SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug Eluting Coronary Stent System
Premarket Approval Application (PMA) Supplement Number:	P070015/S122
Device Trade Name:	XIENCE V® and XIENCE nano® Everolimus Eluting Coronary Stent System
PMA Supplement Number:	P110019/S066
Device Trade Name:	XIENCE PRIME® Everolimus Eluting Coronary Stent System XIENCE PRIME® LL Everolimus Eluting Coronary Stent System XIENCE Xpedition® Everolimus Eluting Coronary Stent System XIENCE Xpedition® SV Everolimus Eluting Coronary Stent System XIENCE Xpedition® LL Everolimus Eluting Coronary Stent System XIENCE Alpine™ Everolimus Eluting Coronary Stent System
Device Procode:	NIQ
Applicant's Name and Address:	Abbott Vascular 3200 Lakeside Drive Santa Clara, CA 95054
Date of Panel Recommendation:	None
Date of FDA Notice of Approval:	October 3, 2014

This is a bundled Premarket Approval (PMA) Supplement for P070015 and P110019 for the XIENCE Family of Everolimus Eluting Coronary Stent Systems (XIENCE Family of Stents). The XIENCE Family of Stents includes the XIENCE V Stent System, approved under P070015 on July 2, 2008, the XIENCE nano, approved on May 24, 2011 under P070015/ S054, the XIENCE PRIME and XIENCE PRIME LL Stent System (XIENCE PRIME Stent System) approved on November 1, 2011 under P110019, and XIENCE Xpedition, XIENCE Xpedition SV, and XIENCE Xpedition LL (XIENCE Xpedition Stent System) approved on December 21, 2012 under P110019/S025 and XIENCE Alpine™ (XIENCE Alpine Stent System) approved September 3, 2014 under P110019/S070.

The Summary of Safety and Effectiveness Data (SSED) to support the indications is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf7/P070015b.pdf and http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110019b.pdf) and is incorporated by reference herein. This bundled PMA supplement, P070015/S122 and P110019/S066 was submitted to request approval for an expanded indication to include patients with chronic total occlusions (CTO).

II. INDICATIONS FOR USE

XIENCE V and XIENCE nano Everolimus Eluting Coronary Stent System

The XIENCE V and XIENCE nano Everolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.25 mm to 4.25 mm. Additionally, the XIENCE V stent system is indicated for treating de novo chronic total coronary occlusions.

XIENCE PRIME and XIENCE PRIME LL Everolimus Eluting Coronary Stent System

The XIENCE PRIME and XIENCE PRIME LL Everolimus Eluting Coronary ~~S~~tent System is indicated for improving coronary 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. Additionally, the XIENCE PRIME stent system is indicated for treating de novo chronic total coronary occlusions.

XIENCE Xpedition, XIENCE Xpedition SV and XIENCE Xpedition LL Everolimus Eluting Coronary Stent System

The XIENCE Xpedition, XIENCE Xpedition SV and XIENCE Xpedition LL Everolimus Eluting Coronary 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. In addition, the XIENCE Xpedition stent system is indicated for treating de novo chronic total coronary occlusions.

XIENCE Alpine Everolimus Eluting Coronary Stent System

The XIENCE Alpine Everolimus Eluting Coronary 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. Additionally, the XIENCE Alpine stent system is indicated for treating de novo chronic total coronary occlusions.

III. CONTRAINDICATIONS

The XIENCE Family of Stents is contraindicated for use in patients:

- Who cannot receive antiplatelet and / or anticoagulant therapy
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the XIENCE V, XIENCE PRIME, XIENCE Xpedition and the XIENCE Alpine labeling.

V. DEVICE DESCRIPTION

XIENCE Family of Everolimus Eluting Coronary Stent Systems Summary

The XIENCE Family of Everolimus Eluting Coronary Stent Systems (EECSS) is a device / drug combination product consisting of a Cobalt Chromium (CoCr) alloy stent coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer mounted on a delivery system. The XIENCE V is offered in sizes 2.5mm to 4.0mm diameter and the XIENCE nano is offered in the 2.25mm diameter. The stent platform and delivery system of the XIENCE V and XIENCE nano are identical to the MULTI-LINK VISION and MULTI-LINK MINI VISION respectively. The XIENCE V was approved under P070015 and the XIENCE nano Stent System is a line extension to the XIENCE V Stent System, which was approved under P070015/S054.

The XIENCE PRIME and XIENCE PRIME LL were approved under P110019 and are available in the 2.25mm to 4.25mm diameters. The XIENCE PRIME LL is available in longer stent lengths compared to XIENCE V which include 33mm and 38mm for the 2.5mm to 4.25mm stents. The stent is coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer, which is identical to the XIENCE V Everolimus Eluting Coronary Stent System; however, there are minor differences between the stent designs and delivery systems. The XIENCE Xpedition, XIENCE Xpedition LL and XIENCE Xpedition SV

and XIENCE Alpine EECSS are line extensions to the XIENCE PRIME Stent System, which was approved under P110019/S025 and P110019/S070 respectively with a modified delivery system.

See the Device Component Description sections below for additional information on the XIENCE family of stents.

XIENCE V and XIENCE nano—Device Component Description

The device component consists of the MULTI-LINK MINI VISION or MULTI-LINK VISION stent mounted onto the MULTI-LINK MINI VISION or MULTI-LINK VISION stent delivery system (SDS), respectively. The device component characteristics are summarized in **Table 1.**

Table 1 XIENCE V Stent System Product Description

	XIENCE V Rapid-Exchange (RX) Stent System	XIENCE V Over-the-Wire (OTW) Stent System
Available Stent Lengths	8, 12, 15, 18, 23, 28	8, 12, 15, 18, 23, 28
Available Stent Diameters (mm)	2.25*, 2.5, 2.75, 3.0, 3.5, 4.0	2.5, 2.75, 3.0, 3.5, 4.0
Stent Material	A medical grade L-605 cobalt chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent	
Drug Component	A conformal coating of a non-erodible polymer loaded with 100µg/cm2 of everolimus with a maximum nominal drug content of 181µg on the largest stent (4.0 x 28 mm)	
Delivery System Working Length	143 cm	143 cm
Delivery System Design	Single access port to inflation lumen. Guide wire exit notch is located 30 cm from tip. Designed for guide wires ≤ 0.014".	Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen. Designed for guide wires ≤ 0.014".
Stent Delivery System Balloon	A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length.	
Balloon Inflation Pressure	Nominal inflation pressure: 8 atm (811 kPa) for 2.25, 2.5 and 2.75 mm diameters; 9 atm (912 kPa) for 3.0, 3.5, and 4.0 mm diameters Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes	
Guiding Catheter Inner Diameter	≥ 5 F (0.056")	
Catheter Shaft Outer Diameter (nominal)		

	2.25 – 3.0 mm	3.5 – 4.0 mm
Distal:	0.032"	0.035"
Proximal:	0.026"	0.026"

	2.5 mm	2.75 x 8 - 3.5 x 18	3.5 x 23 - 4.0 x 28
Distal:	0.032"	0.034"	0.036"
Proximal:	0.042"	0.042"	0.042"

*The 2.25 mm diameter XIENCE V EECSS is only available on the RX platform.

XIENCE PRIME and XIENCE PRIME LL —Device Component Description

The XIENCE PRIME and the XIENCE PRIME LL device component characteristics are summarized in **Table 2 and Table 3.**

Table 2 XIENCE PRIME and XIENCE PRIME LL Reference Vessel Diameter and Stent Length

	REFERENCE VESSEL DIAMETER (RVD)	**LESION LENGTH**
XIENCE PRIME	≥ 2.25 mm and ≤ 4.25 mm Stent Diameter: 2.25, 2.5, 2.75, 3.0, 3.5, 4.0 mm	≤ 22 mm Stent Length: 8, 12, 15, 18, 23, 28 mm
XIENCE PRIME LL	≥ 2.5 mm and ≤ 4.25 mm Stent Diameter: 2.5, 2.75, 3.0, 3.5, 4.0 mm	> 22 mm, and ≤ 32 mm Stent Length: 33 and 38 mm

Table 3 XIENCE PRIME Stent System Product Description

	XIENCE PRIME Stent System	
	XIENCE PRIME	XIENCE PRIME LL
Available Stent Lengths (mm)	8, 12, 15, 18, 23	28*, 33, 38
Available Stent Diameters (mm)	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	2.25**, 2.5, 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/cm^2 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".	

<table>
<tr><td></td><td colspan="2">XIENCE PRIME Stent System</td></tr>
<tr><td></td><td>XIENCE PRIME</td><td>XIENCE PRIME LL</td></tr>
<tr><td>Stent Delivery System Balloon</td><td colspan="2">A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length</td></tr>
<tr><td>Balloon Inflation Pressure</td><td colspan="2">Rated Burst Pressure (RBP): 18 atm (1824 kPa)
<table><tr><th>Stent Diameter (mm)</th><th>In vitro Stent Nominal Pressure (atm)</th></tr><tr><td>2.25</td><td>8</td></tr><tr><td>2.5</td><td>8</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></table></td></tr>
<tr><td>Guiding Catheter Inner Diameter</td><td colspan="2">≥ 5 F (0.056”)</td></tr>
<tr><td>Catheter Shaft Outer Diameter</td><td colspan="2">Distal: 0.034” (0.86 mm)
Proximal: 0.031” (0.79 mm)</td></tr>
</table>

* 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.

XIENCE Xpedition—Device Component Description

The XIENCE Xpedition family of stent systems includes:

- The XIENCE Xpedition SV EECSS (stent diameter 2.25, stent lengths 8, 12, 15, 18, 23, 28 mm)
- The XIENCE Xpedition EECSS (stent diameters 2.5, 2.75, 3.0, 3.25[1], 3.5, 4.0 mm, stent lengths 8, 12, 15, 18, 23, 28 mm)
- The XIENCE Xpedition LL EECSS (stent diameters 2.5,2.75, 3.0, 3.25, 3.5, 4.0 mm, stent lengths 33, 38 mm)

The device component characteristics are summarized in **Table 4**.

[1] The 3.25 mm stent diameter is only available for the XIENCE Xpedition Stent System and not for the XIENCE PRIME Stent System.

Table 4 XIENCE Xpedition, XIENCE Xpedition SV, and XIENCE Xpedition LL Product Description

<table>
<tr><td></td><td colspan="3">XIENCE Xpedition Stent System</td></tr>
<tr><td></td><td>XIENCE Xpedition SV</td><td>XIENCE Xpedition</td><td>XIENCE Xpedition LL</td></tr>
<tr><td>Available Stent Lengths (mm)</td><td>8, 12, 15, 23, 28</td><td>8, 12, 15, 23, 28</td><td>33, 38</td></tr>
<tr><td>Available Stent Diameters (mm)</td><td>2.25</td><td>2.5, 2.75, 3.0, 3.25, 3.5, 4.0</td><td>2.5, 2.75, 3.0, 3.25, 3.5, 4.0</td></tr>
<tr><td>Stent Material</td><td colspan="3">A medical grade L-605 cobalt chromium CoCr alloy identical to the material used in the XIENCE V and XIENCE PRIME stent</td></tr>
<tr><td>Drug Component</td><td colspan="3">
<table>
<tr><th>Stent Design</th><th>Diameters (mm)</th><th>Stent Length (mm)</th><th>Surface Area (cm^2)</th><th>Target Drug Amount (µg)</th></tr>
<tr><td>Small</td><td>2.25, 2.5, 2.75, 3.0, 3.25</td><td>8</td><td>0.3972</td><td>40</td></tr>
<tr><td>Small</td><td>2.25, 2.5, 2.75, 3.0, 3.25</td><td>12</td><td>0.6048</td><td>60</td></tr>
<tr><td>Small</td><td>2.25, 2.5, 2.75, 3.0, 3.25</td><td>15</td><td>0.7431</td><td>74</td></tr>
<tr><td>Small</td><td>2.25, 2.5, 2.75, 3.0, 3.25</td><td>18</td><td>0.8815</td><td>88</td></tr>
<tr><td>Small</td><td>2.25, 2.5, 2.75, 3.0, 3.25</td><td>23</td><td>1.0891</td><td>109</td></tr>
<tr><td>Small</td><td>2.25, 2.5, 2.75, 3.0, 3.25</td><td>28</td><td>1.3658</td><td>137</td></tr>
<tr><td>Small</td><td>2.5, 2.75, 3.0, 3.25</td><td>33</td><td>1.5734</td><td>157</td></tr>
<tr><td>Small</td><td>2.5, 2.75, 3.0, 3.25</td><td>38</td><td>1.8501</td><td>185</td></tr>
<tr><td>Medium</td><td>3.5, 4.0</td><td>8</td><td>0.4979</td><td>50</td></tr>
<tr><td>Medium</td><td>3.5, 4.0</td><td>12</td><td>0.7466</td><td>75</td></tr>
<tr><td>Medium</td><td>3.5, 4.0</td><td>15</td><td>0.9124</td><td>91</td></tr>
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<tr><td>Medium</td><td>3.5, 4.0</td><td>33</td><td>1.9903</td><td>199</td></tr>
<tr><td>Medium</td><td>3.5, 4.0</td><td>38</td><td>2.3219</td><td>232</td></tr>
</table>
</td></tr>
<tr><td>Delivery System Working Length</td><td colspan="3">145 cm</td></tr>
</table>

<table>
<tr><th></th><th>XIENCE Xpedition Stent System</th></tr>
<tr><td>Delivery System Design</td><td>RX: Single access port to inflation lumen; guide wire exit notch is located 25.5 cm from tip; designed for guide wires ≤ 0.014”.
OTW: Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen; designed for guide wires ≤ 0.014”.</td></tr>
<tr><td>Stent Delivery System Balloon</td><td>A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length</td></tr>
<tr><td>Balloon Inflation Pressure</td><td>Rated Burst Pressure (RBP): 18 atm (1824 kPa)
<table><tr><th>Stent Diameter (mm)</th><th>In vitro Stent Nominal Pressure (atm)</th></tr><tr><td>2.25</td><td>10</td></tr><tr><td>2.5</td><td>10</td></tr><tr><td>2.75</td><td>10</td></tr><tr><td>3.0</td><td>10</td></tr><tr><td>3.25</td><td>10</td></tr><tr><td>3.5</td><td>10</td></tr><tr><td>4.0</td><td>10</td></tr></table></td></tr>
<tr><td>Guiding Catheter Inner Diameter</td><td>≥ 5 F (0.056”) for 2.25 – 3.5mm sizes
≥ 5 F (0.056”) for 4.0 x 8-33mm sizes
≥ 6 F (0.066”) for 4.0 x 38mm sizes</td></tr>
<tr><td>Catheter Shaft Outer Diameter</td><td>Distal: 0.034” (0.86 mm)
Proximal (RX): 0.028” (0.71 mm)
Proximal (OTW): 0.045” (1.14 mm)</td></tr>
</table>

XIENCE Alpine—Device Component Description

The XIENCE Alpine family of stent systems includes:

1. stent diameter 2.25, stent lengths 8, 12, 15, 18, 23, 28 mm
2. stent diameters 2.5, 2.75, 3.0, 3.25[2], 3.5, 4.0 mm, stent lengths 8, 12, 15, 18, 23, 28, 33, 38 mm

The device component characteristics are summarized in **Table 5**.

[2] The 3.25 mm stent diameter is only available for the XIENCE Xpedition and XIENCE Alpine Stent Systems and not for the XIENCE PRIME Stent System.

Table 5 XIENCE Alpine Product Description

<table>
<tr><td></td><td colspan="2">XIENCE Alpine Stent System</td></tr>
<tr><td>Available Stent Lengths (mm)</td><td>8, 12, 15, 23, 28</td><td>8, 12, 15, 23, 28, 33, 38</td></tr>
<tr><td>Available Stent Diameters (mm)</td><td>2.25</td><td>2.5, 2.75, 3.0, 3.25, 3.5, 4.0</td></tr>
<tr><td>Stent Material</td><td colspan="2">A medical grade L-605 cobalt chromium CoCr alloy identical to the material used in the XIENCE V, XIENCE PRIME, XIENCE Xpedition stents</td></tr>
<tr><td>Drug Component</td><td colspan="2">
<table>
<tr><th>Stent Design</th><th>Diameters (mm)</th><th>Stent Length (mm)</th><th>Surface Area (cm^2)</th><th>Target Drug Amount (μg)</th></tr>
<tr><td>Small</td><td>2.25, 2.5, 2.75, 3.0, 3.25</td><td>8</td><td>0.3972</td><td>40</td></tr>
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<tr><th></th><th>XIENCE Alpine Stent System</th></tr>
<tr><td>Delivery System Design</td><td>RX: Single access port to inflation lumen; guide wire exit notch is located 25.5 cm from tip; designed for guide wires ≤ 0.014”.
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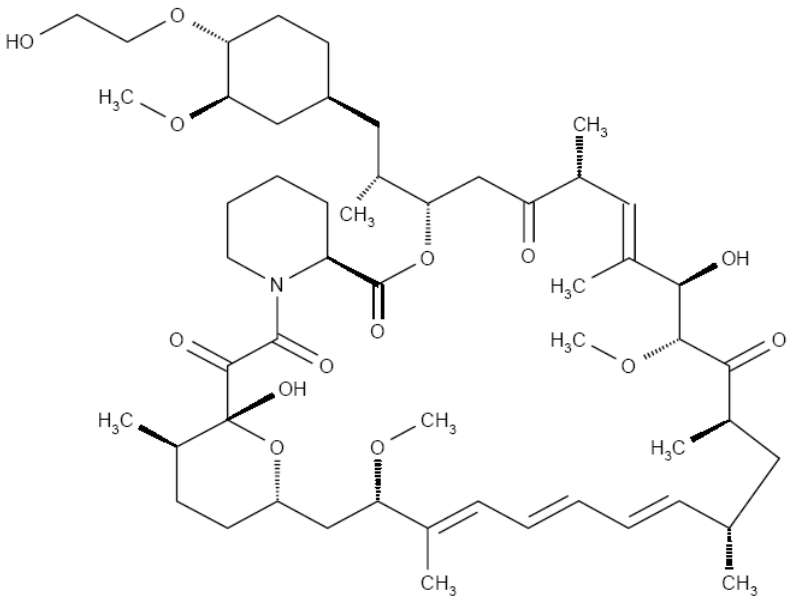
Drug Component Description for the XIENCE Family of Stents

The XIENCE Family of Everolimus Eluting Coronary Stents are coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

Everolimus

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

Figure 1 Everolimus Chemical Structure

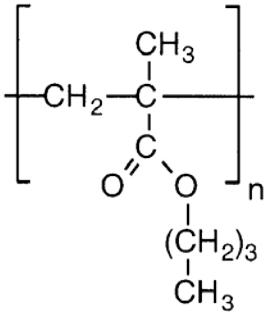
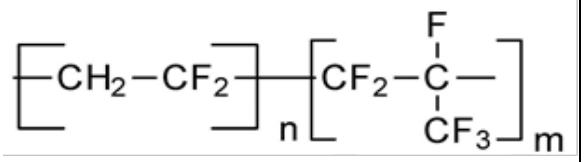


Inactive Ingredients – Non-erodible Polymer

The XIENCE V stent contains inactive ingredients including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA coated stent surface.

The drug load is 100 µg/cm2 for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in **Figure 2** below.

Figure 2 Non-erodible Polymer Chemical Structures

PBMA	PVDF-HFP
	

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of patients with coronary artery disease including exercise, diet, drug therapy, percutaneous coronary interventions (i.e., balloon angioplasty, atherectomy, bare metal stents, coated stents, and other drug-eluting stents), and coronary artery bypass grafting (CABG) surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The XIENCE family of stents is commercially available in the following countries. The devices have not been withdrawn from marketing for any reason related to its safety or effectiveness.

AFGHANISTAN	BULGARIA	FREN.POLYNESIA	IRELAND	MACEDONIA	PANAMA
ALBANIA	CAMBODIA	FRENCH GUYANA	ITALY	MALAYSIA	PARAGUAY
ALGERIA	CANADA	GEORGIA	ISRAEL	MALTA	PHILIPPINES
ARGENTINA	CHILE	GERMANY	JAMAICA	MARTINIQUE	POLAND
AUSTRALIA	CHINA	GREECE	JAPAN	MAURITIUS	PORTUGAL
AUSTRIA	COLOMBIA	GUADELOUPE	JORDAN	MEXICO	PUERTO RICO
AZERBAIJAN	COSTA RICA	GUAM	KAZAKHSTAN	MOROCCO	QATAR
BAHAMAS	CYPRUS	GUATEMALA KOSOVO (DNU)	KOSOVO	NETHERLANDS	REP. OF ARMENIA
BAHRAIN	CZECH REPUBLIC	HONDURAS	KOSOVO (DNU)	NORWAY OMAN	REP. OF YEMEN

BANGLADESH	DENMARK	HONG KONG	KUWAIT	NEW CALEDONIA	REUNION
BARBADOS	DOMINICAN REP.	HUNGARY	LATVIA	NEW ZEALAND	ROMANIA
BELARUS	ECUADOR	ICELAND	LEBANON	NICARAGUA	RUSSIAN FED.
BELGIUM	EGYPT	INDIA	LIBYA	NORTH MARIANA	SAMOA, AMERICAN
BOLIVIA	EL SALVADOR ESTONIA	INDONESIA	LIECHTENSTEIN	NORWAY	SAN MARINO
BRAZIL	FINLAND	IRAN	LITHUANIA	OMAN	SAUDI ARABIA
BRUNEI	FRANCE	IRAQ	LUXEMBOURG	PAKISTAN	SERBIA
SINGAPORE	SLOVAKIA	SLOVENIA	SOUTH AFRICA	SOUTH KOREA	SOUTH YEMEN
SPIAN	SRI LANKA	SWEDEN	SWITZERLAND	TAIWAN	THAILAND
TRINIDAD, TOBAGO	TUNISIA	TURKEY	UKRAINE	UNITED ARAB EMIRATES	UNITED KINGDOM
UNITED STATED	URUGUAY	US VIRGIN IS.	UZBEKISTAN	VENEZUELA	VIETNAM

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the XIENCE Family of Everolimus Eluting Coronary Stents.

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, hematoma, or hemorrhage
- Acute myocardial infarction
- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm
- Arterial perforation and injury to the coronary artery
- Arterial rupture
- Arteriovenous fistula
- Arrhythmias, atrial and ventricular
- Bleeding complications, which may require transfusion
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery

- Distal emboli (air, tissue or thrombotic)
- Emergent or non-emergent 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 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), 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 or PgP
- 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.

IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies related to the XIENCE Family of Stents were performed and the pertinent data is being leveraged from the previously approved PMAs P070015 and P110019.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of percutaneous coronary intervention with XINCE V and/or XIENCE PRIME Everolimus-Eluting Coronary Stent Systems for the treatment of chronic total occlusion coronary artery lesions in the US under IDE, G110103. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between September 13, 2011 and February 7, 2013. The PMA presented data collected through 1-year clinical follow-up and included 222 Intent-To-Treat (ITT) patients. There were 20 investigational sites.

The EXPERT CTO study was a prospective, multi-center, one-arm, (un)masked clinical study and was non-randomized and open-label, with clinical follow-up through 5 years. EXPERT CTO is designed to study the safety and effectiveness of the XIENCE V and XIENCE PRIME Stent Systems for the treatment of chronic total occlusions. A total of 250 subjects were enrolled at 20 sites. The ITT population consisted of 222 subjects and the Per -Protocol (PP) population consisted of 183 subjects. The primary endpoint for EXPERT CTO was major adverse cardiac events (MACE) at 1 year. This composite endpoint includes the following components: Death, MI or Clinically-Driven Target Lesion Revascularization (TLR).

XIENCE Xpedition and XIENCE Alpine stents are identical to the XIENCE PRIME stent. The XIENCE PRIME stent is similar to the XIENCE V stent. In addition, the stent delivery systems for XIENCE Xpedition and XIENCE Alpine are similar to the XIENCE V stent delivery system. The clinical data in the current approved labeling for the XIENCE Xpedition and XIENCE Alpine Stent Systems are leveraged from the XIENCE PRIME Stent System, which in turn leverages clinical data from the XIENCE V Stent System. Therefore, clinical data from the EXPERT CTO clinical trial is applicable to multiple models in the XIENCE family of Everolimus Eluting Coronary Stent Systems and no additional clinical trial data were required to demonstrate the safety and effectiveness of the XIENCE Xpedition and XIENCE Alpine Stent Systems in CTOs.

The statistical analysis was performed via the Frequentist approach. The stent-related endpoint in this trial was MACE which was defined as death, MI (per ARC definition), or clinically-driven TLR at 1 year post-procedure among all enrolled patients for whom recanalization and pre-dilatation of the target lesion were completed when the study stent(s) (XIENCE V and/or

XIENCE PRIME) was inserted into the coronary guiding catheter. This rate was compared with a performance goal (PG) of 24.4%.

The null hypothesis stated that the study stent will have a 1-year MACE rate greater than or equal to the PG. The alternative hypothesis states that the study stent will have a 1-year MACE rate less than the PG where P_{MACE} is the true primary endpoint rate for the study stent and the 24.4% is the meta-analytically derived PG for the primary endpoint rate. Rejection of the null hypothesis will signify that the PG has been met.

Specifically:

$$Ho : P_{MACE} \geq 0.244$$
$$Ha : P_{MACE} < 0.244$$

Assuming a one-sided alpha level of 0.05, with an approximate true event rate of 14.4%, and approximately 94% statistical power utilizing an exact test, an effective sample size of 163 patients was required to demonstrate that the stated PG is achieved. Adjusting this number for an approximate 10% loss to follow-up resulted in a sample size of approximately 180 patients in whom the guide wire had crossed the CTO and the lesion was pre-dilated. Assuming that 72% of the CTO are crossed and pre-dilated, the total enrollment in this study is therefore calculated as 180/0.72 = 250 patients.

The trial monitor is Harvard Clinical Research Institute (HCRI). The Angiographic Core Laboratory is Beth Israel Deaconess Medical Center, Boston, MA. Data monitoring, management, analysis and Clinical Events Committee are also handled by Harvard Clinical Research Institute, Boston, MA.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the EXPERT CTO study was limited to patients who met the following inclusion criteria:

   General Inclusion Criteria:

   a. The patient is ≥ 18 years of age at the time of consent

   b. Patients experiencing clinical symptoms considered suggestive of ischemic heart disease (e.g., chest pain or discomfort, heart failure, etc.) or having evidence of myocardial ischemia (e.g., abnormal functional study) attributed to the CTO target vessel and scheduled for clinically indicated percutaneous revascularization

   c. Subject is eligible and consents to undergo percutaneous coronary intervention (PCI) procedure

d. Patient is an acceptable candidate for percutaneous transluminal coronary angioplasty (PTCA), stenting, and emergency coronary artery bypass grafting (CABG)

e. Subject is willing and able to sign an informed consent form (ICF) approved by local Institutional Review Board/Ethics Committee and to follow the protocol with up to 5-year follow up.

f. Female patients of child-bearing potential must have a negative qualitative or quantitative pregnancy test within 7 days before enrollment and effective birth control must be used up to 1 year following the index procedure.

Angiographic Inclusion Criteria:

a. A maximum of one *de novo* lesion with at least one target segment in a native coronary artery meeting the definition of chronic total occlusion. A "chronic total occlusion" is any non-acute total coronary occlusion fulfilling the following angiographic characteristics and estimated in duration at least 3 months by clinical history and/or comparison with antecedent angiogram or electrocardiogram:

    i. High-grade native coronary stenosis

    ii. TIMI flow 0 or 1 antegrade flow

b. Occluded segment suitable for placement of coronary stents:

    i. Segment without severe tortuosity (angulation $\geq 45^{o}$)

    ii. Segment not located in an excessively distal location

Patients were <u>not</u> permitted to enroll in the EXPERT CTO study if they met any of the following exclusion criteria:

General Exclusion Criteria:

Candidates were excluded from the study if any of the following conditions are present:

1. Patients with any history of allergy to iodinated contrast that cannot be effectively managed medically, or any known allergy to thienopyridine, aspirin, heparin, stainless steel, or everolimus
2. Evidence of acute MI within 72 hours of the intended treatment (defined as: Q-wave or non-Q-wave MI having creatine kinase (CK) enzymes 2 × the upper limit of normal (ULN) with the presence of a creatine kinase myocardial-band isoenzyme (CK-MB) above the Institution's ULN, *or* troponin (I or T) above the Institution's ULN)
3. Previous coronary interventional procedure of any kind within the 30 days prior to the procedure in the target vessel
4. Planned interventional treatment of either the target or any non-target vessel within 30 days post-procedure

5. Planned interventional treatment of either the target or any non-target vessel within 6 months post-procedure with any alternative drug-eluting stent (DES) (e.g., CYPHER® Sirolimus-Eluting stent, TAXUS® Paclitaxel-Eluting stent or Endeavor® Zotarolimus-Eluting Endeavor stent)
6. Any contraindication to cardiac catheterization or to any of the standard concomitant therapies used during routine cardiac catheterization and PCI (e.g., aspirin, thienopyridine, unfractionated heparin)
7. Target lesion requires treatment with a device after successful crossing other than PTCA prior to stent placement (including, but not limited to directional or rotational coronary atherectomy, excimer laser, thrombectomy, etc.). Note: Use of alternative technologies to conventional guide wires that are approved by the United States Food and Drug Administration for CTO revascularization (e.g., Asahi Tornus and Corsair catheters, IntraLuminal Therapeutics SafeCross™ guide wire, Flowcardia CROSSER™ system, Stingray CTO Re-Entry System) is permitted and will be collected in the case report form.

8. Patients with history of clinically significant abnormal laboratory findings including:
    i. Neutropenia (<1000 neutrophils/mm^3) within the previous 2 weeks, or
    ii. Thrombocytopenia (<100,000 platelets/mm^3), or
    iii. AST, ALT, alkaline phosphatase, or bilirubin > 1.5 × ULN, or
    iv. Serum creatinine > 1.5 mg/dL

9. Patients with evidence of ongoing or active clinical instability including the following:
    i. Sustained systolic blood pressure < 100 mmHg or cardiogenic shock
    ii. Acute pulmonary edema or severe congestive heart failure
    iii. Suspected acute myocarditis, pericarditis, endocarditis, or cardiac tamponade
    iv. Suspected dissecting aortic aneurysm
    v. Hemodynamically significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease

10. Target lesion involves a bifurcation including a diseased side branch ≥ 2.25 mm in diameter that would require treatment
11. Target vessel with a patent bypass graft from prior coronary bypass surgery
12. Proximal coronary stenting of target lesion
13. History of stroke or transient ischemic attack within the prior 6 months
14. Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months
15. History of bleeding diathesis or coagulopathy or refusal of blood transfusions

Angiographic Exclusion Criteria

Candidates will be excluded from study if any of the following conditions are met:

1. Occlusion involves segment within previous stent
2. Extensive lesion-related thrombus (TIMI thrombus grade 3 or 4)
3. Previous stenting (drug-eluting or bare metal) in the target vessel unless the following conditions are met:
    i. It has been at least 9 months since the previous stenting.

ii. That target lesion is at least 15 mm away from the previously placed stent.

iii. The previously stented segment (stent plus 5 mm on either side) has no more than 40% diameter stenosis.

4. The target vessel has other lesions proximal to the total occlusion identified with greater than 40% diameter stenosis based on visual estimate or on-line quantitative coronary angiography (QCA). However, planned stenting of the lesion in target vessel which is proximal to the target lesion and can be covered by a single stent (ie, tandem lesions) are acceptable.

2. Follow-up Schedule

Patients, for whom recanalization and pre-dilatation of the CTO were completed and the study stent(s) (XIENCE V and/or XIENCE PRIME) was inserted into the coronary guiding catheter (i.e., the intent-to-treat (ITT) population for the stent-related analysis), will be followed through 5 years post index procedure with follow-up at 30 days, 6 months, 1 year, and annually thereafter through 5 years. All clinical follow-ups will be performed through phone contact or office visit except the 1-year visit which was an office visit. The remaining patients will be followed until hospital discharge.

Preoperatively, the following were obtained: signed informed consent, medical and cardiac history, angina status, pregnancy test, chemistry panel, CBC with differential, lipid panel, liver function test, 12 lead ECG, coronary angiogram, cardiac enzyme measurement, and medication history. The following was collected during the procedure: coronary angiogram, cardiac enzyme measurements, ACT measurements, and medication regimen.

Postoperatively, the objective parameters measured during the study included angina status and medication regimen at all visits and 12 lead ECG at 1 year. Adverse events and complications were recorded at all visits.

The EXPERT CTO trial was not designed or powered to study safety or effectiveness differences for subgroups.

3. Clinical Endpoints

With regard to safety and effectiveness the primary endpoint was: major adverse cardiac events which include death, MI (Q wave and non-Q wave) or clinically-driven target lesion revascularization at 1 year (primary endpoint). Note MACE is a composite of safety and effectiveness.

With regard to success/failure criteria:

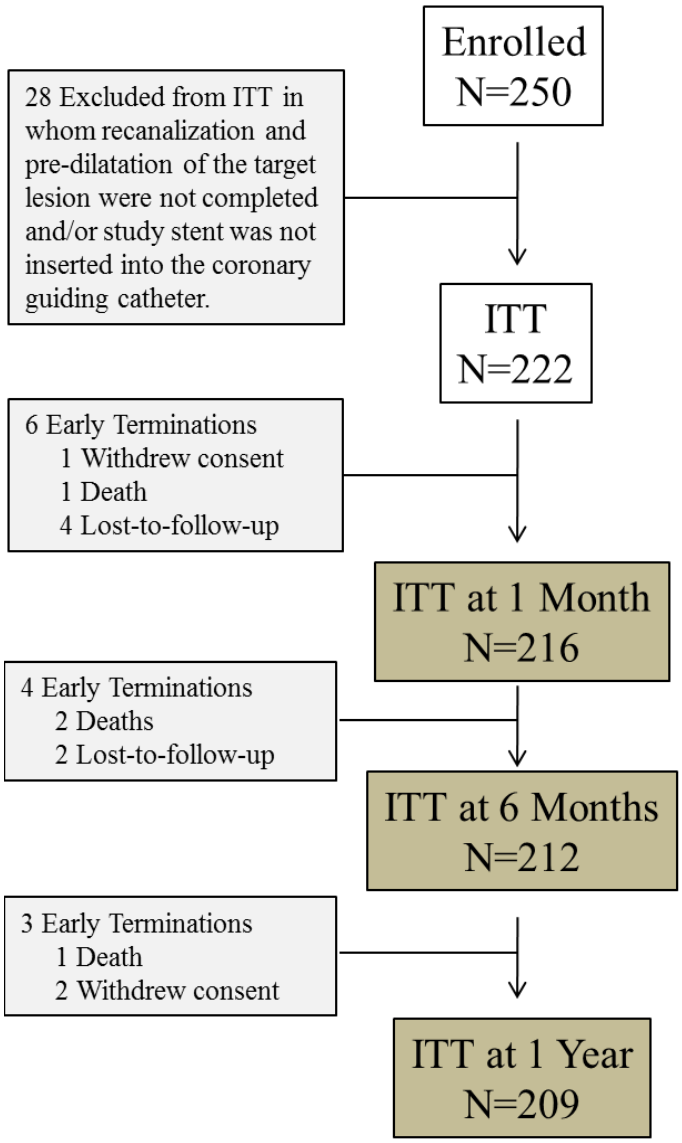
- Device Success was defined as achievement of <50% diameter stenosis within the target lesion segment using assigned study device.
- Procedure Success was defined as device success and absence of in-hospital MACE.

B. Accountability of PMA Cohort

At the time of database lock, of 250 patients enrolled in the PMA study, 88.8% (222) of the patients were available for analysis (ITT population) at the completion of the study, the 1-year post-operative visit.

The ITT population consisted of 222 subjects, and the study available subject flow through 360 days is shown in **Figure 3**. The number of subjects available for 1-month follow-up was 216, due to 6 early terminations (1 subject withdrew consent, 1 subject died, and 4 subjects were lost to follow-up). The number of subjects available for 6-month follow-up was 212, due to 4 early terminations (2 subjects died, and 2 subjects were lost to follow-up). The number of subjects available for 1-year follow-up was 209, due to 3 early terminations (1 subject died, and 2 subjects withdrew consent). However, of the 209 available ITT subjects, 4 did not have a 1-year visit. Therefore, the actual number of ITT subjects with a qualifying 1-year visit was 205 (which equals a 1-year follow-up rate of 92.3%). The denominator in the primary endpoint (211) is therefore composed of those with 1-year follow-up (205) + deaths (4) + subjects who early terminated but had an event (2) = 211. Those who early terminate without an event are excluded from the denominator.

Figure 3 Available ITT subjects at each follow-up time point in the EXPERT-CTO trial



C. Study Population Demographics and Baseline Parameters

Table 10 presents the baseline demographics, risk factors, and angiographic characteristics by gender for subjects in the EXPERT CTO trial. The demographics and baseline risk factors of the study population are typical for a PCI study performed in the US.

Table 10 Demographics, Risk Factors, and Baseline Angiographic Characteristics

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

D. Safety and Effectiveness Results

With regard to safety and effectiveness the primary endpoint was: major adverse cardiac events which include death, MI (Q wave and non-Q wave) or clinically-driven target lesion revascularization at 1 year (primary endpoint). Note MACE is a composite of safety and effectiveness.

The analysis of the primary endpoint of MACE was based on the ITT (N=222) and per-protocol (N=183) cohorts available for the 1-year evaluation. The primary safety outcomes for this study are presented below in **Table 11** and the complete efficacy and safety clinical results are provided in **Table 12**.

The observed MACE rate at 1 year was 18.5%, of which the upper limit of the one-sided 95% confidence interval was 23.4% which is less than the PG of 24.4%. A statistically significant p-value of 0.0248 was observed for this comparison. The second pre-specified primary endpoint analysis compared the MACE rate at 1 year to a PG using the PP population. The observed MACE rate at 1 year was 8.2%, of which the upper limit of the one-sided 95% confidence interval was 12.3% which is less than the PG of 24.4%. A statistically significant p-value of <0.0001 was observed for this comparison.

Table 11 Primary Endpoints Results

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

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

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

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

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

Table 12 Effectiveness and Safety Results

	Outcomes at 1 Year ITT (N = 222)
Composite Effectiveness and Safety	
TLF (per ARC)	15.8% (33/209)
TLF (per protocol)	9.1% (19/209)
Effectiveness	
Clinically driven TLR	6.3% (13/207)
Clinically driven TLR, CABG	0.5% (1/206)
Clinically driven TLR, PCI	5.8% (12/207)
Clinically driven TVR	7.2% (15/207)
Safety	
All Death	1.9% (4/210)
Cardiac Death	1.0% (2/208)
Non-Cardiac Death	1.0% (2/208)
Target Vessel MI (per ARC)	12.0% (25/209)
Target Vessel QMI (per ARC)	1.0% (2/208)
Target Vessel NQMI (per ARC)	11.1% (23/207)
All MI (per ARC)	13.9% (29/209)
QMI (per ARC)	1.0% (2/208)
NQMI (per ARC)	13.0% (27/207)
Target Vessel MI (per protocol)	3.4% (7/208)
Target Vessel QMI (per protocol)	1.0% (2/208)
Target Vessel NQMI (per protocol)	2.4% (5/206)
All MI (per protocol)	3.4% (7/208)
QMI (per protocol)	1.0% (2/208)
NQMI (per protocol)	2.4% (5/206)
ARC Definite+Probable Stent Thrombosis	
Cumulative through 1 year	1.4% (3/207)
Acute (0 – 1 day)	0.0% (0/222)
Subacute (2 – 30 days)	0.9% (2/218)
Late (31 days – 1 year)	0.5% (1/206)
ARC Definite Stent Thrombosis (cumulative)	1.0% (2/207)

Notes:

- TLF is defined as a hierarchical composite of cardiac death, Target Vessel MI, and clinically driven TLR.
- ARC: Academic Research Consortium

Subgroup Analyses

The EXPERT CTO trial was not designed or powered to study safety or effectiveness differences for subgroups, so these analyses are considered exploratory without definitive conclusions.

A post hoc evaluation of the EXPERT CTO clinical trial for possible sex-based differences in baseline characteristics and clinical outcomes, as well as for any interaction between treatment and sex/gender was performed. See **Table 13** for the clinical results for all female and all male subgroups in the study through 1 year.

In the EXPERT CTO study, 81.1% (180/222) were male and 18.9% (42/222) were female. In comparison, the prevalence of coronary artery disease (CAD) is estimated at 9.2 million in males and 8.4 million in females for adults age 20 and older the United States (i.e., the CAD population is estimated to be 52.2% males and 47.7% females). The disproportionate enrollment distribution in this trial may be partly attributable to gender differences in symptoms and pathophysiology, which may lead to under-diagnosis and under-referral of female patients with CAD. The gender proportions enrolled in this trial are similar to other CTO drug-eluting stent trials.[1,2,3]

No statistical difference was detected.

Table 13 Results for All Female and All Male Subgroups in the Study through 1 Year

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

E. Financial Disclosure

To minimize the potential for bias of the clinical study result, the study design included multiple investigators, objective endpoints and the measurement of clinical endpoints by study personnel other than the enrolling investigators. Abbott Vascular follows good clinical practices when selecting qualified investigators to participate in a clinical study and by performing monitoring at the clinical sites during the course of the clinical study.

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 89 of which none were full-time or part-time employees of the sponsor and eight had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 8
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety and Effectiveness Conclusions

With regard to safety and effectiveness the primary endpoint was: major adverse cardiac events which include death, MI (Q wave and non-Q wave) or clinically-driven target lesion revascularization at 1 year (primary endpoint). Note MACE is a composite of safety and effectiveness.

In the EXPERT CTO trial, the observed MACE rate at 1 year was 18.5%, of which the upper limit of the one-sided 95% confidence interval was 23.4% which is less than the PG of 24.4%. A statistically significant p-value of 0.0248 was observed for this comparison. The second pre-specified primary endpoint analysis compared the MACE rate at 1 year to a PG using the per-protocol (PP) population. The observed MACE rate at 1 year was 8.2%, of which the upper limit of the one-sided 95% confidence interval was 12.3% which is less than the PG of 24.4%. A statistically significant p-value of <0.0001 was observed for this comparison. Therefore, the primary endpoint of MACE at 1 year passed both the first and second primary endpoint analyses.

B. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

Percutaneous revascularization with coronary stent placement has been widely used as an alternative to medical or surgical treatment in selected patients with symptomatic coronary artery disease. The major limitations of PTCA (including but not limited to acute closure, intimal dissection, and restenosis) are overcome to a significant extent with coronary stents. The XIENCE V and XIENCE PRIME stents are designed to improve luminal diameter and maintain arterial patency. Aside from the potential for improved late outcomes, more immediate benefits of successful CTO revascularization include decreased ischemic burden and associated symptoms and possible increased tolerance for future ischemic events. Considering the poor historical rates of patency with bare metal stents in the treatment of CTO lesions, avoidance of restenosis and reocclusion provide significant clinical benefit.

Additional factors to be considered in determining probable risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks are discussed in detail in Section VIII, "POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH" of this SSED.

As evaluated in the EXPERT CTO clinical trial, the benefits of treating CTO lesions with XIENCE stents (freedom from MACE, among others) outweigh the risks associated with the device and the procedure. The primary endpoint for EXPERT CTO was major adverse cardiac events (MACE) at 1 year. This composite endpoint includes the following components: Death, MI or Clinically-Driven Target Lesion Revascularization (TLR). The EXPERT CTO clinical trial was designed to test the hypothesis that the study stents (XIENCE V and XIENCE PRIME) would have a primary endpoint 1-year MACE rate less than the performance goal (24.4%). Both the ITT and PP populations met the primary endpoint with MACE rates of 18.5% and 8.2%, respectively which are both significantly lower than the pre-specified performance goal (PG) (24.4%) ($p=0.0248$ and $p<0.0001$, respectively).

In conclusion, based on the 1-year clinical data, the EXPERT CTO clinical trial demonstrates that the benefits outweigh the probable risks of the XIENCE V and XIENCE PRIME Stent Systems in the treatment of coronary artery disease involving chronic total occlusion lesions.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

EXPERT CTO is a non-randomized clinical trial designed to study the safety and effectiveness of the XIENCE V and XIENCE PRIME Stent Systems for the treatment of chronic total occlusions. A total of 250 subjects were enrolled at 20 sites. The ITT population consisted of 222 subjects and the PP population consisted of 183 subjects. The primary endpoint for EXPERT CTO was major adverse cardiac events (MACE) at 1 year. This composite endpoint

includes the following components: Death, MI or Clinically-Driven Target Lesion Revascularization (TLR).

Both the ITT and PP populations met the primary endpoint with MACE rates of 18.5% and 8.2%, respectively which are both significantly lower than the pre-specified PG (24.4%) ($p=0.0248$ and $p<0.0001$, respectively). In addition, the XIENCE V and XIENCE PRIME Stent Systems are associated with low MI, cardiac death, TLR, and stent thrombosis rates. Based on the 1-year clinical data, the EXPERT CTO clinical trial supports the safety and effectiveness of the XIENCE V and XIENCE PRIME Stent Systems in the treatment of coronary artery disease involving chronic total occlusion lesions.

Therefore, clinical data from the EXPERT CTO clinical trial is applicable to multiple models in the XIENCE family of Everolimus Eluting Coronary Stent Systems and no additional clinical trial data were required to demonstrate the safety and effectiveness of the XIENCE Xpedition and XIENCE Alpine Stent Systems in CTOs.

XIII. CDRH DECISION

CDRH issued an approval order on October 3, 2014. The final conditions of approval cited in the approval order are described below.

The Extended Follow-up of the EXPERT CTO Study: This study will be conducted as per IDE G110103 study protocol dated May 7, 2012, Version 5.0 included in P070015/S122 and P110019/S066. This study will continue the follow-up of 205 patients available at one year from the premarket cohort (EXPERT CTO trial). This is a prospective, multi-center study and all available patients will be followed out to 5 years post-procedure.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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

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

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