inflation device / syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube, when connecting to the inflation device / syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to delivery system; pull negative for 30 seconds; release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device / syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.
7. If a syringe was used, attach a prepared inflation device to stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral.

Note: While introducing the delivery system into the vessel, do not induce negative pressure on the delivery system. This may cause dislodgement of the stent from the balloon.

Note: If air is seen in the shaft, repeat *Section 13.3.3 Delivery System Preparation,* steps 3 through 5, to prevent uneven stent expansion.

13.4 Delivery Procedure

1. Prepare the vascular access site according to standard practice.
2. The decision to pre-dilate the lesion with an appropriately sized balloon should be based on patient and lesion characteristics. **If pre-dilatation is performed,** limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the XIENCE Skypoint stent.
3. For long lesions, size the stent to the diameter of the most distal portion of the vessel.

Note: If choosing between two stent diameters for tight lesions, choose the smaller diameter stent and inflate. See *Section 14.0 IN VITRO COMPLIANCE INFORMATION.*

4. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as wide as possible.
5. Backload the delivery system coaxially onto the proximal portion of the guide wire, while maintaining guide wire position across the target lesion.
6. Carefully advance the delivery system into the guiding catheter and over the guide wire to the target lesion. When using a Rapid Exchange (RX) system, be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the EECSS into the coronary artery.

Note: If unusual resistance is felt before the stent exits the guiding catheter, do not force passage. Resistance may indicate a problem and the use of excessive force may result in stent damage or dislodgement. Maintain guide wire placement across the lesion and remove the delivery system and guiding catheter as a single unit.

7. Advance the delivery system over the guide wire to the target lesion under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position. If the position of the stent is not optimal, it should be carefully repositioned or removed (see *Section 5.4 Stent / System Removal*). The balloon markers indicate both the stent edges and the balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion.

Note: If removal of an EECSS is required prior to deployment, ensure that the guiding catheter is coaxially positioned relative to the stent delivery system, and cautiously withdraw the stent delivery system into the guiding catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guiding catheter, the stent delivery system and the guiding catheter should be removed as a single unit. This should be done under direct visualization with fluoroscopy.

8. Tighten the rotating hemostatic valve. The stent is now ready to be deployed.

13.5 Deployment Procedure

CAUTION: Refer to *Table 14-1: XIENCE Skypoint Stent Compliance*, for *in vitro* stent inner diameter, nominal pressure, and RBP.

1. Prior to deployment, reconfirm the correct position of the stent relative to the target lesion using the radiopaque balloon markers.
2. Deploy the stent slowly by pressurizing the delivery system in 2 atm increments, every 5 seconds, until stent is completely expanded. Fully expand the stent by inflating to nominal pressure at a minimum. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter ratio of about 1.1 times the reference vessel diameter (see *Table 14-1: XIENCE Skypoint Stent Compliance*).
3. For long lesions, size the stent to the diameter of the most distal portion of the vessel and expand stent to nominal pressure at minimum. Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall.
4. Maintain pressure for 30 seconds for full expansion of the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

Note: See *Section 13.6 Removal Procedure* for instruction on withdrawal of stent delivery system.

5. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall.

Note: Do not exceed the labeled Rated Burst Pressure (RBP) of 16 atm (1621 kPa).

6. Fully cover the entire lesion and balloon-treated area (including dissections) with the XIENCE Skypoint stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.
7. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to guiding catheter position.

Note: See *Section 13.6 Removal Procedure* for instruction on withdrawal of stent delivery system.

8. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or Intravascular Ultrasound (IVUS).

9. If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is suboptimal, the stent may be further expanded using a low profile, high pressure, noncompliant balloon dilatation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent geometry. Deployed stents should not be left underdilated.

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

Nominal Stent Diameter	**Dilatation Limit**
2.25 mm, 2.5 mm, 2.75 mm, 3.0 mm, and 3.25 mm	**3.75 mm**
3.5 mm, 4.0 mm, 4.5 mm and 5.0 mm	**5.75 mm**

10. If more than one XIENCE Skypoint stent is needed to cover the lesion and balloon-treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between stents, the balloon marker bands of the second XIENCE Skypoint stent should be positioned inside the deployed stent prior to expansion.
11. Reconfirm stent position and angiographic results. Repeat inflations until optimal stent deployment is achieved.

13.6 Removal Procedure

Withdrawal of the stent delivery catheter from the deployed stent:

1. Deflate the balloon by pulling negative on the inflation device. Larger and longer balloons will take more time (up to 30 seconds) to deflate than smaller and shorter balloons. Confirm balloon deflation under fluoroscopy and wait 10 – 15 seconds longer.

2. Position inflation device on “negative” or “neutral” pressure.

3. Stabilize guiding catheter position just outside coronary ostium and anchor in place. Maintain guide wire placement across stent segment.

4. Gently remove the stent delivery system with slow and steady pressure.

5. Tighten the rotating hemostatic valve.

If during withdrawal of the stent delivery catheter resistance is encountered, use the following steps to improve balloon rewrap:

- Re-inflate the balloon up to nominal pressure.
- Repeat steps 1 through 5 above***.***

Post-stent delivery system withdrawal – Stent deployment confirmation

1. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). **Optimal expansion requires that the stent be in full contact with the artery wall.** Stent wall contact should be verified through intravascular imaging.

2. If more than one XIENCE Skypoint stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped.

3. To ensure that there are no gaps between stents, the balloon marker bands of the second XIENCE Skypoint stent should be positioned inside the deployed stent prior to expansion.

4. Reconfirm stent position and angiographic results to assess stented area. Repeat inflations until optimal stent deployment is achieved. If post-dilatation is necessary, ensure that the final stent diameter matches the reference vessel diameter. Intravascular imaging can be utilized to **assure the stent struts wall are in contact with the inner luminal wall of the artery and that the stent has been optimally expanded.**

13.7 Post-Deployment Dilatation of Stent Segments

1. All efforts should be taken to assure that the stent is not underdilated.
2. If the deployed stent size is still inadequate with respect to the vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and noncompliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guide wire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

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

Nominal Stent Diameter	**Dilatation Limit**
2.25 mm and 2.5 mm, 2.75 mm, 3.0 mm, and 3.25 mm	**3.75 mm**
3.5 mm, 4.0 mm, 4.5 mm and 5.0 mm	**5.75 mm**

14.0 *IN VITRO* COMPLIANCE INFORMATION

Table 14-1: XIENCE Skypoint Stent Compliance for 8-38 mm Stent Lengths (Nominal Pressure for Each Diameter Indicated by Bold Font)

Pressure		Stent ID (mm) by System Diameter								
atm	**kPa**	**2.25 mm**	**2.5 mm**	**2.75 mm**	**3.0 mm**	**3.25 mm**	**3.5 mm**	**4.0 mm**	**4.5 mm**	**5.0 mm**
8	811	2.27	2.53	2.60	2.79	2.98	3.36	3.74	4.18	4.69
9	912	**2.31**	**2.58**	2.66	2.86	3.05	3.42	3.82	4.27	4.78
10	1013	2.35	2.63	2.71	2.91	3.11	3.47	3.89	4.35	4.86
11	1115	2.39	2.67	2.75	2.96	3.17	3.52	3.95	4.42	4.93
12	1216	2.42	2.71	**2.79**	**3.00**	**3.22**	**3.56**	**4.01**	**4.48**	**5.00**
13	1317	2.45	2.74	2.82	3.04	3.26	3.59	4.05	4.53	5.06
14	1419	2.48	2.77	2.86	3.07	3.30	3.63	4.10	4.58	5.11
15	1520	2.51	2.80	2.88	3.10	3.33	3.66	4.14	4.63	5.16
16 (RBP)*	1621	2.53	2.83	2.91	3.13	3.37	3.70	4.18	4.67	5.21
17	1723	2.56	2.85	2.94	3.16	3.40	3.73	4.22	4.72	5.26
18	1824	2.58	2.88	2.97	3.19	3.43	3.77	4.26	4.76	5.31
19	1925	2.60	2.91	3.00	3.21	3.46	3.81	4.29		
20	2027	2.63	2.94	3.03	3.24	3.50	3.84	4.34		

Note: These nominal data are based on *in vitro* testing at 37°C and do not take into account lesion resistance. Ensure full deployment of the stent (see *Section 13.5 Deployment Procedure*) and confirm the stent sizing angiographically.
*Do not exceed the rated burst pressure (RBP).

Table 14-2: XIENCE Skypoint Stent Compliance for 48 mm Stent Length (Nominal Pressure for Each Diameter Indicated by Bold Font)

Pressure		Stent ID (mm) by System Diameter				
atm	**kPa**	**2.5 mm**	**2.75 mm**	**3.0 mm**	**3.5 mm**	**4.0 mm**
8	811	2.42	2.52	2.72	3.17	3.70
9	912	**2.47**	2.58	2.79	3.24	3.78
10	1013	2.52	2.63	2.85	3.31	3.86
11	1115	2.57	2.69	2.91	3.37	3.93
12	1216	2.62	**2.73**	**2.97**	**3.43**	**3.99**
13	1317	2.66	2.77	3.02	3.47	4.04
14	1419	2.69	2.80	3.06	3.52	4.08
15	1520	2.72	2.84	3.10	3.55	4.13
16 (RBP)*	1621	2.75	2.87	3.13	3.59	4.17
17	1723	2.78	2.90	3.16	3.62	4.21
18	1824	2.81	2.92	3.19	3.66	4.25

*Do not exceed the rated burst pressure (RBP).

15.0 REUSE PRECAUTION STATEMENT

Do not use if sterile barrier is damaged. If damage is found, call your Abbott Medical representative.

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

Reference Abbott website for patent markings: www.abbott.com/patents

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Graphical Symbols for Medical Device Labeling

Manufacturer	French size	Sterilized using ethylene oxide	ONLY CAUTION: Federal law restricts this device to sale by or on the order of a physician
REF Catalogue number	UDI Unique device identifier	Cobalt Chromium Balloon-Expandable Stent Cobalt Chromium Balloon-Expandable Stent	
POST DILATATION LIMIT Post dilatation limit	Consult instructions for use or consult electronic instructions for use	Do not re-use	Do not resterilize
Use-by date	LOT Batch code	Keep away from sunlight	Keep dry
Date of manufacture	Inner diameter	Do not use if package is damaged and consult instructions for use	Non-pyrogenic
MR MR Conditional	Packaging unit	Guiding catheter	RX Rapid exchange

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