Appendix 3-A

XIENCE PRIME IFU

(Appendix is independently paginated)
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THE COMPONENTS OF THE XIENCE PRIME STENT SYSTEM ARE STERILE.

1.0 PRODUCT DESCRIPTION

The XIENCE PRIME family of stent systems includes:

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

- XIENCE PRIME LL Everolimus Eluting Coronary Stent System (stent diameters 2.25\textsuperscript{1}, 2.5, 2.75, 3.0, 3.5, 4.0 mm, stent lengths 28, 33, 38 mm) Everolimus Eluting Coronary Stent Systems

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

\textsuperscript{1} The 2.25 mm stent diameter for XIENCE PRIME LL is only available in the 28 mm stent length.
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 PRIME stent delivery system. The device component characteristics are summarized in Table 1-1.

### Table 1-1: XIENCE PRIME Stent System Product Description

<table>
<thead>
<tr>
<th>Available Stent Lengths (mm)</th>
<th>XIENCE PRIME</th>
<th>XIENCE PRIME LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>8, 12, 15, 18, 23</td>
<td>28, 33, 38</td>
<td></td>
</tr>
</tbody>
</table>

| Available Stent Diameters (mm) | 2.25, 2.5, 2.75, 3.0, 3.5, 4.0 | 2.25**, 2.5, 2.75, 3.0, 3.5, 4.0 |

| Stent Material | A medical grade L-605 cobalt chromium CoCr alloy identical to the material used in the XIENCE V stent |

| Drug Component | A conformal coating of a non-erodible polymer loaded with 100 μg/cm² of everolimus with a maximum nominal drug content of 232 μg on the large stent (4.0 x 38 mm) |

| Delivery System Working Length | 143 cm |

| Delivery System Design | Single access port to inflation lumen; guide wire exit notch is located 25.5 cm from tip; designed for guide wires ≤ 0.014" |

| Stent Delivery System Balloon | A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length |

| Balloon Inflation Pressure | Rated Burst Pressure (RBP): 18 atm (1824 kPa) |

<table>
<thead>
<tr>
<th>Stent Diameter (mm)</th>
<th>In vitro Stent Nominal Pressure (atm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.25</td>
<td>8</td>
</tr>
<tr>
<td>2.5</td>
<td>9</td>
</tr>
<tr>
<td>2.75</td>
<td>8</td>
</tr>
<tr>
<td>3.0</td>
<td>10</td>
</tr>
<tr>
<td>3.5</td>
<td>10</td>
</tr>
<tr>
<td>4.0</td>
<td>10</td>
</tr>
</tbody>
</table>

| Guiding Catheter Inner Diameter | 0.03 F (0.056") |

| Catheter Shaft Outer Diameter | Proximal: 0.031" (0.79 mm) | Distal: 0.034" (0.86 mm) |

* 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.

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

The XIENCE PRIME 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 PRIME 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 PRIME stent contains inactive ingredients, including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 254,000 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/cm² for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in Figure 1.2.2-2 below.

Figure 1.2.2-1: Non-erodible Polymer Chemical Structures

PBMA

\[
\begin{array}{c}
\text{CH}_2 - \text{C} - \\
\text{O} - \\
(\text{CH}_2)_3 \\
\text{CH}_3 \\
\end{array}
\]

PVDF-HFP

\[
\begin{array}{c}
\text{CH}_2 - \text{CF}_2 - n \\
\text{CF}_2 - \text{CF}_3 - m \\
\end{array}
\]
### Table 1.2.3-1: XIENCE PRIME Stent System Product Matrix and Everolimus Content

<table>
<thead>
<tr>
<th>Model Number (RX)</th>
<th>Nominal Expanded Stent Diameter (mm)</th>
<th>Nominal Unexpanded Stent Length (mm)</th>
<th>Nominal Everolimus Content (µg)</th>
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<td>1011735-38</td>
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<td>38</td>
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</table>
2.0 INDICATIONS

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

3.0 CONTRAINDICATIONS

The XIENCE PRIME stent system is contraindicated for use in patients:

- Who cannot receive antiplatelet and/or anticoagulant therapy (see section 5.2 - Precautions, Pre- and Post-Procedure Antiplatelet Regimen for more information)
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers

4.0 WARNINGS

- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Judicious patient selection is necessary, because the use of this device carries the associated risk of stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy (see section 5.2 for important information regarding antiplatelet therapy).

5.0 PRECAUTIONS

5.1 General Precautions

- Stent implantation should only be performed by physicians who have received appropriate training.
- Stent placement should be performed at hospitals where emergency coronary artery bypass graft surgery is accessible.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent is presently unknown.
- Risks and benefits should be considered in patients with severe contrast agent allergies.
- 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.
- Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death. Data from the SPIRIT family of clinical trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (see section 8.2 - Adverse Events, Stent Thrombosis Definitions and...
When DES 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 DES 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.

Orally administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglyceride levels.

5.2 Pre- and Post-Procedure Antiplatelet Regimen

- 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 92.6% (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 in the aspirin regimen indefinitely.

- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies on sirolimus-eluting or paclitaxel-eluting stents suggest that a longer duration of clopidogrel than was recommended post-procedurally in DES pivotal trials may be beneficial. Current guidelines recommend that patients receive aspirin indefinitely and 75 mg of clopidogrel daily for at least 12 months, if subjects are not at high risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines).

- 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. Prior to percutaneous coronary intervention (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.

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2 Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121
3 King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209
5.3 Multiple Stent Use

A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. In the SPIRIT PRIME study, total stent length per subject was limited to 76 mm with treatment allowed for up to two lesions each in a different epicardial vessel using XIENCE PRIME and XIENCE PRIME LL. Use of more than two XIENCE PRIME stents to treat lesions longer than 32 mm has not been evaluated and may increase patient complication risks. Studies evaluating the effects of higher drug doses have not been conducted.

Effects of multiple stenting using XIENCE PRIME stents combined with other drug-eluting stents are unknown. When multiple drug-eluting stents are required, use only XIENCE PRIME stents in order to avoid potential interactions with other drug-eluting or coated stents.

In addition, only stents composed of similar materials should be implanted in consecutive stent-to-stent contact, to avoid corrosion potential between unrelated materials.

5.4 Brachytherapy

XIENCE PRIME stent safety and effectiveness have not been evaluated in patients with prior target lesion or in-stent restenosis-related brachytherapy.

5.5 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with XIENCE PRIME stent implantation have not been established.

5.6 Use in Special Populations

5.6.1 Pregnancy

Pregnancy Category C. See section 6.5 – Drug Information, Pregnancy. The XIENCE PRIME stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a XIENCE PRIME stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

5.6.2 Lactation

See section 6.6 – Drug Information, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation, considering the importance of the stent to the mother.

5.6.3 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 9.5).
5.6.4 Ethnicity

Insufficient subject numbers prevent ethnicity-related analyses of the XIENCE PRIME stent safety and effectiveness.

5.6.5 Pediatric Use

The safety and effectiveness of the XIENCE PRIME 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.

5.7 Lesion/Vessel Characteristics

Safety and effectiveness of the XIENCE PRIME 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 < 2.5 mm or > 4.25 mm
- Lesion lengths > 32 mm
- Lesions located in saphenous vein grafts
- Lesions located in unprotected left main coronary artery, ostial lesions, chronic total occlusions, and 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
- Moderate or severe lesion calcification
- Multivessel disease
- In-stent restenosis

5.8 Drug Interactions

See section 6.3 - Drug Information, Interactions with Drugs or Other Substances. Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein (pGp). Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE PRIME stent because of limited systemic exposure to everolimus eluted from XIENCE PRIME (see section 6.2 - Drug Information, 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 PRIME 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 PRIME stent.

5.9 Immune Suppression Potential

Everolimus, the XIENCE PRIME stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the SPIRIT family of clinical trials. However, for patients who receive several XIENCE PRIME 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.

5.10 Lipid Elevation Potential

Oral everolimus use in renal transplant and advanced renal cell carcinoma patients was associated with increased serum cholesterol and triglycerides, 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 PRIME stent is expected to be significantly lower than concentration exposure usually obtained in transplant patients. Increased serum cholesterol and triglycerides were not observed in the SPIRIT family of clinical trials.

5.11 Magnetic Resonance Imaging (MRI)

Nonclinical testing has demonstrated that the XIENCE PRIME stent, in single and in overlapped configurations up to 71 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for up to 15 minutes of scanning for each sequence

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

Stent heating was derived by using the measured nonclinical, in vitro temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil in combination with the local specific absorption rates (SARs) in a digitized human heart model. The maximum whole body averaged SAR was determined by validated calculation. At overlapped lengths of up to 71 mm, the XIENCE PRIME stent produced a nonclinical maximum local temperature rise of 3.3°C at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.
The effects of MRI on overlapped stents greater than 71 mm in length or stents with fractured struts are unknown.

As demonstrated in nonclinical testing, an image artifact can be present when scanning the XIENCE PRIME stent. MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the XIENCE PRIME stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of XIENCE PRIME stent.

It is suggested that patients register the conditions under which the implant can safely be scanned with the MedicAlert Foundation (www.medicalert.org) or an equivalent organization.

5.12 Stent Handling

- Each stent is for single use only. Do not resterilize or reuse this device. Note the "Use by" (expiration) date on the product label.
- 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.
- Do not remove the stent from the delivery system. Removal may damage the stent and/or lead to stent embolization. These components are intended to perform together as a system.
- The delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or disrupt the stent on the balloon, particularly during delivery system 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 with your fingers, which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.
- Use only the appropriate balloon inflation media (see section 13.3.3 - Operator’s Instructions, Delivery System Preparation). Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in stent deployment.

5.13 Stent Placement

5.13.1 Stent Preparation

- Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed. Use the balloon purging technique described in section 13.3.3 - Operator’s Instructions, Delivery System Preparation.
- 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.
- Use guiding catheters which have lumen sizes that are suitable to accommodate the stent delivery system (see section 1.1 - Product Description, Device Component Description).

5.13.2 Stent Implantation

- The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the difficulty of stent placement and cause procedural complications.
- Do not expand the stent if it is not properly positioned in the vessel (see section 5.14 – Precautions, Stent System Removal).
- Implanting a stent may lead to vessel dissection and acute closure requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- Although the safety and effectiveness of treating more than one lesion per coronary artery with XIENCE PRIME stents have not been established, if this is performed, place the stent in the distal lesion before the proximal lesion in order to minimize dislodgement risk incurred by traversing through deployed stents.
- Stent placement may compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** See Table 14-1: XIENCE PRIME Stent Compliance. Balloon pressures should be monitored during inflation. Applying pressures higher than specified on the product label may result in a ruptured balloon with possible arterial damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.
- 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 when retracting the undeployed stent back into the guiding catheter.
- Should **resistance** be felt at any time during coronary stent system withdrawal, please follow the steps provided in Section 5.14 – Precautions, Stent System Removal.
- Stent retrieval methods (i.e., using 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.
- 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.
- Ensure the stented area covers the entire lesion/dissection site and that no gaps exist between stents.

### 5.14 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 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.

**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 the inflation device to “negative” or “neutral” pressure.

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

5. Tighten the rotating hemostatic valve.

If during withdrawal of the 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.

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

Stent retrieval methods (i.e., additional wires, snares, and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include, but are not limited to, bleeding, hematoma, or pseudoaneurysm.

5.15 Post-Procedure

- When crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter or delivery system, exercise care to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Antiplatelet therapy should be administered post-procedure (see section 5.2 – Precautions, Pro- and Post-Procedure Antiplatelet Regimen. 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 physician, the antiplatelet therapy should be restarted as soon as possible.
- If the patient requires imaging, see section 5.11 – Precautions, Magnetic Resonance Imaging (MRI).

6.0 DRUG INFORMATION

6.1 Mechanism of Action

The mechanism by which the XIENCE PRIME 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 PRIME stent, but were conducted on the similar XIENCE V stent. The XIENCE PRIME stent is similar to XIENCE V 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 pharmacokinetic studies, as described below, are applicable to the XIENCE PRIME stent. Everolimus pharmacokinetics when eluted from the XIENCE V stent post-implantation has been evaluated in three different substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the US randomized arm and a pharmacokinetic substudy in the Japanese nonrandomized arm. The third PK substudy was conducted as part of the SPIRIT II clinical trial at sites in Europe, India, and New Zealand. Whole blood everolimus PK parameters determined from subjects receiving the XIENCE V stent are provided in Table 6.2-1.

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>t_{max} (h)</th>
<th>C_{max} (ng/mL)</th>
<th>t_{1/2} (h)</th>
<th>AUC_{0-1} (ng.h/mL)</th>
<th>AUC_{0-∞} (ng.h/mL)</th>
<th>CL (L/h)</th>
<th>SPIRIT III RCT and 4.0 Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5-3.0 x 18 mm (n = 3)</td>
<td>88 µg</td>
<td>0.50 (0.50 - 1.86)</td>
<td>0.3867 ± 0.0986</td>
<td>5.31 ± 4.114</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5-4.0 x 28 mm (n = 6)</td>
<td>181 µg</td>
<td>0.50 (0.07 - 1.00)</td>
<td>1.175 ± 0.6517</td>
<td>70.08 ± 57.24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>t_{max} (h)</th>
<th>C_{max} (ng/mL)</th>
<th>t_{1/2} (h)</th>
<th>AUC_{0-1} (ng.h/mL)</th>
<th>AUC_{0-∞} (ng.h/mL)</th>
<th>CL (L/h)</th>
<th>SPIRIT III Japanese Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5-3.0 x 18 mm (n = 3)</td>
<td>88 µg</td>
<td>1.00 (0.50 - 1.02)</td>
<td>0.5017 ± 0.1356</td>
<td>45.22 ± 33.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5-4.0 x 18 mm (n = 4)</td>
<td>113 µg</td>
<td>0.51 (0.50 - 0.53)</td>
<td>0.6500 ± 0.00966</td>
<td>53.57 ± 19.34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>t_{max} (h)</th>
<th>C_{max} (ng/mL)</th>
<th>t_{1/2} (h)</th>
<th>AUC_{0-1} (ng.h/mL)</th>
<th>AUC_{0-∞} (ng.h/mL)</th>
<th>CL (L/h)</th>
<th>SPIRIT II Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5-3.0 x 18 mm (n = 3)</td>
<td>88 µg</td>
<td>0.60 (0.13 - 2.17)</td>
<td>0.4369 ± 0.1507</td>
<td>54.08 ± 36.57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5-4.0 x 18 mm (n = 4)</td>
<td>113 µg</td>
<td>0.60 (0.50 - 0.50)</td>
<td>0.5600 ± 0.2630</td>
<td>47.60 ± 62.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5-4.0 x 28 mm (n = 4)</td>
<td>181 µg</td>
<td>0.46 (0.17 - 1.00)</td>
<td>0.7925 ± 0.1406</td>
<td>103.4 ± 64.17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Accurate determination not possible due to rapid disappearance of everolimus from the blood
+ n = 5 for t_{1/2} and CL.
+ n = 3 for t_{max} and CL.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_{max}</td>
<td>Time to maximum concentration</td>
</tr>
<tr>
<td>C_{max}</td>
<td>Maximum observed blood concentration</td>
</tr>
<tr>
<td>t_{1/2}</td>
<td>Terminal phase half-life</td>
</tr>
<tr>
<td>AUC_{0-1}</td>
<td>The area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration</td>
</tr>
<tr>
<td>AUC_{0-∞}</td>
<td>The area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time</td>
</tr>
<tr>
<td>CL</td>
<td>Total blood clearance</td>
</tr>
</tbody>
</table>

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, 1 subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all 3 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 PK parameters...
representing elimination, $t_{1/2}$, $\text{AUC}_{0-t}$, $\text{AUC}_{\text{tot}}$, $\text{AUC}_{\text{ast}}$, and $\text{CL}$, 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 XIENCE PRIME due to the similarities with XIENCE V stated above.

### 6.3 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 countertransporter P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect CYP3A4 and PgP pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the XIENCE PRIME or XIENCE V stents because of limited systemic exposure to everolimus eluted from XIENCE V (see section 6.2 - Drug Information, Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the XIENCE PRIME stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods listed below. Medications that are strong inhibitors of CYP3A4 or PgP might reduce everolimus metabolism in vivo. Hence, co-administration of strong inhibitors of CYP3A4 or PgP may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers [verapamil and diltiazem], aprepitant, atazanavir, nefazodone, amphetamines, indinavir, nelfinavir, delavirdine, fosamprenavir, saquinavir and telithromycin)
- Inducers of CYP3A4 isozyme (St. John’s Wort, rifampin, rifabutin, carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, dexamethasone)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Pgp inhibitors (Delavirdine, fosamprenavir)
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra$^\text{TM}$) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit/grapefruit juice

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 under the name of Afinitor for the treatment of patients with advanced renal cell carcinoma (cancer) after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The amount of drug that circulates in the bloodstream following implantation of a XIENCE PRIME stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day).

6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

The carcinogenicity, genotoxicity, and reproductive toxicity of the XIENCE PRIME 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 XIENCE PRIME, 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.

6.5 Pregnancy

Pregnancy Category C: There are no adequate everolimus or XIENCE PRIME stent related studies in pregnant women. Effects of a similar stent, XIENCE V, on prenatal and postnatal rat development were no different than the controls (see section 6.4 - Drug Information, Carcinogenicity, Genotoxicity, and Reproductive Toxicity). When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential. Effective contraception should be initiated before implanting a XIENCE PRIME stent and continued for one year post-implantation. The XIENCE PRIME stent should be used in pregnant women only if potential benefits outweigh potential risks.
The safety of the XIENCE PRIME stent has not been evaluated in males intending to father children.

6.6 Lactation

It is unknown whether everolimus is distributed in human milk. Also, 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 PRIME stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

7.0 OVERVIEW OF CLINICAL EXPERIENCE

SPIRIT PRIME is a prospective, open-label, multicenter nonrandomized clinical trial using the core size XIENCE PRIME and XIENCE PRIME LL stent system. 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 do 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 (stent diameters 2.25, 2.5, 3.0, 3.5 or 4.0 mm with stent lengths 8, 18, or 28 mm). The Long Lesion Registry was to enroll approximately 100 subjects in which all were to be treated with at least one XIENCE PRIME LL (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 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 5 years. Follow-up through 1 year is presented here, and yearly follow-up for clinical parameters through 5 years is ongoing. The SPIRIT PRIME clinical trial is Abbott Vascular's pivotal US trial evaluating XIENCE PRIME. Long-term risks and benefits associated with XIENCE PRIME are currently unknown.

The XIENCE PRIME stent is similar to the FDA approved XIENCE V stent system. 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 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 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 in subjects with symptomatic ischemic disease due to do 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 (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 TVR) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and annually from 1 to 5 years), as well as angiographic results and intravascular ultrasound (IVUS) results at 240 days. Follow-up through 3 years is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT IV trial was a prospective, randomized, active-controlled, single-blinded, multicenter evaluation of the XIENCE V stent compared to the TAXUS Express Stent7 (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. nondiabetic) and lesion characteristics (complex vs. noncomplex). 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 5 years. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

Table 7-1 summarizes the clinical trial designs for the SPIRIT family of trials.

7 in the TAXUS stent arm, there was 1 subject who received 1 TAXUS® Liberte® Stent.
<table>
<thead>
<tr>
<th>Study Type/Design</th>
<th>SPIRIT PRIME Clinical Trial</th>
<th>SPIRIT III Clinical Trial</th>
<th>SPIRIT IV Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Core Size Registry</td>
<td>Long Lesion Registry</td>
<td>4.0 Arm (Registry)</td>
</tr>
<tr>
<td></td>
<td>Multicenter</td>
<td>Multicenter</td>
<td>Multicenter</td>
</tr>
<tr>
<td></td>
<td>Single-arm</td>
<td>Single-arm</td>
<td>Randomized</td>
</tr>
<tr>
<td></td>
<td>Open-label</td>
<td>Open-label</td>
<td>Single-blinded</td>
</tr>
<tr>
<td>Number of Subjects Enrolled</td>
<td>Total: 400</td>
<td>Total: 100</td>
<td>Total: 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 1,002</td>
<td>Total: 3,690</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XIENCE V: 668</td>
<td>XIENCE V: 2,480</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TAXUS Express Control: 344</td>
<td>TAXUS Express Control: 1,230</td>
</tr>
<tr>
<td>Treatment</td>
<td>Up to two de novo lesions in different epicardial vessels</td>
<td>Up to two de novo lesions in different epicardial vessels</td>
<td>Up to three de novo lesions, maximum of two lesions per epicardial vessel</td>
</tr>
<tr>
<td>Lesion Size</td>
<td>RVD: ≥ 2.25 ≤ 4.25 mm</td>
<td>XIENCE PRIME CS:</td>
<td>RVD: ≥ 2.5 ≤ 3.75 mm</td>
</tr>
<tr>
<td></td>
<td>Length: ≤ 22 mm</td>
<td>RVD: ≥ 2.5 ≤ 4.25 mm</td>
<td>Length: ≤ 28 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XIENCE PRIME LL:</td>
<td>RVD: ≥ 2.5 ≤ 4.25 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RVD: ≥ 2.5 ≤ 4.25 mm</td>
<td>Length: ≤ 28 mm</td>
</tr>
<tr>
<td>Stent Sizes</td>
<td>XIENCE PRIME</td>
<td>XIENCE PRIME LL:</td>
<td>XIENCE V</td>
</tr>
<tr>
<td>(XIENCE PRIME/ XIENCE V)</td>
<td>Diameter: 2.5, 3.0, 3.5, 4.0 mm</td>
<td>Diameter: 2.5, 3.0, 3.5, 4.0 mm</td>
<td>Diameter: 4.0 mm</td>
</tr>
<tr>
<td></td>
<td>Length: 8, 18, 28</td>
<td>Length: 33, 38 mm</td>
<td>Length: 8, 18, 28 mm</td>
</tr>
<tr>
<td>Post-Procedure Antiplatelet Therapy</td>
<td>Clopidogrel 12 months</td>
<td>Clopidogrel 6 months</td>
<td>Clopidogrel 12 months</td>
</tr>
<tr>
<td></td>
<td>minimum (or ticlopidine per site standard), aspirin 5 years</td>
<td>(or ticlopidine per site standard), aspirin 5 years</td>
<td>minimum (or ticlopidine per site standard), aspirin 5 years</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>TLF (Target lesion failure) at 1 year</td>
<td>TLF (Target Lesion failure) at 1 year</td>
<td>TLF (Target Lesion failure) at 1 year</td>
</tr>
<tr>
<td></td>
<td>◦ TLF (per ARC) at 1-year compared to PG* of 9.2%</td>
<td>◦ In-segment late loss at 240 days</td>
<td>◦ Aspirin 5 years</td>
</tr>
<tr>
<td></td>
<td>◦ TLF (per protocol) at 1-year compared to PG* of 9.2%</td>
<td>◦ In-segment late loss at 240 days</td>
<td>◦ Aspirin 5 years</td>
</tr>
<tr>
<td></td>
<td>◦ TLF (per ARC) at 1-year compared to PG* of 15.3%</td>
<td>◦ In-segment late loss at 240 days</td>
<td>◦ Aspirin 5 years</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>SPIRIT PRIME Clinical Trial</th>
<th>SPIRIT III Clinical Trial</th>
<th>SPIRIT IV Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-Primary Endpoint</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Major Secondary</td>
<td>None</td>
<td>None</td>
<td>Ischemic-driven Target</td>
</tr>
<tr>
<td>endpoint</td>
<td></td>
<td></td>
<td>Lesion Revascularization</td>
</tr>
<tr>
<td>Clinical Follow-up</td>
<td>30, 180 days, 1 to 5 years</td>
<td>30, 180 days, 1 to 5 years</td>
<td>30, 180, 240, 270 days,</td>
</tr>
<tr>
<td>Status</td>
<td>One year reported; 2, 3, 4</td>
<td>One year reported; 2, 3, 4</td>
<td>30, 180, 270 days,</td>
</tr>
<tr>
<td></td>
<td>and 5 years planned</td>
<td>and 5 years planned</td>
<td>1 to 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One year reported; 4 and 5</td>
<td>1 to 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years planned</td>
<td></td>
</tr>
</tbody>
</table>

* Performance Goal (PG)

** In the TAXUS arm, there was 1 patient who received 1 TAXUS Libert® 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.
# 8.0 ADVERSE EVENTS

## 8.1 Observed Adverse Events

Principal adverse event information is derived from the SPIRIT PRIME Core Size Registry, SPIRIT IV, and SPIRIT III clinical trials and is shown in Table 8.1-1. See also section 8.3 – Adverse Events, Potential Adverse Events. See section 9.0 – SPIRIT 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 II (RCT) | |
| | Core Size Registry (N = 401) | XIENCE V (N = 2451) | TAXUS (N = 1229) | XIENCE V (N = 669) | TAXUS (N = 333) |
| **In Hospital Adverse Events** | | | | | |
| TLF | 2.0% (84/401) | 1.4% (35/2451) | 1.9% (231/224) | 0.9% (66/669) | 2.4% (8/330) |
| MACE | 2.0% (84/401) | 1.4% (35/2451) | 1.9% (231/224) | 0.9% (66/669) | 2.4% (8/330) |
| All Death | 0.0% (0/401) | 0.0% (0/2451) | 0.0% (0/224) | 0.0% (0/669) | 0.0% (0/330) |
| Non-Cardiac Death | 0.0% (0/401) | 0.0% (0/2451) | 0.0% (0/224) | 0.0% (0/669) | 0.0% (0/330) |
| Cardiac Death | 0.0% (0/401) | 0.0% (0/2451) | 0.0% (0/224) | 0.0% (0/669) | 0.0% (0/330) |
| MI | 1.7% (7/401) | 1.4% (35/2451) | 1.8% (22/1224) | 0.7% (6/669) | 2.4% (8/330) |
| QMI | 0.2% (1/401) | 0.1% (3/2451) | 0.2% (2/1224) | 0.0% (0/669) | 0.0% (0/330) |
| NQMI | 1.5% (6/401) | 1.3% (32/2451) | 1.6% (20/1224) | 0.7% (6/669) | 2.4% (8/330) |
| Cardiac Death or MI | 1.7% (7/401) | 1.4% (35/2451) | 1.8% (22/1224) | 0.7% (6/669) | 2.4% (8/330) |
| Ischemia-Driven Revascularization | 0.5% (2/401) | 0.4% (9/2451) | 0.5% (2/1224) | 0.1% (1/669) | 0.0% (0/330) |
| Ischemia – Driven TLR | 0.2% (1/401) | 0.3% (8/2451) | 0.4% (5/1224) | 0.1% (1/669) | 0.0% (0/330) |
| 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) |
| Stent Thrombosis (Per Protocol) | 0.5% (2/401) | 0.1% (3/2451) | 0.4% (5/1224) | 0.3% (2/669) | 0.0% (0/330) |
| 30-Day TLF | 2.2% (84/401) | 1.6% (38/2451) | 2.7% (33/1224) | 1.3% (9/669) | 2.7% (9/330) |
| 6-Month TLF | 3.8% (15/399) | 2.5% (62/2451) | 5.1% (62/1224) | 2.8% (17/669) | 4.9% (10/330) |
| 9-Month TLF | NA | 3.4% (83/2415) | 6.1% (73/1201) | 4.5% (35/800) | 8.4% (27/320) |
| 1-Year TLF | 4.5% (18/399) | 4.2% (101/2416) | 6.6% (81/1195) | 5.3% (35/655) | 9.7% (31/319) |

<p>| 1-Year Subject Counts of Adverse Events |
|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|
| All Death | 0.8% (3/399) | 1.0% (25/2451) | 1.3% (15/1195) | 1.2% (8/669) | 1.3% (4/330) |
| Cardiac Death | 0.3% (10/399) | 0.4% (10/2451) | 0.4% (5/1195) | 0.8% (5/669) | 0.9% (3/330) |
| Non-Cardiac Death | 0.6% (25/399) | 0.6% (15/2451) | 0.8% (10/1195) | 0.5% (3/669) | 0.3% (1/330) |
| All MI | 1.8% (7/399) | 1.9% (45/2451) | 3.1% (37/1195) | 2.7% (18/669) | 4.1% (13/330) |
| QMI | 0.3% (10/399) | 0.1% (3/2451) | 0.4% (5/1195) | 0.3% (2/669) | 0.3% (1/330) |
| NQMI | 1.5% (6/399) | 1.7% (42/2451) | 2.8% (33/1195) | 2.4% (16/669) | 3.8% (12/330) |</p>
<table>
<thead>
<tr>
<th>Event</th>
<th>SPIRIT PRIME Core Size Registry (N = 401)</th>
<th>XIENCE PRIME (N = 2456)</th>
<th>TAXUS (N = 1229)</th>
<th>XIENCE PRIME (N = 669)</th>
<th>TAXUS (N = 313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Vessel MI</td>
<td>1.8% (73/399)</td>
<td>1.6% (44/2416)</td>
<td>2.9% (35/1195)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac Death or all MI</td>
<td>2.0% (80/399)</td>
<td>2.2% (54/2416)</td>
<td>3.3% (39/1195)</td>
<td>1.4% (22/1655)</td>
<td>4.7% (15/319)</td>
</tr>
<tr>
<td>ID* TVR</td>
<td>4.5% (18/399)</td>
<td>3.9% (94/2416)</td>
<td>5.9% (73/1195)</td>
<td>6.1% (40/655)</td>
<td>7.8% (25/319)</td>
</tr>
<tr>
<td>ID* TLR</td>
<td>2.6% (10/399)</td>
<td>2.5% (61/2416)</td>
<td>4.6% (55/1195)</td>
<td>3.4% (22/555)</td>
<td>5.6% (18/319)</td>
</tr>
<tr>
<td>ID* Non-TLR TVR</td>
<td>2.8% (11/399)</td>
<td>2.5% (56/2416)</td>
<td>5.1% (37/1195)</td>
<td>3.2% (21/655)</td>
<td>4.7% (15/319)</td>
</tr>
<tr>
<td>Protocol Defined Stent Thrombosis*</td>
<td>0.5% (2/209)</td>
<td>0.17% (42/2389)</td>
<td>0.85% (12/1311)</td>
<td>0.6% (5/549)</td>
<td>0.0% (2/316)</td>
</tr>
<tr>
<td>ARC Definite+Probable Stent Thrombosis*</td>
<td>0.5% (2/209)</td>
<td>0.26% (72/2391)</td>
<td>1.10% (13/1181)</td>
<td>0.9% (6/549)</td>
<td>0.0% (2/316)</td>
</tr>
<tr>
<td>2-Years TLF*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3-Years TLF*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7.4% (47/637)</td>
<td>13.3% (41/309)</td>
</tr>
<tr>
<td>3-Years Subject Counts of Adverse Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Death</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.8% (18/636)</td>
<td>4.5% (14/312)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.6% (10/636)</td>
<td>1.9% (9/312)</td>
</tr>
<tr>
<td>Non-Cardiac Death</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.3% (8/636)</td>
<td>2.6% (8/312)</td>
</tr>
<tr>
<td>All MI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.6% (24/689)</td>
<td>6.6% (20/305)</td>
</tr>
<tr>
<td>QMI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.5% (3/659)</td>
<td>0.7% (2/305)</td>
</tr>
<tr>
<td>NQMI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.3% (21/629)</td>
<td>5.9% (16/305)</td>
</tr>
<tr>
<td>Target Vessel MI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac Death or all MI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5.1% (32/629)</td>
<td>8.2% (25/305)</td>
</tr>
<tr>
<td>ID* TVR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>11.1% (73/659)</td>
<td>14.8% (45/305)</td>
</tr>
<tr>
<td>ID* TLR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5.7% (36/629)</td>
<td>9.2% (28/305)</td>
</tr>
<tr>
<td>ID* Non-TLR TVR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6.7% (42/629)</td>
<td>8.9% (27/305)</td>
</tr>
</tbody>
</table>

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 is excluded from all data analyses.
- TLF includes cardiac death, target vessel MI (per protocol definition) and ischemia-driven TLR. SPIRIT III is based on 4-year database, other trials are based on 1-year databases.
- SPIRIT III and SPIRIT IV include 14-day window. SPIRIT PRIME includes 28-day window.
- SPIRIT III and SPIRIT IV include 14-day window.
- SPIRIT III, SPIRIT IV, and SPIRIT PRIME include 28-day window.
- See section 8.2 - Adverse Events, Stent Thrombosis Definitions.
- For Long Lesion Registry data, see Table 9.1-4.
- For SPIRIT PRIME, it is captured as clinically-indicated (CIL).
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:

- 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)\(^8\) 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)\(^9\). This was performed by an independent event committee blinded to the treatment group of the individual subject. The committee categorized each incident of ST by timing and level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

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

Level of probability:
- Definite ST - considered to have occurred by either angiographic or pathologic confirmation
- Probable ST - considered to have occurred after intracoronary stenting in the following cases:
  1. Any unexplained death within the first 30 days
  2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause
- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up\(^10\)

8.3 Potential Adverse Events

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

- Abrupt closure
- Access site pain, hematoma, or hemorrhage
- Acute myocardial infarction

\(^8\) 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.
\(^9\) Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.
\(^11\) All data within these Instructions for Use are presented as definite+probable only.
- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm
- Arterial perforation and injury to the coronary artery
- Arterial rupture
- Arteriovenous fistula
- Arrhythmias, atrial and ventricular
- Bleeding complications, which may require transfusion
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery
- Distal emboli (air, tissue or thrombotic)
- Emergent or non-emergent coronary artery bypass graft surgery
- Fever
- Hypotension and/or hypertension
- Infection and pain at insertion site
- Injury to the coronary artery
- Ischemia (myocardial)
- Myocardial infarction (MI)
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Renal failure
- Restenosis of the stented segment of the artery
- Shock/pulmonary edema
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of coronary artery
- Unstable or stable angina pectoris
- Vascular complications including at the entry site which may require vessel repair
- Vessel dissection

Zortress, the oral formulation of developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day.

Outside the U.S., Zortress is sold under the brand name, Certican, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor for 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 following list includes the known risks of everolimus at the oral doses listed above:

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dysgeusia
- Dyspepsia
- Dyspnea
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperkalemia
- Hyperlipidemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CYP3A4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain: extremity, incision site and procedural, back, chest, musculoskeletal
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis
- Thrombocytopenia
- Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/Hemolytic uremic syndrome (HUS)
- Tremor
- Upper respiratory tract infection
Urinary tract infection
Vomiting

Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. Fetal harm can occur when administered to a pregnant woman. There may be other potential adverse events that are unforeseen at this time.

9.0 SPIRIT FAMILY OF CLINICAL TRIALS

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

9.1 SPIRIT PRIME Clinical Trial

The SPIRIT PRIME clinical trial was designed to demonstrate the safety and effectiveness of the XIENCE PRIME family of stent systems. 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 family of stent systems in improving coronary luminal diameter in subjects with symptomatic heart disease due to a maximum of two de novo native coronary artery lesions, each in a different epicardial vessel.

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

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

Subjects in the Long Lesion Registry were allowed to have: one target lesion treated with the XIENCE PRIME stent system (stent diameters 2.5-4.0 mm with stent lengths 33 or 38 mm) or two target lesions in separate epicardial vessels, treated with two XIENCE PRIME stent system (stent diameters 2.5-4.0 mm with stent lengths 33 or 38 mm) or one XIENCE PRIME stent system (stent diameters 2.5-4.0 mm with stent lengths 33 or 38 mm) and one XIENCE PRIME

12 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.

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stent system (stent diameters 2.25-4.0 mm with stent lengths 8, 18, 28 mm). All subjects in the Long Lesion Registry were required to be treated with at least one XIENCE 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 (Cl-TLR). The primary endpoint rates of TLF at 1 year (per protocol and per ARC definitions) were compared to a set of pre-specified performance goals (PGs) for both Core Size Registry and Long Lesion Registry as shown below.

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

<table>
<thead>
<tr>
<th>TLF</th>
<th>Core Size Registry* Performance Goal</th>
<th>Long Lesion Registry** Performance Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLF Cardiac Death, ARC-Defined TV-MI, Cl-TLR</td>
<td>9.2%¹</td>
<td>19.2%¹</td>
</tr>
<tr>
<td>TLF Cardiac Death, Protocol-Defined TV-MI, Cl-TLR</td>
<td>9.2%¹</td>
<td>19.2%¹</td>
</tr>
<tr>
<td>TLF Cardiac Death, ARC-Defined TV-MI, Cl-TLR</td>
<td>15.3%²</td>
<td>26.0%²</td>
</tr>
</tbody>
</table>

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/m² and 50.3% (192/382) of subjects were obese, with a BMI ≥ 30. Regarding medical risk factors in the Core Size Registry, 19.2% (77/401) were tobacco users, 76.6% (307/401) were hypertensive requiring medication, and 80.3% (322/401) were hypercholesterolemic requiring medication. There were 11.1% (44/397) of subjects having had a prior cardiac intervention on the target vessel and 23.0% (91/395) had a prior MI. In addition, there were 45.6% (185/401) of subjects with stable angina and 24.9% (100/401) of subjects with unstable angina. Furthermore, the Core Size Registry consisted of 34.8% (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% (98/104) were white. The average body mass index (BMI) was 30.67 ± 5.84 kg/m², and 49.5% (50/101) of subjects were obese, with a BMI ≥ 30. Regarding medical risk factors in the Long Lesion Registry, 26.9% (28/104) were tobacco users, 75.0% (78/104) were hypertensive requiring medication, and 80.8% (84/104) were hypercholesterolemic requiring medication. There were 11.8% (12/102) of subjects having had a prior cardiac intervention on the target vessel and 22.5% (23/102) had a prior MI. In addition, there were 49.0% (51/104) of subjects with stable angina and 23.1% (24/104) of subjects with unstable angina. Furthermore, the Long Lesion Registry consisted of 35.6% (37/104) diabetics, 31.7% (33/104) diabetics requiring medication and 1.9% (2/104) diabetics requiring diet and exercise only.

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 stent system (stent diameters 2.25 – 4.0 mm with stent lengths 8, 18, 28 mm) or the XIENCE PRIME LL stent system (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, respectively.
Table 9.1-2: SPIRIT PRIME Primary Endpoint Results

<table>
<thead>
<tr>
<th>Registry</th>
<th>XIENCE PRIME (N = 401)</th>
<th>Performance Goal</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year TLF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Death, ARC-Defined TV-MI, CI-TLR</td>
<td>6.5% (26/399)</td>
<td>9.2%§</td>
<td>0.0338</td>
</tr>
<tr>
<td>Cardiac Death, Protocol-Defined TV-MI, CI-TLR</td>
<td>4.5% (18/399)</td>
<td>9.2%§</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cardiac Death, ARC-Defined TV-MI, CI-TLR</td>
<td>6.5% (26/399)</td>
<td>15.3%*</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Long Lesion Registry**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Death, ARC-Defined TV-MI, CI-TLR</td>
<td>12.5% (13/104)</td>
<td>19.2%§</td>
<td>0.0484</td>
</tr>
<tr>
<td>Cardiac Death, Protocol-Defined TV-MI, CI-TLR</td>
<td>7.7% (8/104)</td>
<td>19.2%§</td>
<td>0.0009</td>
</tr>
<tr>
<td>Cardiac Death, ARC-Defined TV-MI, CI-TLR</td>
<td>12.5% (13/104)</td>
<td>26.0%*</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

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).
- 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 Core Lesion 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*

<table>
<thead>
<tr>
<th>Composite Effectiveness and Safety</th>
<th>Outcomes at 1 Year Core Size Registry* (N=401)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLF (per protocol)</td>
<td>4.5% (18/399)</td>
</tr>
<tr>
<td>TLF (per ARC)</td>
<td>6.5% (26/399)</td>
</tr>
<tr>
<td>Effectiveness*</td>
<td></td>
</tr>
<tr>
<td>CT-TLR</td>
<td>2.5% (10/399)</td>
</tr>
<tr>
<td>CT-TLR, CABG</td>
<td>0.3% (1/399)</td>
</tr>
<tr>
<td>CT-TLR, PCI</td>
<td>2.5% (10/399)</td>
</tr>
<tr>
<td>CT-TVR</td>
<td>4.5% (18/399)</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>All Death</td>
<td>0.8% (3/399)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0.3% (1/399)</td>
</tr>
<tr>
<td>Non-Cardiac Death</td>
<td>0.5% (2/399)</td>
</tr>
<tr>
<td>Target Vessel MI (per protocol)</td>
<td>1.8% (7/399)</td>
</tr>
<tr>
<td>Target Vessel QMI (per protocol)</td>
<td>0.3% (1/399)</td>
</tr>
<tr>
<td>Target Vessel NQMI (per protocol)</td>
<td>1.5% (6/399)</td>
</tr>
<tr>
<td>All MI (per protocol)</td>
<td>1.8% (7/399)</td>
</tr>
<tr>
<td>QMI (per protocol)</td>
<td>0.3% (1/399)</td>
</tr>
<tr>
<td>NQMI (per protocol)</td>
<td>1.5% (6/399)</td>
</tr>
<tr>
<td>Target Vessel MI (per ARC)</td>
<td>4.0% (16/399)</td>
</tr>
<tr>
<td>Target Vessel QMI (per ARC)</td>
<td>0.3% (1/399)</td>
</tr>
<tr>
<td>Target Vessel NQMI (per ARC)</td>
<td>3.3% (15/399)</td>
</tr>
<tr>
<td>All MI (per ARC)</td>
<td>4.5% (18/399)</td>
</tr>
<tr>
<td>QMI (per ARC)</td>
<td>0.3% (1/399)</td>
</tr>
<tr>
<td>NQMI (per ARC)</td>
<td>4.3% (17/399)</td>
</tr>
<tr>
<td>Cardiac Death or All protocol MI</td>
<td>2.0% (8/399)</td>
</tr>
<tr>
<td>Cardiac Death or All ARC MI</td>
<td>4.8% (19/399)</td>
</tr>
<tr>
<td>ARC Definite + Probable Stent Thrombosis</td>
<td></td>
</tr>
<tr>
<td>Cumulative through 1 year</td>
<td>0.5% (2/399)</td>
</tr>
<tr>
<td>Acute/Subacute (0 – 30 days)</td>
<td>0.5% (2/401)</td>
</tr>
<tr>
<td>Late (31 days – 1 year)</td>
<td>0.0% (0/399)</td>
</tr>
</tbody>
</table>

Notes:
- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI, and clinically-induced 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

<table>
<thead>
<tr>
<th>Composite Effectiveness and Safety</th>
<th>Outcomes at 1 Year (Long Lesion Registry) (N = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLF (per protocol)</td>
<td>7.7% (8/104)</td>
</tr>
<tr>
<td>TLF (per ARC)</td>
<td>12.5% (13/104)</td>
</tr>
</tbody>
</table>

**Effectiveness**

- CI-TLR: 2.9% (3/104)
- CI-TLR, CABG: 0.0% (0/104)
- CI-TLR, PCI: 2.9% (3/104)
- CI-TVR: 4.8% (5/104)

**Safety**

- All Death: 1.0% (1/104)
- Cardiac Death: 0.0% (0/104)
- Non-Cardiac Death: 1.0% (1/104)
- Target Vessel MI (per protocol): 4.8% (5/104)
- Target Vessel QMI (per protocol): 1.9% (2/104)
- Target Vessel NQMI (per protocol): 2.9% (3/104)
- All MI (per protocol): 4.8% (5/104)
- QMI (per protocol): 1.9% (2/104)
- NQMI (per protocol): 2.9% (3/104)
- Target Vessel MI (per ARC): 10.6% (11/104)
- Target Vessel QMI (per ARC): 1.9% (2/104)
- Target Vessel NQMI (per ARC): 8.7% (9/104)
- All MI (per ARC): 10.6% (11/104)
- QMI (per ARC): 1.9% (2/104)
- Cardiac Death or All protocol MI: 4.8% (5/104)
- Cardiac Death or All ARC MI: 10.6% (11/104)
- ARC Definite+Probable Stent Thrombosis:
  - Cumulative through 1 year: 0.0% (0/104)
  - Acute/Subacute (0 - 30 days): 0.0% (0/104)
  - Late (31 days - 1 year): 0.0% (0/104)

**Notes:**
- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI, and clinically-indicated TLR.
- Population for SPIRIT PRIME Core Size Registry consists of those subjects who were treated with at least one 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.
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Coronary Vasculature

Aortic Arch

Plaque

Bypass Graft

Left Main

Left Anterior Descending (LAD)

Circumflex (CX)

Right Coronary Artery (RCA)

Obtuse Marginal (OM)

Acute Marginal

Diagonal

Posterior Descending
Your Heart
Your heart is a muscle that pumps blood throughout your body. The blood carries oxygen and nutrients that your body needs to work correctly. For the heart to be able to function properly, it also needs a constant supply of oxygen-filled blood. The vessels that supply this blood to the heart are called coronary arteries. If these arteries become blocked or narrowed, treatment may be required to restore blood flow and the vital supply of oxygen to the heart.

What is CAD?
CAD is the most common form of heart disease. It is a condition that occurs when the arteries that supply oxygen-rich blood and nutrients to the heart muscle become narrowed or blocked by a gradual buildup of “plaque.” Plaque is made up of fatty deposits (cholesterol), white blood cells, calcium, and other substances that collect over time in the wall of a coronary artery. As the plaque narrows the opening (lumen) of a coronary artery, it makes it difficult for adequate quantities of blood to flow to the heart muscle. This process is called “atherosclerosis.”
Gradual reduction of blood flow to the heart muscle can cause chest pain (angina). A heart attack (myocardial infarction) can occur if the artery suddenly becomes completely blocked, usually by a blood clot that forms over ruptured (broken) plaque. Heart attacks cause irreversible damage to the heart muscle. The first symptom of CAD can also be sudden death.

Improved medical treatment, combined with earlier diagnosis, and increased public awareness of the symptoms and risk factors that contribute to this disease are helping to decrease the death rate from CAD.

**What are the Symptoms of CAD?**

Two common symptoms of CAD are chest pain, also known as angina, and shortness of breath, which are caused by the reduction of blood flow to the heart muscle. If plaque build-up does not reduce blood flow excessively, there may be no noticeable symptoms at rest, but symptoms such as heaviness in the chest may occur with increased activity or stress.
Coronary Artery Disease (CAD)
(continued)

Other symptoms that may be experienced are:

- Pain in the jaw or neck
- Pain radiating to the arms or back
- Heartburn
- Nausea
- Vomiting
- Heavy sweating

When blood flow is significantly reduced and the heart muscle does not receive enough blood to meet its needs, severe symptoms such as chest pain (angina pectoris), heart attack (myocardial infarction), or heart rhythm disturbances (arrhythmias) may occur.

There are some patients who report no symptoms of CAD. It is possible to have a heart attack without experiencing any symptoms.

Recent research has shown that some women experience different CAD symptoms from men and are less likely than men to report chest pain, heaviness in the chest, or chest discomfort during a heart attack. Women may notice other early symptoms, such as unusual tiredness or sleep disturbances up to one month prior to a heart attack.
These differences in symptoms may cause some women to delay seeking help or treatment.

What are the Risk Factors of CAD?

Two main risk factors for CAD are:

- Increasing age (over age 65)
- Being male or a menopausal female

Other risk factors that may increase your chances of developing CAD are:

- Family history of heart disease (close relatives with heart disease at a young age)
- Diabetes
- High blood cholesterol levels
- Smoking
- High blood pressure
- Stress
- Obesity (being overweight)
- High fat diet
- Lack of exercise

---

1 Menopausal women begin to develop and die of heart disease at a rate equal to men. 
Menopause is the transition in a woman's life when production of the hormone estrogen in the body falls permanently to very low levels, the ovaries stop producing eggs, and menstrual periods stop.
How Can My Doctor Tell if I Have CAD?
If your doctor suspects that you have CAD or if you have symptoms of the disease, he or she will ask you about your risk factors and your symptoms. A complete physical exam and blood tests to identify injury to your heart muscle will also be completed. In addition, some of the tests used to make the diagnosis are:

**Electrocardiogram (ECG/EKG)** is a commonly used test that records your heart’s electrical activity and can show certain problems such as abnormal heartbeats or damage to the heart muscle. An ECG can be done at rest or while you are walking or running on a treadmill or pedaling a stationary bicycle (Stress ECG).

**Stress Tests** are used to evaluate your heart rate, heart rhythm, and ECG while you are exercising. The results of a stress test can help your doctor determine the areas of heart muscle that are affected by lack of blood flow due to CAD.

**Echocardiography** is an exam of the heart using sound waves.
Coronary Angiogram or Heart Catheterization is a procedure carried out in the cardiac catheterization laboratory (cath lab) by a cardiologist. Angiography is a procedure in which coronary arteries are visualized using X-rays. A catheter (long, thin, hollow tube) is inserted into an artery in the groin or arm. The tip of this tube is positioned at the beginning of the arteries supplying blood to the heart. A special fluid called contrast dye is injected through the tube to visualize the blood vessels on X-rays so that pictures called angiograms can be taken. These angiograms allow the doctor to see any blockage and/or narrowings in your coronary arteries and determine their severity.

Using the information gathered from one or more of these tests, your doctor is better able to decide the best treatment plan for you.
Coronary Artery Disease (CAD) (continued)

Cardiac Catheterization Laboratory
Once a diagnosis has been made, your doctor will recommend the most appropriate form of treatment, depending on the condition and severity of your CAD. CAD can be managed by a combination of changes in lifestyle (eating a healthy, diet low in saturated fat, regular exercise, and quitting smoking) and medical treatment. Your treatment may include medications to relieve your chest pain and/or to expand the coronary arteries, increasing blood flow to your heart.

However, because medicine alone may not clear blocked arteries, you may need more treatment, including surgery, angioplasty, and/or stenting to treat your symptoms.

Your doctor will explain the risks and benefits of your treatment options and answer any questions you or your family may have. You are encouraged to discuss your treatment options with your doctor.

Surgery
Coronary artery bypass grafting is a common surgical procedure that removes a section of artery or vein from another part of your body. This vessel is then connected (grafted) to the coronary artery at the
blockage site. This creates a new path for blood to flow around (bypass) the blocked artery and to your heart. Often, several blocked arteries are bypassed during the same operation. Most coronary bypass patients remain in the hospital for about a week, followed by a recovery period at home.

**Angioplasty**

Angioplasty is a procedure used to open blocked arteries. You may also hear it referred to as Percutaneous Transluminal Coronary Angioplasty (PTCA). This procedure is performed under local anesthetic in a cardiac catheterization laboratory. A catheter with a small balloon mounted on the end is passed into the coronary artery. The catheter is then positioned at the narrowed portion of the artery and the balloon is inflated. As the balloon inflates, it pushes out against the wall of the coronary artery and compresses the plaque. The balloon is then deflated and the catheter is removed from the artery. This opens the narrowing in the coronary artery and improves the blood flow to the heart muscle. In balloon angioplasty, no permanent device remains in the artery after the balloon catheter is removed. Balloon angioplasty can be performed with a balloon
Your Treatment Options
(continued)

alone or can involve placement of a permanent device called a stent, within the coronary artery.

Although balloon angioplasty enlarges the lumen of coronary arteries, many patients develop re-narrowing of the vessel in the months following the procedure. This process is called restenosis, and it is caused by the growth of scar tissue within the coronary artery.

**Step 1:**
The doctor guides a catheter with a small balloon through the blood vessel to the narrowed section of the artery. By watching the progress of this catheter on the fluoroscope (an X-ray device that creates real-time images of the internal structures of the body that can be viewed on a TV monitor), the doctor is able to maneuver it into the blocked coronary artery.
Step 2:
The balloon is inflated, pushing out against the wall of the artery and compressing the plaque. The balloon is deflated and the catheter is removed.

Step 3:
The inside of the blood vessel is now larger and the blood flow is improved.
Coronary Artery Stents

Coronary artery stents are devices (small metallic mesh tubes) that are placed over a balloon catheter and delivered to the narrowed portion of the coronary artery. The balloon is used to expand the stent. The stent presses against the narrowed vessel wall, holding the vessel open. This makes a wider channel to improve blood flow to the heart muscle. This may be followed by repeat balloon inflations within the stent to achieve the result desired by your doctor. Once the balloon has been deflated and withdrawn, the stent stays in place permanently, holding the coronary artery open. The inner lining of the artery grows over the surface of the stent, making the stent a permanent part of your artery.

Step 1:
The doctor maneuvers the catheter into the blocked artery and inflates the balloon.
Step 2:
The stent expands against the vessel wall as the balloon is inflated.

Step 3:
Once the balloon has been deflated and the catheter is withdrawn, the stent stays in place permanently, holding the blood vessel open, and improving blood flow.

Coronary artery stents are less invasive than bypass surgery. Stenting involves a shorter hospital stay — usually one to three days — and faster recovery than surgery. However, restenosis can also occur in some patients who receive stents (in-stent restenosis), due to the build-up of scar tissue within the stent leading to narrowing of the stent lumen.
To help prevent restenosis, "drug-eluting" stents have been developed. These stents are coated with a drug and provide the same structural support as uncoated stents. The drug is released over time, helping to prevent restenosis by limiting the overgrowth of normal tissue within the stent.
The illustration shown is an artist's rendition of one of Abbott's XIENCE Family of drug-eluting stents.

The XIENCE Family of Coronary Stents is intended for use by or under the direction of a physician.
The XIENCE Family of Coronary Stents includes the following: Everolimus Eluting Coronary Stent Systems – XIENCE V, XIENCE nano, XIENCE PRIME, and XIENCE PRIME LL. The differences between the various XIENCE systems involve differences in sizes (diameter and length) as well as differences in the stent design and delivery system. Going forward in this document, the XIENCE V, XIENCE nano, XIENCE PRIME, and XIENCE PRIME LL systems will be referred to as the “XIENCE Family of Coronary Stents” or as “XIENCE stents.” The XIENCE Family of Coronary Stents is designed to prevent re-narrowing within the stent (in-stent restenosis). They consist of a medical grade cobalt chromium stent with a thin coating of a drug called everolimus on its surface. This stent is based on the design of the FDA-approved MULTI-LINK VISION uncoated stent and provides mechanical support to the artery while everolimus is slowly released into the artery wall around the stent from a thin polymer (a type of plastic) coating. The polymer coating helps control the release of everolimus into the arterial wall. The polymer used on XIENCE stents has a long history of being used in medical products in contact with blood. The release of everolimus is intended to limit the overgrowth of tissue within the coronary stent.
The XIENCE Family of Coronary Stents is available in various diameters and lengths (reference Table 1 below).

Table 1: XIENCE Family Size Matrix

<table>
<thead>
<tr>
<th>Stent</th>
<th>Available Stent Diameters</th>
<th>Available Stent Lengths</th>
</tr>
</thead>
<tbody>
<tr>
<td>XIENCE V</td>
<td>2.5, 2.75, 3.0, 3.5, 4.0 mm</td>
<td>8, 12, 15, 18, 23, 28 mm</td>
</tr>
<tr>
<td>XIENCE nano</td>
<td>2.25 mm</td>
<td>8, 12, 15, 18, 23, 28 mm</td>
</tr>
<tr>
<td>XIENCE PRIME</td>
<td>2.25, 2.5, 2.75, 3.0, 3.5, 4.0 mm</td>
<td>8, 12, 15, 18, 23 mm</td>
</tr>
<tr>
<td>XIENCE PRIME LL</td>
<td>2.25*, 2.5, 2.75, 3.0, 3.5, 4.0 mm</td>
<td>28, 33, 38 mm</td>
</tr>
</tbody>
</table>

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

Contraindications

- If you have a known hypersensitivity (allergy) or contraindication to everolimus or structurally-related compounds cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers
- If you cannot take aspirin or blood-thinning medications (also called antiplatelet or anticoagulant therapy)
- If your physician decides that the coronary artery blockage will not allow complete inflation of the angioplasty balloon or proper placement of the stent
Potential Adverse Events Associated with the XIENCE Family of Coronary Stents

The risk of using the XIENCE Family of Coronary Stents is similar to those that are associated with standard stent procedures. If the stent clots, you may need another angioplasty procedure. It may also lead to a heart attack, the need for urgent bypass surgery, or death. Even with successful stent implants, there is a chance of re-narrowing of your coronary artery. This may require further treatments, such as repeat angioplasty and/or bypass surgery, to reopen the artery and to increase blood flow to the heart. The risks from using balloon catheters after stent implants are similar to the risks that may occur during the initial stent implant. These may be serious enough to require surgery or cause death.

Other risks from these devices are the same as treatment procedures for a narrowed coronary artery. Some problems associated with standard balloon angioplasty and stenting include, but are not limited to:

Common Risks
- Bruise or bleeding at the catheter insertion site in the groin or arm
- Pain at the catheter insertion site
- Irregular heartbeats
- Chest pains during and after the procedure
- Spasm of the coronary artery
- Decreased or increased blood pressure
Potential Adverse Events Associated with the XIENCE Family of Coronary Stents (continued)

Rare Risks
- Tearing, puncture, or rupture of the coronary artery
- Air, pieces of devices, or fragments of clots blocking the coronary or peripheral arteries
- Complete blockage of the coronary artery, which may require a repeat procedure to reopen the coronary artery
- Compression of the heart due to accumulation of blood around the heart
- Re-narrowing of the coronary artery
- Heart attack
- Damage to the stent or injury to the coronary artery, requiring emergency heart surgery
- Bleeding, requiring transfusion or surgery
- Allergic reaction (may include X-ray dye, cobalt, chromium, nickel, tungsten, everolimus, acrylic, and fluoropolymer)
- Infection
- Nerve injury
- Kidneys fail to function normally
- Aneurysm (weakening of a portion of the wall of a blood vessel)
- Shock
- Stroke
- Death
Potential Adverse Events Associated with the XIENCE Family of Coronary Stents (continued)

Zortress, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5 mg/day. Outside the U.S., Zortress is sold under the brand name Certican in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor for patients with advanced renal cell carcinoma (cancer) at doses of 5 to 20 mg/day when taken by mouth. The amount of drug in your blood from the XIENCE V stent is several fold lower than that obtained with oral doses (1.5 mg to 20 mg/day). Potential adverse events related to taking everolimus daily by mouth (based on long-term everolimus drug studies in organ transplant patients and in patients with advanced renal cell carcinoma) may include:

- Abdominal pain
- Abnormal collection of a clear fluid containing white blood cells
- Acne
- Blood clot in the vein
- Constipation
- Cough
- Decreased functioning of sexual organs in men
- Decreased platelet cell count
- Decreased red or white blood cells
Potential Adverse Events Associated with the XIENCE Family of Coronary Stents (continued)

- Decreased sense of taste
- Destruction of red blood cells
- Destruction of the kidney tubules
- Diarrhea
- Dry or itchy skin
- Fatigue
- Fever
- Headache
- Higher levels of potassium and lower levels of magnesium and phosphorus in the blood
- Increased blood cholesterol
- Increased blood pressure
- Increased blood sugar
- Increased fat and triglyceride fats in the blood
- Infections
- Inflammation of the lining of the digestive system
- Infection of the lungs
- Insomnia
- Kidney function test abnormality
- Lack or loss of strength
- Liver function test abnormality
- Loss of appetite
- Loss of blood supply to the bone
- Mouth ulcers or sores
- Muscle pain
- Nausea
- Nose bleeds
Potential Adverse Events Associated with the XIENCE Family of Coronary Stents (continued)

- Pain in the arms and legs
- Painful urination
- Presence of red blood cells in the urine
- Rash
- Shortness of breath, and lung or breathing problems
- Surgical wound complication
- Tremor
- Vomiting
- Water retention in the body

Exposure to drug and polymer on the XIENCE Family of Coronary Stents is directly related to the number and lengths of the stents implanted. The use of multiple XIENCE stents will result in you receiving larger amounts of drug and polymer. It should be noted that a kidney transplant patient usually receives a daily dose of the drug everolimus by mouth that is about seven times more than the maximum dose of the drug contained on one XIENCE stent.

Everolimus, when given by mouth daily to organ transplant patients, may interact with other drugs or substances. Please tell your physician about any medications you are taking.

There have been five clinical trials thus far that together have shown the safety and effectiveness of the XIENCE Family of Coronary Stents in patients
with coronary artery disease. A short description of these trials, known as the SPIRIT Family of Trials, is detailed below:

**SPIRIT FIRST**
SPIRIT FIRST was the first clinical trial. This study had 60 patients and was performed outside the United States. The purpose of the study was to compare the XIENCE V stent that is coated with a drug to that of an approved metallic stent that is not coated with a drug. There were 28 patients who received the XIENCE V stent and 32 patients who received the metallic stent (patients who received the metallic stent are also known as the "control" group).

After six months, the XIENCE V stent was significantly better than the metallic stent at reducing the re-narrowing of the artery where the stent was placed. After five years, patients who had received the XIENCE V stent had fewer major adverse cardiac events (16.7%) compared to patients who received the metallic stent (28.0%). (Patients were considered to have major adverse cardiac events if they died due to cardiac causes, or had heart attacks, or underwent bypass surgery or repeat angioplasty at the site of the lesion.)
SPIRIT II
The SPIRIT II clinical trial was the second study of the XIENCE V stent. The purpose of the study was to compare the XIENCE V stent to an approved drug-eluting stent, called TAXUS Express stent or TAXUS Liberté stent (TAXUS stent). The SPIRIT II study was conducted outside of the United States.

After six months, the XIENCE V stent was significantly better than the TAXUS stent at reducing the re-narrowing of the artery where the stent was placed. At four years, patients who had received the XIENCE V stent had a rate of major adverse cardiac events of 7.7% compared to a rate of 16.4% for those patients receiving the TAXUS stent.

SPIRIT III
SPIRIT III was the third clinical study of the XIENCE V stent. This was a much bigger study than either the SPIRIT FIRST or SPIRIT II studies, and was conducted in the United States. In one part of this study, 1002 patients were given either the XIENCE V stent or the TAXUS stent. There were 669 patients who received the XIENCE V stent and 333 patients who received the TAXUS Express stent (TAXUS stent).
After eight months, the XIENCE V stent was significantly better than the TAXUS stent at reducing the re-narrowing of the artery where the stent was placed. At three years, patients who had received the XIENCE V stent had a rate of major adverse cardiac events of 9.7% compared to a rate of 16.4% for those patients receiving the TAXUS stent.

SPIRIT IV
SPIRIT IV was the fourth clinical study of the XIENCE V stent. This is the largest study of the four randomized SPIRIT clinical trials and was conducted in the United States. A total of 3,687 patients were given either the XIENCE V stent or the TAXUS Express stent (TAXUS stent). There were 2,458 patients who received the XIENCE V stent and 1,229 patients who received the TAXUS stent.

After one year, the XIENCE V stent was significantly better than the TAXUS stent at reducing the necessity for bypass surgery or repeat angioplasty at the site of the lesion where the stent was placed. The occurrence of events related to target lesion failure, which is comprised of cardiac death, heart attacks, bypass surgery or repeat angioplasty at the site of the lesion, was significantly lower for the XIENCE V stent (4.2%) compared to the TAXUS stent (6.8%) at one year.
SPIRIT Small Vessel

The SPIRIT Small Vessel clinical study was conducted in the United States to evaluate the performance of the 2.25 mm diameter XIENCE stent (XIENCE nano) in small coronary arteries. There were 144 patients who received the XIENCE nano stent.

After one year, the rate of occurrence of events related to target lesion failure, which is comprised of cardiac death, heart attacks, bypass surgery or repeat angioplasty at the site of the lesion, was 8.1% with the XIENCE nano stent.

SPIRIT PRIME

The SPIRIT PRIME clinical study was conducted globally to evaluate the performance of the XIENCE PRIME family of stent systems. There were 415 patients enrolled in the Core Size Registry (stent diameters 2.25, 2.5, 3.0, 3.5, 4.0 mm with stent lengths 8, 18, and 28 mm) and 110 patients enrolled in the Long Lesion Registry (stent diameters 2.5, 3.0, 3.5, 4.0 mm, with stent lengths 33 and 38 mm) at up to 75 global sites.

After one year, the occurrence of events related to target lesion failure, which is comprised of cardiac...
death, heart attacks, bypass surgery or repeat angioplasty at the site of the lesion, was 4.5% in the Core Size Registry. The occurrence of events for the Long Lesion Registry was 7.7%.

For patients treated with the XIENCE Family of Coronary Stents in ways not studied in these clinical trials, clinical results may vary.
How Do I Prepare for My Procedure?

In the days prior to your treatment, make sure you:

- Take all of your prescribed medicines
- Tell your doctor if you are taking any other medication
- Tell your doctor if, for any reason, you cannot take aspirin and/or thienopyridine medications such as Plavix or Effient
- Make sure your doctor knows about any allergies you have
- Refrain from eating and drinking after midnight on the night before your treatment
- Follow all instructions given to you by your doctor or nurse

You may be given a mild sedative to help you relax, but you will not be put to sleep. There are two reasons for this. Firstly, most people find they experience little to no discomfort from the procedure. Secondly, your doctor may need to ask you to take a deep breath while X-rays are being taken, to improve the quality of the pictures.

The procedure usually lasts about 90 minutes, during which time your doctor will ask you to remain very still. For the most part, you will be comfortable, but
you may feel some pressure or chest pain when the balloon is inflated. This is normal and will quickly fade when the balloon is deflated.

Your Drug-Eluting Stent Placement Procedure
Your procedure will be performed in a cardiac catheterization laboratory (cath lab). You will lie on the X-ray table, and an X-ray camera will move over your chest during the procedure. The staff will monitor your heart by attaching several small sticky patches to your chest and using a specialized ECG recorder and monitor.

The groin is the most common site for catheter introduction and requires a very small skin incision to be made on the inside of your upper thigh. The area will be shaved and cleaned with an antiseptic, and you will be given a local anesthetic to numb the area. This incision will allow an introducer sheath (short tube) to be inserted into your femoral artery (the main artery of the thigh, supplying blood to the leg). Your doctor will then insert a guiding catheter (long, flexible tube) into the introducer sheath and advance it to where the coronary arteries branch off to the heart. A guide wire is then advanced through the guiding catheter to the narrowing in the coronary
Your Drug-Eluting Stent Procedure
(continued)

artery. This helps carry all the necessary devices required during the stenting procedure.

Additional options for catheter introduction are the arm/brachial approach (incision is made on the inside of your elbow) and the wrist/radial approach (incision is made on the inside of your wrist).
Blood vessel access for heart catheterization through the femoral, radial or brachial artery
After the catheters are inserted, your doctor will inject a contrast dye through the guiding catheter into your artery to view the narrowing. Your doctor will watch the injection on an X-ray monitor, much like a TV screen. While these X-rays are being taken, your doctor may ask you to take a deep breath and hold it for a few seconds. You may also be asked to cough after the X-ray picture is completed to help speed the removal of the contrast dye from the arteries.

Using the guiding catheter, a balloon catheter is positioned in the narrowing in the coronary artery and the balloon is then inflated. This compresses the plaque and widens the coronary artery. This procedure is called pre-dilatation.

**Step 1:**

The stent mounted on a balloon catheter is delivered to the narrowing in the coronary artery by a delivery catheter.
Your Drug-Eluting Stent Procedure

(continued)

Step 2:
The balloon is then inflated and this expands the stent, pressing it against the coronary artery wall. Your doctor may choose to expand the stent further by using another balloon so that the stent can make better contact with the artery wall. This is known as post-dilatation.

Step 3:
Once in place, the XIENCE stent will remain as a permanent implant in your coronary artery.
Immediately after Procedure

You will be asked to lie flat for four to six hours following the procedure and to not bend your leg or arm, depending on which area your doctor used to insert the catheters. Pressure will also be placed on the area.

A vascular closure device may be used to seal the incision site in your groin or arm. You will be allowed to get up and walk around sooner if this type of device is used. Your hospital stay may range from one to three days.

Medications will be prescribed for you before and after stent placement. Antiplatelet medications such as aspirin and thienopyridine medications (such as Plavix or Effient) are the most commonly prescribed. They help prevent a blood clot (thrombus) from forming and blocking the stent lumen. Your doctor or nurse will give you instructions about your medications before you leave the hospital.

CAUTION: If you have any chest pain, or discomfort or bleeding from your incision site, call your doctor immediately. If your doctor is unavailable, call for an ambulance to take you to the nearest hospital emergency room.
Take All Medications as Instructed
After you leave the hospital, your cardiologist will instruct you to take a daily dose of aspirin and another antiplatelet drug such as Plavix or Effient. Your doctor will tell you how long you should continue taking the antiplatelet drugs. It is very important that you take these medications exactly as your doctor instructs you:

- Follow your medication schedule exactly to avoid possible complications after you receive your stent. Do not miss any doses.
- Call your doctor if you cannot keep taking your medications because of side effects such as rash, bleeding, or upset stomach.
- **CAUTION:** Do not stop taking your prescribed medications unless you are instructed to do so by the doctor who performed your stent procedure.
- **CAUTION:** Notify your cardiologist or family doctor if you are scheduled to see the dentist while on antiplatelet medication. Your doctor may prescribe antibiotics to avoid the potential of an infection. You should review with your doctor any recommendations from your dentist to stop your prescribed medications.
• CAUTION: Before undergoing implantation of a drug-eluting stent, if you plan to have any type of surgery that may require you to stop taking antiplatelet medications, you and your cardiologist should discuss whether or not placement of a drug-eluting stent is the right treatment choice for you.

If surgery or dental work that would require you to stop taking antiplatelet medications is recommended after you have received the stent, you and your doctors should carefully consider the risks and benefits of this surgery or dental work versus the possible risks from early discontinuation of these medications.

If you do require discontinuation of antiplatelet medications because of significant bleeding, your cardiologist will carefully monitor you for possible complications. Once your condition has stabilized, your cardiologist may put you back on these medications.
Follow-up Care
You will be discharged to the care of your cardiologist or family doctor. You should be able to return to your normal activities soon.

CAUTION: Notify your doctor immediately if you experience chest pain (angina), or notice any changes such as more severe or frequent chest discomfort, especially in the first month after a procedure. These symptoms may indicate a re-narrowing in your coronary arteries.

Your doctor will ask you to return for follow-up visits. The first visit is usually two to four weeks after your stent is implanted, with follow-up visits every six months for the first year. Be sure to keep all appointments for follow-up care, including blood tests.
Your Drug Eluting Stent Procedure (continued)

Keep Your ID Card Handy

CAUTION: Show your identification card if you report to an emergency room. This card identifies you as a patient who has had a stent implanted.

If you require a magnetic resonance imaging (MRI) scan, tell your doctor or MRI technician that you have a stent implant. Test results indicate that patients with single or overlapped XIENCE V stents can undergo MRI scans safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning for each sequence.

The stent(s) should not migrate in this MRI environment, and MRI may be performed immediately following the implantation of the XIENCE stent(s). Prior to undergoing an MRI scan, inform your doctor that you have a XIENCE stent.
Coronary artery disease can be treated effectively, but it has no cure. You can help to prevent your coronary artery disease from progressing by carefully following your doctor's advice. Your doctor may prescribe medications to help control your blood pressure, diabetes, and/or high cholesterol. Your doctor may also recommend some lifestyle changes. Among the healthy choices you can make:

**Stop smoking.** If you smoke, quitting is the single most important thing you can do to lower your risk of coronary artery disease. Chemicals in cigarette smoke may make it easier for plaque to build up on your artery walls. And smoking increases your heart rate and blood pressure, raising your risk of heart attack and stroke. If you are ready to quit, ask your doctor for advice — he or she can recommend smoking cessation aids to help you quit.

**Increase your activity and eat a healthy diet.** A sedentary lifestyle increases your risk. Your doctor can recommend an activity program tailored for your situation. Regular exercise can help you lower your blood pressure and blood cholesterol and reach a healthy weight. It can also help you manage the daily stresses of modern life more easily. Choose
a healthy diet. A diet low in saturated fats and cholesterol, and rich in lean protein, fresh fruits, vegetables, and whole grains, can help you achieve a healthy weight, as well as help you control your blood pressure, and cholesterol levels.

**Manage your stress.** Stress is an inescapable aspect of modern day living, but you can help lessen its negative health effects by practicing the “relaxation response.” Research has shown that relaxation techniques can improve your ability to
cope with stressful events while decreasing your heart rate, blood pressure, and stress hormone levels.

How long will the stent stay in my body?
Stents are designed to stay in your body permanently.

What are the restrictions or cautions after I've received a stent?
If you require magnetic resonance imaging (MRI), tell your doctor or MRI technician that you have an implanted stent.

When can I resume my regular activities?
Your doctor will advise you. Many patients can return to work and follow their normal routine about a week after their stent procedure.

Will my stent set off the metal detector at airport security checkpoints?
No, your stent implant will not trigger alarms at security checkpoints.
Frequently Asked Questions (continued)

Will I be able to feel the stent inside me?
No, you will not be able to feel the stent once it has been implanted in your artery.

Could I have recurring symptoms?
Yes, it is possible that you will experience symptoms again, either due to a new blockage in the region treated with the stent or due to a blockage at another place in your coronary arteries. Your doctor will monitor your progress.

How can I help prevent a recurrence of symptoms?
While there is no sure way to prevent a recurrence of symptoms, you can reduce the risk through exercise, not smoking, and eating a healthy diet. Your doctor can advise you about lifestyle changes.
Angina: Chest pain caused by inadequate supply of blood to the heart.

Angioplasty (also referred to as PTCA): A minimally invasive procedure in which a balloon dilatation catheter is passed through to the blocked area of an artery. Once inflated the catheter compresses the plaque against the blood vessel wall and enlarges the vessel opening. An angioplasty can also be performed with placement of a stent.

Anticoagulant: A medication to prevent or slow the clotting of blood.

Antiplatelet: A substance to reduce clumping of platelets in the blood.

An antiplatelet medicine helps thin the blood to prevent clot formation.

Atherosclerosis: A disease that causes narrowing or blockage of arteries caused by a build-up of fat (cholesterol) within the artery wall. The build-up is sometimes referred to as “plaque.”

Cardiac Catheterization Laboratory (Cath Lab): A sterile X-ray theater in which heart catheterization is performed.
Catheter: A thin, hollow, flexible tube used to access the coronary arteries during an angiogram or during an angioplasty procedure. This catheter can be used to inject medication, fluids, or contrast dye during your procedure. Catheter is also used to describe the device used to deliver the balloon or stent during an angioplasty procedure.

Coronary Angiography (or Heart Catheterization or Cardiac Cath): A test in which contrast dye is injected to create images of the coronary arteries and the chamber of the heart. This allows the doctor to see the extent of the disease in the coronary arteries and make a decision on how to best treat the blockages.

Coronary Arteries: The blood vessels that carry oxygenated blood from the aorta to the heart muscle. There are four major coronary arteries: the left main, the right coronary artery, the left anterior descending, and the circumflex.

Coronary Artery Bypass Graft Surgery (CABG): Open-heart surgery to treat CAD.
Coronary Artery Disease (CAD): The formation of blockages or atherosclerotic plaques within coronary arteries that result in restricted blood flow to the heart muscle.

Electrocardiogram (ECG/EKG): A test that records changes in the electrical activity of the heart. An ECG/EKG may show whether parts of the heart muscle are damaged due to decreased blood flow to the heart muscle.

Femoral Artery: The main artery of the thigh, supplying blood to the leg.

Fluoroscope: An X-ray device that creates an image of the body that can be viewed on a TV monitor. This permits the doctor to obtain real-time images of the internal structures of a patient.

In-stent Restenosis: Recurrent blockage or narrowing of a previously stented vessel.

Local Anesthetic: A substance used to numb the area to which it is applied.

Lumen: The inner channel or cavity of a vessel or tube. In a blood vessel, it is the opening through which blood flows.
**Myocardial Infarction (MI):** Also called a heart attack. Permanent damage of an area of the heart tissue, due to interruption in the blood flow to the heart muscle (myocardium).

**Magnetic Resonance Imaging (MRI):** A non-invasive diagnostic procedure used to obtain images of internal body structures through the use of magnets and radio waves.

**Percutaneous:** Performed through the skin.

**Plaque:** An accumulation or build-up of fatty deposits, calcium, white blood cells, and other substances in the wall of an artery that results in narrowing of the vessel lumen.

**Restenosis:** A recurring blockage caused by the excessive growth of scar tissue inside the artery or stent, following an interventional procedure such as angioplasty.

**Stent:** A metallic mesh tube that is implanted into an artery during an angioplasty, providing a scaffold to help hold the artery open, ensuring blood flow to the heart muscle.

**Transluminal:** Through the inside opening of a vessel or artery.