SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Coronary Stent System
Device Trade Name:	XIENCE Alpine Everolimus Eluting Coronary Stent Systems (XIENCE Alpine EECSS) XIENCE Sierra Everolimus Eluting Coronary Stent Systems (XIENCE Sierra EECSS) XIENCE Skypoint Everolimus Eluting Coronary Stent Systems (XIENCE Skypoint EECSS)
Device Procode:	NIQ
Applicant's Name and Address:	Abbott Vascular 3200 Lakeside Drive Santa Clara, California 95054
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P110019/S115
Date of FDA Notice of Approval:	6/25/2021

The first XIENCE Everolimus Eluting Coronary Stent System PMAs (P070015 and P110019) were originally approved on July 2, 2008 and November 1, 2011. The XIENCE [Alpine / Sierra / Skypoint] stent system is indicated for improving coronary artery luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease due to *de novo* native coronary artery lesions (length ≤ 32 mm) with reference vessel diameters of ≥ 2.25 mm to ≤ 4.25 mm. Additionally, the XIENCE [Alpine / Sierra / Skypoint] system is indicated for treating *de novo* chronic total coronary occlusions.

The SSED documents to support the indications are available on the following FDA websites and are incorporated by reference herein:

- P110019: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110019b.pdf
- P110019/S066: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110019S066B.pdf
- P110019/S075: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110019S075B.pdf

The current supplement was submitted to expand the indication for the XIENCE Alpine, XIENCE Sierra, and XIENCE Skypoint Everolimus Eluting Coronary Stent Systems to include patients at high bleeding risk (HBR). Hereafter, the XIENCE Alpine, XIENCE Sierra, and XIENCE Skypoint Everolimus Eluting Coronary Stent Systems are referred to as the XIENCE family of stents.

II. INDICATIONS FOR USE

The XIENCE [Alpine / Sierra / Skypoint] stent system is indicated for improving coronary artery luminal diameter in patients, including those at high risk for bleeding and those with diabetes mellitus, 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 [Alpine / Sierra / Skypoint] stent system is indicated for treating *de novo* chronic total coronary occlusions.

III. CONTRAINDICATIONS

The XIENCE [Alpine / Sierra / Skypoint] stent system is contraindicated for use in:

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in XIENCE [Alpine / Sierra / Skypoint] respective labeling.

V. DEVICE DESCRIPTION

The XIENCE family of stents 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.

The XIENCE family of stents are balloon-expandable stents made of L-605 cobalt chromium (CoCr) with a poly(n-butyl methacrylate) (PBMA) and copolymer vinylidene fluoride and hexafluoropropylene (PVDF-HFP)/everolimus coating.

The XIENCE Alpine delivery catheter is available in two configurations, a rapid-exchange (RX) and an over-the-wire (OTW) co-axial design with the balloon and stent at the distal end of the catheter. The XIENCE Sierra and XIENCE Skypoint delivery catheters are available in a rapid-exchange (RX) design.

The characteristics of the XIENCE family of stents are described in **Table 1**.

Table 1. XIENCE Family of Stents Product Description

	XIENCE Alpine	XIENCE Sierra	XIENCE Skypoint
Available Stent Lengths (mm)	8, 12, 15, 18, 23, 28, 33, 38		
Available Stent Diameters (mm)	2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0		
Stent Material	A medical grade L-605 cobalt chromium (CoCr) alloy		
Drug Component	A conformal (all surfaces of the stent) 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)	A conformal coating of a non-erodible polymer loaded with 100 µg/cm^2 of everolimus with a maximum nominal drug content of 236 µg on the large stent (4.0 x 38 mm)	
Delivery System			
Delivery System Working Length	145 cm		
Delivery System Design	RX: Single access port to inflation lumen; guide wire exit notch is located 25.5 cm from tip; designed for guide wires ≤ 0.014". OTW: Sidearm adaptor provides access to balloon inflation / deflation lumen and guide wire lumen; designed for guide wires ≤ 0.014".	RX: 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><th></th><th colspan="2">XIENCE Alpine</th><th colspan="2">XIENCE Sierra</th><th colspan="2">XIENCE Skypoint</th></tr>
<tr><td>Stent Delivery System Balloon</td><td colspan="6">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 rowspan="10">Balloon Inflation Pressure</td><td colspan="2">Rated Burst Pressure (RBP): 18 atm (1824 kPa)</td><td colspan="4">Rated Burst Pressure (RBP): 16 atm (1621 kPa)</td></tr>
<tr><td>Stent Diameter (mm)</td><td>In vitro Stent Nominal Pressure (atm)</td><td>Stent Diameter (mm)</td><td>In vitro Stent Nominal Pressure (atm)</td><td>Stent Diameter (mm)</td><td>In vitro Stent Nominal Pressure (atm)</td></tr>
<tr><td>2.25</td><td>10</td><td>2.25</td><td>9</td><td>2.25</td><td>9</td></tr>
<tr><td>2.5</td><td>10</td><td>2.5</td><td>9</td><td>2.5</td><td>9</td></tr>
<tr><td>2.75</td><td>10</td><td>2.75</td><td>12</td><td>2.75</td><td>12</td></tr>
<tr><td>3.0</td><td>10</td><td>3.0</td><td>12</td><td>3.0</td><td>12</td></tr>
<tr><td>3.25</td><td>10</td><td>3.25</td><td>12</td><td>3.25</td><td>12</td></tr>
<tr><td>3.5</td><td>10</td><td>3.5</td><td>12</td><td>3.5</td><td>12</td></tr>
<tr><td>4.0</td><td>10</td><td>4.0</td><td>12</td><td>4.0</td><td>12</td></tr>
<tr><td>Minimum Guiding Catheter Inner Diameter</td><td colspan="2">2.25 – 3.5 mm Stent Diameters 5 F (0.056” / 1.42 mm ID)
4.0 Stent Diameter, 8 – 33 mm lengths 5 F (0.056” / 1.42 mm ID)
4.0 Stent Diameter, 38 mm length 6 F (0.066” / 1.68 mm ID)</td><td colspan="4">2.25 – 4.0 mm Stent Diameters
5 F (0.056” / 1.42 mm ID)</td></tr>
<tr><td>Catheter Shaft Outer Diameter</td><td colspan="2">Distal: 0.034” (0.86 mm)
Proximal (RX): 0.029” (0.74 mm)
Proximal (OTW): 0.045” (1.14 mm)</td><td colspan="2">Distal: 0.037” (0.94 mm)
Proximal (RX): 0.029” (0.74 mm)</td><td colspan="2">Mid Shaft: 0.039” (0.99 mm)
Proximal Shaft (RX): 0.029” (0.74 mm)</td></tr>
<tr><td>Shelf Life</td><td colspan="2">36 months</td><td colspan="4">24 months</td></tr>
</table>

A. Device Component Description

The XIENCE family of stents are fabricated from a single piece of medical grade L-605 CoCr alloy tubing. The stents include two designs – small and medium. The small and medium designs of the XIENCE family of stents all have 3 links connecting adjacent rings. Each link has an undulating portion called a "non-linear link" which provides flexibility to the stent in the longitudinal direction. In order to allow for different expansion ranges, each design varies the number of short and long crests per ring.

- Small stent design: 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm and 3.25 mm
- Medium stent design: 3.50 mm and 4.00 mm

The commercial matrix is shown in **Table 2** below.

Table 2. U.S. Commercial Matrix for XIENCE Alpine, Sierra, and Skypoint

Stent Design	Product Diameter (mm)	Maximum Post Dilatation Expansion Diameter (mm)	Product Length (mm)							
			08	12	15	18	23	28	33	38
Small	2.25	3.25[2]	√	√	√	√	√	√	√[1]	√[1]
	2.50		√	√	√	√	√	√	√	√
	2.75		√	√	√	√	√	√	√	√
	3.00	3.75	√	√	√	√	√	√	√	√
	3.25		√	√	√	√	√	√	√	√
Medium	3.50	4.50 (XIENCE Alpine) 5.50 (XIENCE Sierra) 5.75 (XIENCE Skypoint)	√	√	√	√	√	√	√	√
	4.00		√	√	√	√	√	√	√	√

[1] XIENCE Alpine stent diameter 2.25 mm is not available in 33 mm and 38 mm length

[2] 3.25 mm maximum post dilatation expansion diameter is for XIENCE Alpine 2.25 mm and 2.5 mm diameter only

B. Drug Component Description

The XIENCE family of stents are coated with everolimus (active ingredient) embedded in a non-erodible polymer (inactive ingredient).

1. Everolimus

Everolimus is the active pharmaceutical ingredient in the XIENCE family of stents. The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in **Figure 1**. The nominal everolimus content per nominal stent length/diameter is shown in **Table 3**.

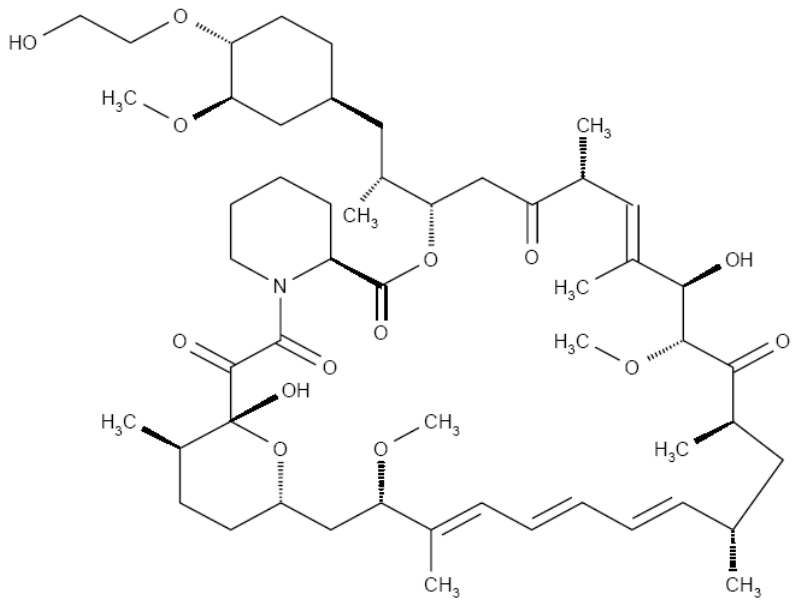

Figure 1. Everolimus Chemical Structure

Table 3. Nominal Everolimus Content (μg) per Nominal Stent Length and Diameter

Stent Design	Diameters (mm)	Stent Length (mm)	XIENCE Alpine Nominal Drug Amount (μg)	XIENCE Sierra Nominal Drug Amount (μg)	XIENCE Skypoint Nominal Drug Amount (μg)
Small	2.25, 2.5, 2.75, 3.0, 3.25	8	40	39	39
Small	2.25, 2.5, 2.75, 3.0, 3.25	12	60	58	58
Small	2.25, 2.5, 2.75, 3.0, 3.25	15	74	72	72
Small	2.25, 2.5, 2.75, 3.0, 3.25	18	88	85	85
Small	2.25, 2.5, 2.75, 3.0, 3.25	23	109	111	111
Small	2.25, 2.5, 2.75, 3.0, 3.25	28	137	131	131
Small	2.25* ,2.5, 2.75, 3.0, 3.25	33	157	157	157
Small	2.25*, 2.5, 2.75, 3.0, 3.25	38	185	177	177
Medium	3.5, 4.0	8	50	53	53
Medium	3.5, 4.0	12	75	72	72
Medium	3.5, 4.0	15	91	99	99
Medium	3.5, 4.0	18	116	117	117
Medium	3.5, 4.0	23	141	145	145
Medium	3.5, 4.0	28	174	181	181
Medium	3.5, 4.0	33	199	209	209
Medium	3.5, 4.0	38	232	236	236

*XIENCE Alpine stent diameter 2.0 mm and 2.25 mm are not available in 33 mm and 38 mm length

2. Inactive Ingredients

The XIENCE family of stents contain 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 daltons. PVDF-HFP is a non-erodible semicrystalline random copolymer with a molecular weight (MW) of 254,000 to 293,000 daltons. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA-coated stent surface. The drug load is 100 μg/cm^2 for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in **Figure 2** below.

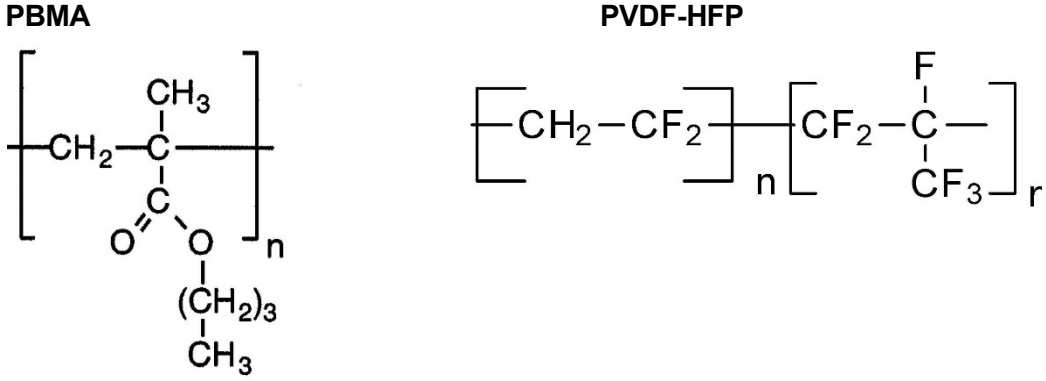

Figure 2. Non-erodible Polymer Chemical Structures

3. Mechanism of Action of Everolimus

On a cellular level, everolimus inhibits, in a reversible manner, growth factor-stimulated cell proliferation. On a molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of protein synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of FRAP (FKBP-12-rapamycin associated protein, also called mTOR, mammalian target of rapamycin) this finding suggests that the everolimus-FKBP-12 complex binds to and thus interferes with the function of FRAP. FRAP is a key regulatory protein that governs cell metabolism, growth, and proliferation. Disabling FRAP function explains the cell cycle arrest at the late G1 stage caused by everolimus.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of coronary artery disease. These may include exercise, diet, smoking cessation, drug therapy, percutaneous coronary interventions (such as angioplasty and placement of bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass graft surgery (CABG). 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

US Marketing History
XIENCE Alpine Everolimus Eluting Coronary Stent System (EECSS) received PMA approval on September 3, 2014 under P110019/S070. XIENCE Sierra EECSS received PMA approval on May 22, 2018 under P110019/S094. XIENCE Skypoint received PMA approval on May 13, 2021 under P110019/S113.

International Marketing/Outside the US (OUS) History
XIENCE Alpine EECSS was commercially available in OUS markets as of October 2014. XIENCE Sierra EECSS was commercially available OUS as of October 2017. XIENCE Skypoint was approved in Japan on October 6, 2020.

Table 4 lists countries where the XIENCE Alpine and Sierra are currently commercially available. XIENCE Skypoint is currently only available in the U.S. and Japan.

The XIENCE family of stents have not been withdrawn from either U.S. or international marketing for any reason related to its safety or effectiveness.

Table 4. Countries with XIENCE Alpine and Sierra Commercial Availability

Argentina	Albania*	Algeria*	Amer.Virgin Is.
Armenia	Aruba	Australia	Austria
Bahrain	Bangladesh*	Barbados	Belarus*
Belgium	Brazil	Brunei Darussalam*	Bulgaria
Canada	Chile	China	Colombia*
Costa Rica	Croatia	Cyprus*	Czech Republic
Denmark	Dominican Rep.	Ecuador*	Egypt
Estonia	Finland	France	French Polynesia
French Guiana	Georgia	Germany	Greece
Guadeloupe	Guam	Guatemala*	Hong Kong
Hungary	Indonesia	Iran	Iraq*
Ireland	Israel*	Italy	Jamaica
Japan	Jordan	Kazakhstan*	Kosovo*
Kuwait	Latvia	Lebanon	Libya*
Lithuania	Luxembourg	Macedonia	Malaysia
Malta*	Martinique	Mauritius	Mexico
Mongolia*	Morocco*	Nepal*	Netherlands
New Caledonia	New Zealand	Norway	Oman
Pakistan*	Palestine*	Panama	Peru*
Philippines**	Poland	Portugal	Qatar
Reunion	Romania	Russian Federation	Saudi Arabia
Serbia*	Singapore	Slovakia**	Slovenia
South Africa	South Korea	Spain	Sri Lanka*
Sweden	Switzerland	Taiwan	Thailand
Trinidad & Tobago	Tunisia*	Turkey	Turkmenistan

Ukraine*	United Kingdom	Uruguay	United Arab Emir.
Venezuela*	Vietnam	Yemen*	

* Countries that have XIENCE Alpine or its rebrands commercialized only
** Countries that have XIENCE Sierra commercialized only

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may be associated with the use of a stent in native coronary arteries include but are not limited to:

- Allergic reaction or hypersensitivity to latex, contrast agent, anesthesia, device materials (cobalt, chromium, nickel, tungsten, methacrylic polymer, and fluoropolymers), and drug reactions to everolimus, anticoagulation, or antiplatelet drugs
- Vascular access complications which may require transfusion or vessel repair, including:
    - Catheter site reactions
    - Bleeding (ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage)
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation/rupture
    - Embolism (air, tissue, plaque, thrombotic material or device)
    - Peripheral nerve injury
    - Peripheral ischemia
- Coronary artery complications which may require additional intervention, including:
    - Total occlusion or abrupt closure
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation/rupture
    - Tissue prolapse/plaque shift
    - Embolism (air, tissue, plaque, thrombotic material, or device)
    - Coronary or stent thrombosis (acute, subacute, late, very late)
    - Stenosis or restenosis
- Pericardial complications which may require additional intervention, including:
    - Cardiac tamponade
    - Pericardial effusion
    - Pericarditisc
- Cardiac arrhythmias
    - Conduction disorders
    - Atrial arrhythmia
    - Ventricular arrhythmia
- Cardiac ischemic conditions:
    - Myocardial ischemia
    - Myocardial infarction (including acute)
    - Coronary artery spasm
    - Unstable or stable angina pectoris

- Neurologic complications:
    - Stroke/Cerebrovascular Accident (CVA)
    - Transient Ischemic Attack (TIA)
- System organ failures:
    - Cardio-respiratory arrest
    - Cardiac failure
    - Cardiopulmonary failure (including pulmonary edema)
    - Renal insufficiency/failure
    - Shock
- Bleeding
- Blood cell disorders (including heparin induced thrombocytopenia (HIT)
- Hypotension/hypertension
- Infection
- Nausea and vomiting
- Palpitations, dizziness, and syncope
- Chest pain
- Fever
- Death

Adverse events associated with daily oral administration of everolimus in doses varying from 1.5 mg to 10 mg daily can be found in the Summary of Product Characteristics (SPC) and labels for the drug[1]. The risks described below include the anticipated adverse events relevant for the cardiac population referenced in the contraindications, warnings and precaution sections of the everolimus labels/SPCs and/or observed at incidences ≥10% in clinical trials with oral everolimus for different indications. Please refer to the drug SPCs and labels for more detailed information and less frequent adverse events.

- Abdominal pain
- Anemia
- Angioedema (increased risk with concomitant ACE inhibitor use)
- Arterial thrombotic events
- Bleeding and coagulopathy (including hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and thrombotic microangiopathy; increased risk with concomitant cyclosporine use)
- Constipation
- Cough
- Diabetes mellitus
- Diarrhea
- Dyspnea
- Embryo-fetal toxicity
- Erythema

1 Certican® UK label 2015, Afinitor® EU authorization SPC 2014, Votubia® EU SPC 2014, Afinitor® US label 2015, and Zortress® US label 2015. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SPC/labels.

- Erythroderma
- Headache
- Hepatic artery thrombosis (HAT)
- Hepatic disorders (including hepatitis and jaundice)
- Hypersensitivity to everolimus active substance, to other rapamycin derivates
- Hypertension
- Infections: bacterial, viral, fungal, and protozoan, including infections with opportunistic pathogens. Polyoma virus-associated nephropathy (PVAN), JC virus-associated progressive multiple leukoencephalopathy (PML), fatal infections and sepsis have been reported in patients treated with oral everolimus
- Kidney arterial and venous thrombosis
- Laboratory test alterations (elevations of serum creatinine, proteinuria, hypokalemia; hyperglycemia, dyslipidemia including hypercholesterolemia and hypertriglyceridemia; abnormal liver function tests; decreases in hemoglobin, lymphocytes, neutrophils, and platelets)
- Lymphoma and skin cancer
- Male infertility
- Nausea
- Nephrotoxicity (in combination with cyclosporine)
- Non-infectious pneumonitis (including interstitial lung disease)
- Oral ulcerations
- Pain
- Pancreatitis
- Pericardial effusion
- Peripheral edema
- Pleural effusion
- Pneumonia
- Pyrexia
- Rash
- Renal failure
- Upper respiratory tract infection
- Urinary tract infection
- Venous thromboembolism
- Vomiting
- Wound healing complications (including wound infections and lymphocele)

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.
For the specific adverse events that occurred in the XIENCE 90 and XIENCE 28 clinical studies, please see Section X: Summary of Primary Clinical Studies, below.

IX. SUMMARY OF NONCLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA. Because the previously collected data sufficiently represent the performance of the device for the new indications for use, no new non-clinical testing was conducted.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed clinical studies to establish a reasonable assurance of safety and effectiveness of the XIENCE family of stents in patients at high bleeding risk (HBR) treated with shorter duration dual antiplatelet therapy (DAPT) in the US under IDE G170081. Data from the XIENCE Short DAPT studies were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

The XIENCE 90 trial, which was conducted in the United States, evaluated the safety of 3-month DAPT post-PCI, while the combined population from the XIENCE 28 USA (conducted in United States and Canada) and the XIENCE 28 Global (conducted in Europe and Asia) trials assessed the safety of 1-month DAPT post-PCI. Both XIENCE 28 trials had similar designs, and analysis of the combined population from the two XIENCE 28 trials was pre-specified in the statistical analysis plan (SAP) of the XIENCE 28 USA trial. The analysis of the combined populations from XIENCE 28 USA and XIENCE 28 Global will herein be referred to as "XIENCE 28".

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

(1) XIENCE 90 Clinical Trial

A. Study Design

XIENCE 90 is a prospective, single arm, multi-center, open label trial to evaluate the safety of 3-month DAPT in subjects at high risk of bleeding undergoing PCI with the approved XIENCE family of stents. Subjects were considered to be high bleeding risk if, in the opinion of the referring physician, the risk of major bleeding with >3-month DAPT outweighed the benefit and they met one or more of the following criteria: ≥75 years of age; clinical indication for chronic (at least 6 months) or lifelong anticoagulation therapy; history of major bleeding which required medical attention within 12 months of the index procedure; history of stroke (ischemic or hemorrhagic); renal insufficiency (creatinine ≥2.0 mg/dl) or failure (dialysis dependent); systemic conditions associated with an increased bleeding risk (e.g., hematological disorders, including a history of or current thrombocytopenia defined as a platelet count <100,000/mm^3, or any known coagulation disorder associated with increased bleeding risk); anemia with hemoglobin < 11g/dl. Subjects were prescribed DAPT ($P2Y_{12}$ inhibitor + aspirin) between 0-3 months post-procedure. Subjects were considered as

"3-month clear" and were to discontinue $P2Y_{12}$ inhibitor at 3 months if they were compliant with the prescribed DAPT and were free from events between 0-3 months (myocardial infarction, repeat coronary revascularization, stroke, or stent thrombosis). Subjects that discontinued $P2Y_{12}$ inhibitor at 3 months were prescribed aspirin through the end of the study.

For the primary endpoint of all death or all MI and the secondary endpoint of BARC[2] 2-5 bleeding, the primary analysis population for the XIENCE 90 study was the 3-month clear subjects, and these subjects were compared with the 3-month clear population of the historical control of non-complex HBR subjects treated with DAPT duration of up to 12 months from the XIENCE V USA study. For the powered secondary endpoint of stent thrombosis, XIENCE 90 3-month clear subjects were evaluated against a performance goal. For these primary and secondary endpoints, the comparison with the 3-month clear population of the historical control was done after propensity score (PS) adjustment.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the XIENCE 90 trial was limited to subjects who met the inclusion criteria listed in **Table 5**. Subjects were not permitted to enroll in the XIENCE 90 trial if they met any of the exclusion criteria in **Table 5**.

Table 5. XIENCE 90 Trial Enrollment Inclusion and Exclusion Criteria

General Inclusion Criteria	1. Subject is considered at high risk for bleeding, defined as meeting one or more of the following criteria at the time of registration and in the opinion of the referring physician, the risk of major bleeding with >3 months of DAPT outweighs the benefit: • ≥75 years of age, • clinical indication for chronic (at least 6 months) or lifelong anticoagulation therapy, • history of major bleeding that required medical attention within 12 months of the index procedure, • history of stroke (ischemic or hemorrhagic), • renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent), • systemic conditions associated with an increased bleeding risk (e.g., hematological disorders, including a history of or current thrombocytopenia defined as a platelet count <100,000/mm^3, or any known coagulation disorder associated with increased bleeding risk), • anemia with hemoglobin <11g/dl. 2. Subject must be at least 18 years of age. 3. Subject or a legally authorized representative must provide written informed consent as approved by the Institutional Review Board

[2] The BARC (Bleeding Academic Research Consortium) classification classifies bleeding events by severity, with BARC 1 being the least severe and BARC 5 being the most severe (fatal bleeding), and BARC 0 being no bleeding.

	(IRB)/Ethics Committee (EC) of the respective clinical site prior to any study related procedure. 4. Subject is willing to comply with all protocol requirements, including agreement to stop taking P2Y12 inhibitor at 3 months, if eligible per protocol. 5. Subject must agree not to participate in any other clinical trial for a period of one year following the index procedure.
General Exclusion Criteria	1. Subject with an indication for the index procedure of acute ST-segment elevation MI (STEMI). 2. Subject has a known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, P2Y12 inhibitors (clopidogrel/prasugrel/ticagrelor), everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated. 3. Subject with implantation of another drug-eluting stent (other than XIENCE) within 9 months prior to index procedure. 4. Subject has a known left ventricular ejection fraction (LVEF) <30%. 5. Subject judged by physician as inappropriate for discontinuation from $P2Y_{12}$ inhibitor use at 3 months, due to another condition requiring chronic $P2Y_{12}$ inhibitor use. 6. Subject with planned surgery or procedure necessitating discontinuation of $P2Y_{12}$ inhibitor within 3 months following index procedure. 7. Subject with a current medical condition with a life expectancy of less than 12 months 8. Subject intends to participate in an investigational drug or device trial within 12 months following the index procedure. 9. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test. **Note**: Female patients of childbearing potential should be instructed to use safe contraception (e.g., intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches, hormonal vaginal devices, injections with prolonged release.) It is accepted, in certain cases, to include subjects having a sterilised regular partner or subjects using a double barrier contraceptive method. However, this should be explicitly justified in special circumstances arising from the study design, product characteristics and/or study population. 10. Subject is part of a vulnerable population, defined as subject whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable subjects include: individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children,

	impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor**,** members of the armed forces, and persons kept in detention. 11. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.
Angiographic Inclusion Criteria	1. Up to three target lesions with a maximum of two target lesions per epicardial vessel. Note: • The definition of epicardial vessels means left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX) and right coronary artery (RCA) and their branches. For example, the patient must not have >2 lesions requiring treatment within both the LAD and a diagonal branch in total. • If there are two target lesions within the same epicardial vessel, the two target lesions must be at least 15 mm apart per visual estimation; otherwise this is considered as a single target lesion. 2. Target lesion ≤ 32 mm in length by visual estimation. 3. Target lesion must be located in a native coronary artery with visually estimated reference vessel diameter between 2.25 mm and 4.25 mm. 4. Exclusive use of XIENCE family of stent systems during the index procedure. 5. Target lesion has been treated successfully, which is defined as achievement of a final in-stent residual diameter stenosis of <20% with final TIMI (Thrombolysis in Myocardial Infarction)-3 flow assessed by online quantitative angiography or visual estimation, with no residual dissection NHLBI (National Heart Lung and Blood Institute) grade ≥ type B, and no transient or sustained angiographic complications (e.g., distal embolization, side branch closure), no chest pain lasting >5 minutes, and no ST segment elevation >0.5 mm or depression lasting >5 minutes.
Angiographic Exclusion Criteria	1. Target lesion is in a left main location. 2. Target lesion is located within an arterial or saphenous vein graft. 3. Target lesion is restenotic from a previous stent implantation. 4. Target lesion is a total occluded lesion (TIMI flow 0). 5. Target lesion contains thrombus as indicated in the angiographic images (per SYNTAX score thrombus definition). 6. Target lesion is implanted with overlapping stents, whether planned or for bailout.

2. <u>Follow-up Schedule</u>

All patients were scheduled to have follow-up examinations at the following time points: 3, 6, and 12 months post index procedure. Study follow-up through 12 months

is complete.

Preoperatively, laboratory assessments were conducted per standard of care (SOC) to determine subject's eligibility for PCI and confirm eligibility for the study. Post-procedure, ECG and cardiac enzyme collection were performed per SOC. Use and compliance of protocol required antiplatelet medication and adverse events and complications were recorded at all visits.

The key time points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Primary Endpoint

The primary endpoint is a composite rate of all death or all myocardial infarction (MI, modified ARC[3]) from 3 to 12 months post index procedure.

Major Secondary Endpoints

- Major bleeding rate (BARC type 2-5) from 3 to 12 months
- Stent thrombosis (ARC definite/probable) from 3 to 12 months

Other Secondary Endpoints

The following endpoints were assessed from 3 to 12 months:
- All death, cardiac death, vascular death, non-cardiovascular death
- All MI (modified ARC) and MI attributed to target vessel (TV-MI, modified ARC)
- Composite of cardiac death or MI (modified ARC)
- All stroke, ischemic stroke and hemorrhagic stroke
- Clinically-indicated target lesion revascularization (CI-TLR)
- Clinically-indicated target vessel revascularization (CI-TVR)
- Target lesion failure (TLF, composite of cardiac death, TV-MI and CI-TLR)
- Target vessel failure (TVF, composite of cardiac death, TV-MI and CI-TVR)
- Major bleeding defined by the Bleeding Academic Research Consortium (BARC) type 3-5

[3] Modified Academic Research Consortium (ARC) MI definition: clinical or imaging evidence of ischemia (any of the following: clinical symptoms of ischemia, ECG changes indicative of new ischemia – new ST-T changes or new left bundle branch block (LBBB), development of pathological Q waves, imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality) AND elevated cardiac biomarkers (peri-procedural MI within 48 hours after PCI: creatine kinase myocardial band (CK-MB) >3 x URL or Troponin > 3 x URL (Upper Range Limit) with baseline value < URL; peri-procedural MI within 72 hours after CABG: CK-MB >5 x URL or Troponin > 5 x URL with baseline value < URL; Spontaneous MI (> 48h following Percutaneous Coronary Intervention (PCI) , > 72h following CABG): CK-MB > URL or Troponin > URL with baseline value < URL).

B. Accountability of PMA Cohort

Between July 19, 2017 and August 9, 2019, 2047 subjects were enrolled in XIENCE 90 from 101 US sites. Of the 2047 subjects, 1693 subjects met the 3-month clear criteria and are the primary analysis group. A total of 274 subjects did not meet the 3-month clear criteria and these subjects were not included in the primary analysis population. At 12 months, 1653 of the 3-month clear subjects completed their visit (97.6%). The subject enrollment and disposition up to 12 months for XIENCE 90 are shown below in **Figure 3**.

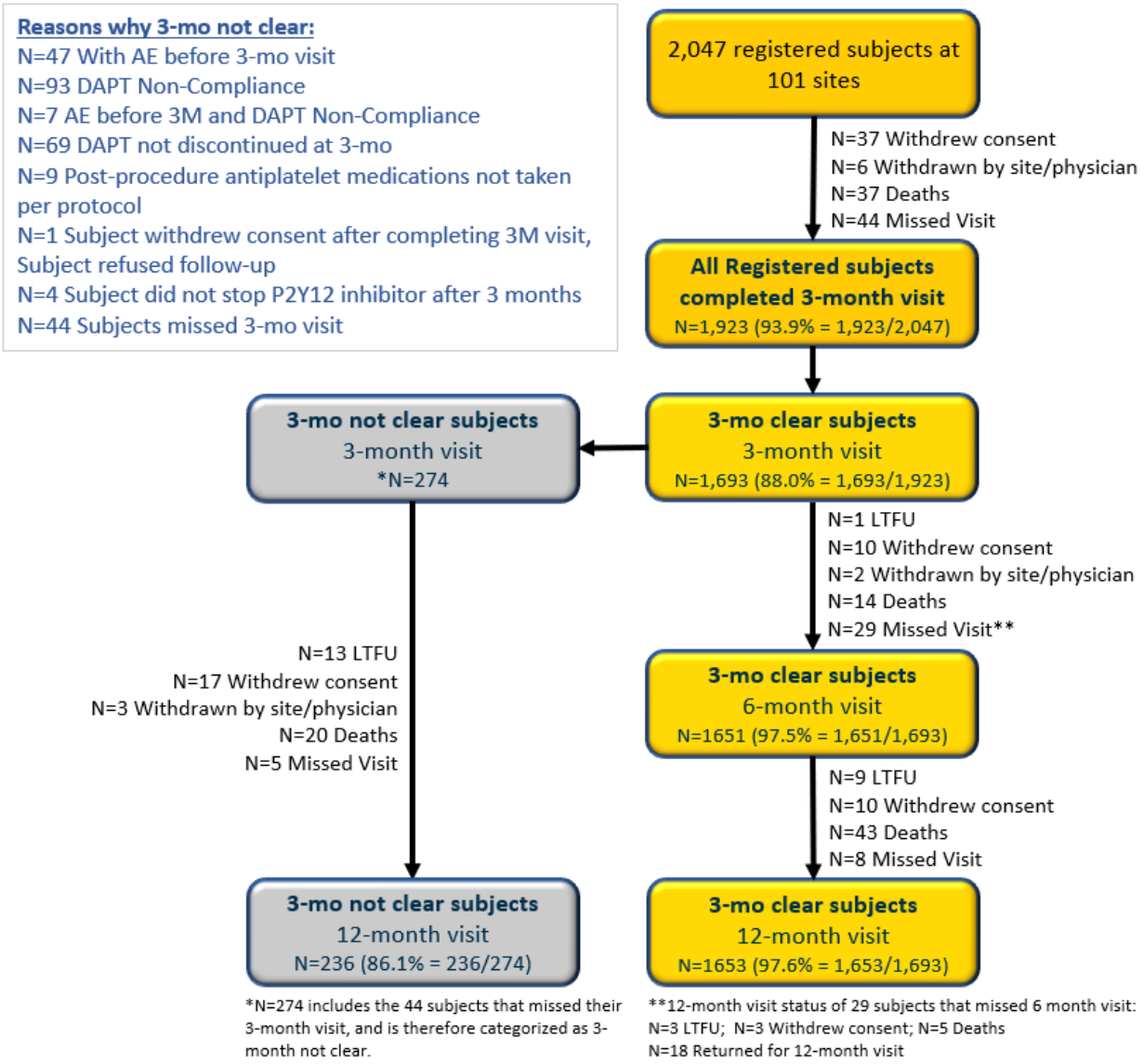

Figure 3. Subject Enrollment and Disposition

Note: LTFU = Lost to Follow Up

C. Study Population Demographics and Baseline Parameters

Table 6 presents demographics for the primary analysis group (XIENCE 90 3-month clear subjects) and the historical control group (XIENCE V USA 3-month clear subjects). The mean age in the XIENCE 90 3-month clear subjects was 75.25 years and 35.2% were female. Subjects were predominantly white (88.4%) and obese (mean body mass index (BMI) 30.13). Demographics were similar in the XIENCE 90 group and historical control group.

Table 6. XIENCE 90 Primary Analysis Demographics

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE V USA 3-Month Clear Subjects (N=1280)
Age (years)	75.25 ± 9.29 (1693) (39.0, 98.0)	72.70 ± 10.26 (1280) (34.9, 100.4)
Gender		
Male	64.8% (1097/1693)	59.1% (756/1280)
Female	35.2% (596/1693)	40.9% (524/1280)
Race		
American Indian or Alaska Native	0.6% (11/1693)	0.7% (9/1280)
Asian	2.2% (37/1693)	1.3% (17/1280)
Black or African American	5.7% (96/1693)	8.6% (110/1280)
Hispanic or Latino	2.7% (45/1689)	3.2% (41/1280)
Native Hawaiian or Pacific Islander	0.3% (5/1693)	0.3% (4/1280)
White	88.4% (1496/1693)	86.0% (1101/1280)
Did not wish to disclose	2.8% (47/1693)	NA
Not available	0.1% (1/1693)	0.3% (4/1280)
BMI (kg/m^2)	30.13 ± 6.46 (1692) (14.0, 67.4)	29.52 ± 6.40 (1265) (13.7, 82.1)
Note: Numbers presented here are % (n/N) or mean ± SD (N).		

Table 7 shows the baseline clinical characteristics and medical history for the primary analysis group (3-month clear subjects). Thirty-nine percent of XIENCE 90 3-month clear subjects had diabetes, 15.8% had prior MI, and 34.7% presented with an acute coronary syndrome (ACS). In general, baseline clinical characteristics were comparable between the XIENCE 90 and XIENCE V USA 3-month clear subjects. Any imbalances were mitigated after propensity score stratification.

Table 7. XIENCE 90 Primary Analysis Baseline Clinical Characteristics

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE V 3-Month Clear Subjects (N=1280)
Current/Recent Smoker*	11.6% (197/1693)	11.9% (144/1210)

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE V 3-Month Clear Subjects (N=1280)
Diabetes Mellitus	39.2% (663/1692)	42.7% (546/1273)
Diabetic (Medically Treated)	24.3% (412/1692)	27.3% (347/1273)
Diabetic (Insulin Dependent)	15.6% (264/1692)	16.5% (210/1273)
Dyslipidemia	82.8% (1401/1693)	90.7% (1140/1257)
Hypertension	89.5% (1516/1693)	91.7% (1167/1272)
History of Major Bleeding	2.9% (49/1693)	2.7% (34/1280)
Chronic Kidney Disease (eGFR < 60 mL/min)	40.2% (677/1682)	44.3% (532/1202)
History of MI	15.8% (264/1669)	30.1% (353/1174)
Prior CABG	12.1% (205/1693)	14.1% (174/1230)
ACS at Presentation	34.7% (588/1693)	33.9% (405/1195)
NSTEMI	7.1% (120/1693)	10.4% (113/1089)
Unstable angina	28.7% (486/1693)	21.6% (257/1190)
History of Stroke	10.7% (181/1693)	12.1% (155/1280)
PARIS score	6.0 ± 2.3 (1693)	5.2 ± 2.2 (1280)
PRECISE-DAPT score	26.1 ± 11.5 (1606)	25.4 ± 10.9 (1154)

eGFR: estimated Glomerular Filtration Rate; CABG: Coronary Artery Bypass Graft; NSTEMI: Non-ST Elevation Myocardial Infarction

* In XIENCE 90, "current/recent smoker" is defined as actively smoking or quit < 1 year ago. In XIENCE V USA "current/recent smoker" is defined as actively smoking or quit < 1 month ago.

Key Baseline Lesion Characteristics: In XIENCE 90 three-month clear subjects, visually estimated mean reference vessel diameter was 2.99 ± 0.49 mm, mean lesion length was 16.0 ± 7.1 mm, and mean percent diameter stenosis was 83.7 ± 10.3%. The target lesion location distribution is generally reflective of patients presenting for PCI with approximately 43% in the LAD, 25% in the LCX, and 32% in the RCA. Approximately one third of lesions were classified as complex (B2/C). Additional baseline lesion characteristics can be found in **Table 8**.

Table 8. XIENCE 90 Primary Analysis Baseline Lesion Characteristics

	XIENCE 90 3-Month Clear (N=1693 Subjects N=2078 Lesions)	XIENCE V USA 3-Month Clear (N=1280 Subjects N=1668 Lesions)
Pre-Procedure		
Target Vessel		
LAD	43.2% (898/2078)	42.8% (711/1661)
LCX	24.7% (513/2078)	24.9% (414/1661)
RCA	32.0% (665/2078)	32.3% (536/1661)
Left Main	0.1% (2/2078)	0.0% (0/1661)
Mean lesion length (mm)	16.0 ± 7.1 (2078)	14.3 ± 6.2 (1579)

	XIENCE 90 3-Month Clear (N=1693 Subjects N=2078 Lesions)	XIENCE V USA 3-Month Clear (N=1280 Subjects N=1668 Lesions)
Mean RVD (mm)	2.99 ± 0.49 (2078)	2.97 ± 0.43 (1589)
% Diameter Stenosis (DS)	83.7 ± 10.3 (2078)	82.8 ± 10.6 (1661)
TIMI flow		
0	0.1% (2/2078)	0.0% (0/1598)
1	1.3% (28/2078)	1.7% (27/1598)
2	11.3% (235/2078)	11.5% (184/1598)
3	87.2% (1813/2078)	86.8% (1387/1598)
B2/C lesion	32.1% (667/2078)	46.2% (658/1425)
Thrombus	0.1% (2/2078)	NA
Bifurcation	6.6% (138/2078)	8.7% (145/1666)
Post-Procedure		
TIMI Flow of 3	100.0% (2078/2078)	NA
% DS	0.44 ± 2.12 (2078)	0.90 ± 3.68 (1662)
Dissection	0.18% (3/1693)	NA
Perforation	0.05% (1/1693)	NA

Key Procedural Characteristics: The majority of the XIENCE 90 3-month clear subjects had 1 lesion treated (80.2%) and 1 vessel treated (89.7%). In addition, most subjects had 1 stent implanted (79.1%). Additional procedural characteristics can be found in **Table 9**.

Table 9. XIENCE 90 Primary Analysis Procedural Characteristics

	XIENCE 90 3-Month Clear Subjects (N=1693 Subjects) N=2078 Lesions N=2119 Stents)	XIENCE V USA 3-Month Clear Subjects (N=1280 Subjects N=1668 Lesions N=1822 Stents)
Number of Lesions Treated/Subject	1.2 (1693)	1.3 (1280)
1	80.2% (1358/1693)	74.0% (947/1280)
2	16.9% (286/1693)	21.7% (278/1280)
3 or more	2.9% (49/1693)	4.3% (55/1280)
Number of Vessels Treated/Subject	1.1 (1693)	1.1 (1274)
1	89.7% (1518/1693)	88.3% (1125/1274)
2	10.0% (170/1693)	11.5% (147/1274)
3	0.3% (5/1693)	0.2% (2/1274)
Number of Stents Placed/Subject	1.25 (1693)	1.42 (1280)
1	79.1% (1339/1693)	66.6% (852/1280)
2	17.1% (289/1693)	25.9% (332/1280)
3 or more	3.8% (65/1693)	7.5% (96/1280)
Stent Type		
XIENCE Sierra	66.4% (1406/2119)	0.0% (0/1822)
XIENCE Alpine	33.6% (711/2119)	0.0% (0/1822)

	XIENCE 90 3-Month Clear Subjects (N=1693 Subjects) N=2078 Lesions N=2119 Stents)	XIENCE V USA 3-Month Clear Subjects (N=1280 Subjects N=1668 Lesions N=1822 Stents)
XIENCE V	0.0% (0/2119)	100.0% (1822/1822)
Stents Other than XIENCE	0.1% (2/2119)	0.0% (0/1822)
Total XIENCE Stent Length (mm)/Subject	20.4 ± 7.7 (2117)	17.6 ± 6.0 (1821)

HBR Characteristics of Patients Enrolled in XIENCE 90: Table 10 below provides an overview of the study HBR criteria met by all registered subjects. The mean number of HBR criteria met per XIENCE 90 subject was 1.5 ± 0.7. The most common HBR criteria met were age ≥ 75 years (65.6% of all XIENCE 90 subjects) and the need for chronic or lifelong oral anticoagulation (40.8% of all XIENCE 90 subjects). Most of the HBR criteria in XIENCE 90 are comparable with the XIENCE V USA historical control arm, with the exception of "Clinical Indication for Chronic or Lifelong Anticoagulation Therapy" (40.8% for XIENCE 90 vs. 10.7% for XIENCE V USA control) and "Renal Insufficiency (Creatinine ≥ 2.0 mg/dl) or Failure (Dialysis Dependent)" (9.0% for XIENCE 90 vs. 30.2% for the XIENCE V USA control arm). These imbalances may reflect the PCI subject baseline demographic shift and the change in site standard of care over time since the XIENCE V USA study was completed in 2012. The imbalances in baseline characteristics were mitigated after the subjects were stratified based on their propensity scores.

Table 10. XIENCE 90 Subjects Meeting One or More of the HBR Inclusion Criteria

HBR Inclusion Criteria	XIENCE 90 All Registered (N = 2047)	XIENCE 90 3-Month Clear (N = 1693)	XIENCE V USA 3-Month Clear (N=1280)
Patients satisfying one or more of the following criteria:			
≥ 75 years of age	65.6% (1342/2047)	66.5% (1125/1693)	55.3% (708/1280)
≥ 75 years of age only (and no other criteria met)	35.5% (727/2047)	36.5% (618/1693)	38.5% (493/1280)
Clinical indication for chronic or lifelong anticoagulation therapy	40.8% (836/2047)	41.6% (705/1693)	12.5% (160/1280)
History of major bleeding which required medical attention within 12 months of the index procedure	2.9% (60/2047)	2.9% (49/1693)	2.7% (34/1280)
History of stroke (ischemic or hemorrhagic)	11.3% (232/2047)	10.7% (181/1693)	12.1% (155/1280)
Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent)	8.0% (164/2047)	7.7% (131/1693)	29.9% (383/1280)

HBR Inclusion Criteria	XIENCE 90 All Registered (N = 2047)	XIENCE 90 3-Month Clear (N = 1693)	XIENCE V USA 3-Month Clear (N=1280)
Systemic conditions associated with an increased bleeding risk	3.0% (61/2047)	2.8% (48/1693)	1.6% (20/1280)
Anemia with hemoglobin < 11g/dl	16.2% (332/2047)	15.0% (254/1693)	16.3% (209/1280)
Number of HBR criteria met	1.5 ± 0.7 (2047)	1.5 ± 0.7 (1693)	1.3 ± 0.6 (1280)
One criterion met	61.7% (1262/2047)	61.9% (1048/1693)	74.4% (952/1280)
≥ 2 criteria met	38.3% (784/2047)	38.1% (645/1693)	25.6% (328/1280)
≥ 3 criteria met	8.2% (167/2047)	7.9% (133/1693)	4.2% (54/1280)
Note: Numbers presented here are % (n/N) or mean ± SD (N).			

Antiplatelet Medication Usage: Use of dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) at procedure, discharge, 3 months, 6 months, and 12 months are shown in **Table 11**. Antiplatelet compliance was generally good. Clopidogrel was the predominant $P2Y_{12}$ inhibitor (81.7% usage) used at discharge. After 3 months, there were 18.8% (318/1693) of 1-month clear subjects who were $P2Y_{12}$ non-adherent (meaning subjects took $P2Y_{12}$ for a certain amount of time between 3-12 months when they should have stopped $P2Y_{12}$) and 1.7% (29/1693) who were aspirin non-adherent (did not continue to take aspirin for a certain amount of time between 1-6 months when they should have continued). There were 0.6% (11/1693) 1-month clear subjects who were medication non-adherent for both $P2Y_{12}$ and aspirin between 1-6 months.

Table 11. XIENCE 90 Antiplatelet Medication Usage

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE 90 Other Registered Subjects* (N=354)	XIENCE V USA 3-Month Clear Subjects (N=1280)
Procedure			
$P2Y_{12}$ Inhibitor	99.6% (1687/1693)	99.7% (353/354)	74.8% (775/1036)
Clopidogrel	74.0% (1253/1693)	73.4% (260/354)	73.2% (758/1036)
Prasugrel	4.7% (80/1693)	3.7% (13/354)	4.5% (13/289)
Ticagrelor	24.9% (422/1693)	27.4% (97/354)	NA
Aspirin	96.6% (1636/1693)	97.1% (344/354)	72.3% (749/1036)

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE 90 Other Registered Subjects* (N=354)	XIENCE V USA 3-Month Clear Subjects (N=1280)
DAPT (Aspirin and $P2Y_{12}$)	96.3% (1630/1693)	97.1% (344/354)	48.7% (505/1036)
Discharge			
$P2Y_{12}$ Inhibitor	100.0% (1693/1693)	100.0% (354/354)	99.5% (1274/1280)
Clopidogrel	81.7% (1384/1693)	80.8% (286/354)	98.0% (1252/1277)
Prasugrel	2.2% (38/1693)	2.2% (8/354)	4.2% (16/382)
Ticagrelor	16.2% (274/1693)	16.9% (60/354)	NA
Aspirin	91.2% (1544/1693)	91.8% (325/354)	98.8% (1262/1277)
DAPT (Aspirin and $P2Y_{12}$)	91.2% (1544/1693)	91.8% (325/354)	98.6% (1260/1278)
Anticoagulant	40.7% (689/1693)	37.3% (132/354)	8.9% (114/1274)
Double Therapy (Anticoagulant and $P2Y_{12}$ Inhibitor)	8.8% (149/1693)	8.2% (29/354)	0.8% (10/1274)
Triple Therapy (Anticoagulant, Aspirin, and $P2Y_{12}$ Inhibitor)	31.9% (540/1693)	29.1% (103/354)	8.1% (103/1274)
3 months			
$P2Y_{12}$ Inhibitor	99.4% (1682/1693)	86.9% (253/291)	100.0% (1280/1280)
Clopidogrel	84.2% (1426/1693)	76.6% (223/291)	98.0% (1254/1280)
Prasugrel	2.7% (46/1693)	1.7% (5/291)	1.3% (16/1280)
Ticagrelor	12.5% (212/1693)	8.9% (26/291)	NA
Aspirin	89.5% (1515/1693)	78.3% (228/291)	99.1% (1253/1265)
DAPT (Aspirin and $P2Y_{12}$)	88.3% (1495/1693)	68.7% (200/291)	97.9% (1253/1280)
6 months			
$P2Y_{12}$ Inhibitor	11.4% (191/1671)	73.6% (184/250)	99.1% (1254/1266)

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE 90 Other Registered Subjects* (N=354)	XIENCE V USA 3-Month Clear Subjects (N=1280)
Clopidogrel	10.1% (168/1671)	66.0% (165/250)	97.2% (1231/1266)
Prasugrel	0.2% (4/1671)	2.4% (6/250)	1.0% (13/1266)
Ticagrelor	1.1% (19/1671)	5.6% (14/250)	NA
Aspirin	96.5% (1613/1671)	80.0% (200/250)	97.7% (1225/1254)
DAPT (Aspirin and $P2Y_{12}$)	9.8% (163/1671)	57.6% (144/250)	96.1% (1217/1266)
12 months			
$P2Y_{12}$ Inhibitor	12.2% (199/1627)	64.8% (147/227)	95.6% (1145/1198)
Clopidogrel	10.7% (174/1627)	57.7% (131/227)	93.7% (1122/1198)
Prasugrel	0.2% (4/1627)	2.2% (5/227)	1.1% (13/1198)
Ticagrelor	1.3% (21/1627)	4.8% (11/227)	NA
Aspirin	95.1% (1548/1627)	78.4% (178/227)	95.1% (1129/1187)
DAPT (Aspirin and $P2Y_{12}$)	10.1% (165/1627)	48.4% (110/227)	91.1% (1091/1198)

*Includes all subjects not categorized as "3 month clear", including subjects with events prior to 3 months, subjects non-compliant with DAPT, losses to follow up, etc.
NA, not available. Ticagrelor usage was not collected for the XIENCE V USA study, as Ticagrelor was not commercially available at that time.

D. Safety and Effectiveness Results

1. Study Results

The analysis of safety and effectiveness was based on the 1653 3-month clear patients evaluable at 12 months.

The primary study safety results between 3-12 months for the primary analysis population (3-month clear subjects) in the XIENCE 90 trial are summarized in **Tables 12, 13 and 14**. Additional supportive individual and composite safety and effectiveness outcomes are presented in **Table 15**.

Primary Endpoint (Safety):

The primary endpoint of all death/all MI was met. Non-inferiority of the primary endpoint of all death or all MI (modified ARC) from 3 to 12 months following XIENCE implantation in HBR subjects treated with 3-month DAPT compared to the XIENCE V USA historical control arm was demonstrated after propensity score adjustment (as pre-specified in the XIENCE 90 SAP). Propensity score stratification was performed by an independent statistician.

Based on the number of patients and observed rates in each stratum, the results show a non-inferiority p-value of 0.0063, meeting the pre-specified significance level of 0.025. The 3-12 months propensity score stratification mean rate for all death/all MI in 3-month clear patients was 5.4% for both XIENCE 90 and the XIENCE V USA historical control (**Table 12**). This demonstrated that the 3-12 months composite rate of all death/all MI following XIENCE implantation in HBR subjects treated with 3 months of DAPT was non-inferior to the historical control subjects treated with up to 12 months of DAPT.

Major Secondary Endpoint - Bleeding (Effectiveness):

The propensity score stratification method was also used to compare the XIENCE 90 trial arm to the XIENCE V USA historical control for the major secondary endpoint of BARC 2-5 bleeding. Based on the number of patients and observed rates in each stratum, the results show a superiority p-value of 0.0687, which did not meet the pre-specified significance level of 0.025. Although the significance level was not met, the 3-12 months propensity score stratification mean rate of BARC 2-5 bleeding, in 3-month clear patients, was numerically lower in XIENCE 90 as compared to the historical control (5.1% vs 7.0%; **Table 12**).

Table 12. XIENCE 90 Primary Death/MI and Secondary Bleeding Endpoint Results Between 3-12 Months

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

*Stratified Farrington-Manning method is carried out using propensity score stratified data in each imputed dataset, and Rubin's combination rule is applied to integrate the final test results from each imputed dataset.
**The test is carried out with a non-inferiority margin of 2.8% against a one-sided significance level of 0.025.
***The superiority test is carried out against a one-sided significance level of 0.025.
Note:
- Subjects are only counted once for each type of event in each time period.
- Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators.
- Subjects who are lost to follow-up without any DMR event (death, MI (modified ARC), revascularization) are excluded
- Subjects who are lost to follow-up without any bleeding event (BARC 1-5) are excluded.

In a post-hoc analysis, the propensity score stratification methodology was used to compare BARC 3-5 bleeding rates between XIENCE 90 and the XIENCE V USA historical control. BARC 3-5 excludes less severe bleeds. The observed 3-12 months

BARC 3-5 bleeding rate was 2.2% in XIENCE 90 subjects as compared to 6.3% in XIENCE V USA HBR subjects after propensity score adjustment.

Major Secondary Endpoint – Stent Thrombosis (Safety): The stent thrombosis rate for the XIENCE 90 trial arm was 0.2% between 3 to 12 months, which was significantly lower than the pre-specified performance goal (PG) of 1.2% (p-value < 0.0001; **Table 13**).**Table 13. XIENCE 90 Secondary Stent Thrombosis Endpoint Result**

	3-Month Clear Subjects (N=1693)	Upper Limit of Two-Sided 95% Confidence Interval	PG	p-value
Stent Thrombosis (ARC Definite/Probable)	0.2% (4/1635)	0.63%	1.2%	< 0.0001

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

Other supportive individual and composite safety and effectiveness endpoints between 3 and 12 months are listed in **Table 14**. Most adverse clinical events in the "not clear" population were higher than those in the overall "clear" population for the primary analysis time window (3-12 months). The values provided are without propensity score adjustment.

Table 14. XIENCE 90 Unadjusted Additional Secondary Endpoint Results 3-12 Months

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE 90 3-Month Not Clear Subjects with 3-Month Visit (N=230)	XIENCE V USA 3-Month Clear Subjects (N=1280)
Safety			
All Death/All MI (Modified ARC)	5.5% (92/1672)	13.8% (30/218)	4.4% (55/1246)
All Death	3.2% (54/1672)	7.8% (17/218)	2.6% (32/1246)
Cardiac Death	1.7% (29/1672)	4.6% (10/218)	1.2% (15/1246)
Vascular Death	0.1% (2/1672)	0.0% (0/218)	0.2% (3/1246)
Non-cardiovascular Death	1.4% (23/1672)	3.2% (7/218)	1.1% (14/1246)
All MI (Modified ARC)	2.9% (48/1672)	7.8% (17/218)	2.2% (28/1246)
Target Vessel MI (TV-MI, Modified ARC)	2.4% (40/1672)	5.0% (11/218)	2.1% (26/1246)
Cardiac Death/All MI (Modified ARC)	4.0% (67/1672)	11.0% (24/218)	3.1% (39/1246)
Major Bleeding (BARC 2-5)	5.8% (95/1629)	9.4% (19/203)	5.2% (63/1217)
Major Bleeding (BARC 3-5)	2.5% (41/1629)	4.9% (10/203)	4.4% (53/1217)
Stent Thrombosis (ARC Definite/Probable)	0.2% (4/1635)	0.5% (1/209)	0.3% (4/1225)
All Stroke	1.3% (21/1624)	1.5% (3/202)	0.6% (2/355)

	XIENCE 90 3-Month Clear Subjects (N=1693)	XIENCE 90 3-Month Not Clear Subjects with 3-Month Visit (N=230)	XIENCE V USA 3-Month Clear Subjects (N=1280)
Ischemic Stroke	1.2% (19/1624)	1.5% (3/202)	0.6% (2/355)*
Hemorrhagic Stroke	0.1% (2/1624)	0.0% (0/202)	NA*
Effectiveness			
Clinically-indicated Target Lesion Revascularization (CI-TLR)	1.0% (16/1672)	3.2% (7/218)	1.4% (18/1246)
Clinically-indicated Target Vessel Revascularization (CI-TVR)	1.6% (26/1672)	5.5% (12/218)	2.9% (36/1246)
Safety and Effectiveness			
Target Lesion Failure (TLF)	3.9% (66/1672)	10.6% (23/218)	4.1% (51/1246)
Target Vessel Failure (TVF)	4.2% (70/1672)	12.8% (28/218)	5.0% (62/1246)

Note:

- Subjects are only counted once for each type of event in each time period.
- Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators.
- Subjects who are lost to follow-up without any DMR event (death, MI (modified ARC), revascularization) are excluded; for Stent Thrombosis, Major Bleeding, and Stroke, subjects who are lost to follow-up without a related event (Stent Thrombosis, BARC (1-5), or Stroke, respectively) are excluded.

*Hemorrhagic and ischemic strokes not collected for XIENCE V USA Phase I; hemorrhagic strokes not collected for XIENCE V USA Phase II.

2. Results by Subgroups

The following preoperative characteristics were evaluated for potential association with outcomes:

Sex/Gender
Although not powered to evaluate safety or effectiveness of the XIENCE family of stents in gender-specific subgroups, outcomes for male and female subjects from the XIENCE 90 trial are available (**Table 15**).

The composite rate of all death/all MI in the 3-month clear XIENCE 90 subjects between 3-12 months was 5.3% in male subjects and 5.8% in female subjects.

The stent thrombosis rate from 3-12 months was 0.2% in males and 0.3% in females. The BARC 2-5 bleeding rate was 5.5% in male subjects and 6.5% in female subjects.

Table 15. Unadjusted Primary and Secondary Endpoints By Sex/Gender

	XIENCE 90 3-Month Clear Subjects (N=1693)		XIENCE V USA 3-Month Clear Subjects (N=1280)	
	Male (N=1097)	**Female (N=596)**	**Male (N=756)**	**Female (N=524)**
***All Death/All MI**	5.3% (58/1085)	5.8% (34/587)	4.3% (32/738)	4.5% (23/508)
****BARC 2-5**	5.5% (58/1059)	6.5% (37/570)	4.6% (33/721)	6.0% (30/496)
*****Stent thrombosis**	0.2% (2/1061)	0.3% (2/574)	0.3% (2/725)	0.4% (2/500)
All Death	3.1% (34/1085)	3.4% (20/587)	2.6% (19/738)	2.6% (13/508)
Cardiac Death	1.6% (17/1085)	2.0% (12/587)	1.2% (9/738)	1.2% (6/508)
Vascular Death	0.2% (2/1085)	0.0% (0/587)	0.4% (3/738)	0.0% (0/508)
Non-cardiovascular Death	1.4% (15/1085)	1.4% (8/587)	0.9% (7/738)	1.4% (7/508)
All MI (modified ARC)	2.6% (28/1085)	3.4% (20/587)	2.2% (16/738)	2.4% (12/508)
Target Vessel MI (TV-MI, modified ARC)	2.1% (23/1085)	2.9% (17/587)	1.9% (14/738)	2.4% (12/508)
Cardiac Death/All MI (modified ARC)	3.8% (41/1085)	4.4% (26/587)	3.1% (23/738)	3.1% (16/508)
Major Bleeding (BARC 3-5)	2.8% (30/1059)	1.9% (11/570)	3.9% (28/721)	5.0% (25/496)
All Stroke	1.2% (13/1054)	1.4% (8/570)	0.9% (2/221)	0.0% (0/134)
Ischemic Stroke	1.0% (11/1054)	1.4% (8/570)	0.9% (2/221)	0.0% (0/134)
Hemorrhagic Stroke	0.2% (2/1054)	0.0% (0/570)	NA	NA
Clinically-indicated Target Lesion Revascularization (CI-TLR)	1.1% (12/1085)	0.7% (4/587)	1.4% (10/738)	1.6% (8/508)
Clinically-indicated Target Vessel Revascularization (CI-TVR)	1.8% (19/1085)	1.2% (7/587)	2.4% (18/738)	3.5% (18/508)
Target Lesion Failure (TLF)	3.8% (41/1085)	4.3% (25/587)	3.9% (29/738)	4.3% (22/508)
Target Vessel Failure (TVF)	4.1% (44/1085)	4.4% (26/587)	4.6% (34/738)	5.5% (28/508)

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

The overall conclusions of the trial regarding the safety of the XIENCE family of stents when used with 3 months of DAPT in patients at high risk of bleeding can be generalized to males and females.

Age

Of the 1693 3-month clear subjects in XIENCE 90, 1446 were ≥ 65 years old at the time of registration. The rates of all death/all MI, BARC 2-5 bleeding and ST between 3 and 12 months, in subjects age 65 or older were 5.5%, 5.3% and 0.2%, respectively. These rates were comparable to those observed in the overall 3-month clear population.

Race and Ethnicity

Outcomes by race in the 1693 3-month clear subjects from XIENCE 90 are presented in **Table 16**. 1496 (88.4%) were white, while 149 (8.80%) subjects were non-white (identified as American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, or Other). The available race and ethnicity information is too limited to comment on any potential associations.

Table 16. Unadjusted Primary and Secondary Endpoints By Race

	XIENCE 90 3-Month Clear Subjects (N=1693)						**XIENCE V USA 3-Month Clear Subjects (N=1280)**					
	White (N=1496)	**American Indian or Alaska Native (N=11)**	**Asian (N=37)**	**Black or African American (N=96)**	**Hispanic or Latino (N=45)**	**Native Hawaiian or Pacific Islander (N=5)**	**White (N=1101)**	**American Indian or Alaska Native (N=9)**	**Asian (N=17)**	**Black or African American (N=110)**	**Hispanic or Latino (N=41)**	**Native Hawaiian or Pacific Islander (N=4)**
***All Death/All MI**	5.8% (85/1478)	0.0% (0/11)	0.0% (0/36)	6.3% (6/95)	8.9% (4/45)	0.0% (0/5)	3.8% (41/1076)	11.1% (1/9)	6.7% (1/15)	9.4% (10/106)	5.4% (2/37)	0.0% (0/4)
****BARC 2-5 bleeding**	5.7% (82/1438)	0.0% (0/11)	5.6% (2/36)	6.5% (6/92)	11.1% (5/45)	20.0% (1/5)	5.3% (56/1053)	0.0% (0/8)	6.7% (1/15)	4.0% (4/101)	5.4% (2/37)	0.0% (0/4)
*****Stent Thrombosis (ARC definite/probable)**	0.3% (4/1444)	0.0% (0/11)	0.0% (0/36)	0.0% (0/92)	0.0% (0/44)	0.0% (0/5)	0.3% (3/1058)	0.0% (0/9)	0.0% (0/15)	1.0% (1/103)	0.0% (0/37)	0.0% (0/4)
All Death	3.3% (49/1478)	0.0% (0/11)	0.0% (0/36)	5.3% (5/95)	2.2% (1/45)	0.0% (0/5)	2.4% (26/1076)	11.1% (1/9)	0.0% (0/15)	4.7% (5/106)	0.0% (0/37)	0.0% (0/4)
Cardiac Death	1.7% (25/1478)	0.0% (0/11)	0.0% (0/36)	4.2% (4/95)	0.0% (0/45)	0.0% (0/5)	1.0% (11/1076)	11.1% (1/9)	0.0% (0/15)	2.8% (3/106)	0.0% (0/37)	0.0% (0/4)
Vascular Death	0.1% (2/1478)	0.0% (0/11)	0.0% (0/36)	0.0% (0/95)	2.2% (1/45)	0.0% (0/5)	0.3% (3/1076)	0.0% (0/9)	0.0% (0/15)	0.0% (0/106)	0.0% (0/37)	0.0% (0/4)
Non-cardiovascular Death	1.5% (22/1478)	0.0% (0/11)	0.0% (0/36)	1.1% (1/95)	0.0% (0/45)	0.0% (0/5)	1.1% (12/1076)	0.0% (0/9)	0.0% (0/15)	1.9% (2/106)	0.0% (0/37)	0.0% (0/4)
All MI (modified ARC)	2.9% (43/1478)	0.0% (0/11)	0.0% (0/36)	4.2% (4/95)	6.7% (3/45)	0.0% (0/5)	1.8% (19/1076)	0.0% (0/9)	6.7% (1/15)	5.7% (6/106)	5.4% (2/37)	0.0% (0/4)
Target Vessel MI (TV-MI, modified ARC)	2.4% (35/1478)	0.0% (0/11)	0.0% (0/36)	4.2% (4/95)	6.7% (3/45)	0.0% (0/5)	1.7% (18/1076)	0.0% (0/9)	6.7% (1/15)	4.7% (5/106)	5.4% (2/37)	0.0% (0/4)
Cardiac Death/All MI (modified ARC)	4.1% (61/1478)	0.0% (0/11)	0.0% (0/36)	5.3% (5/95)	6.7% (3/45)	0.0% (0/5)	2.5% (27/1076)	11.1% (1/9)	6.7% (1/15)	7.5% (8/106)	5.4% (2/37)	0.0% (0/4)

	XIENCE 90 3-Month Clear Subjects (N=1693)						XIENCE V USA 3-Month Clear Subjects (N=1280)					
	White (N=1496)	American Indian or Alaska Native (N=11)	Asian (N=37)	Black or African American (N=96)	Hispanic or Latino (N=45)	Native Hawaiian or Pacific Islander (N=5)	White (N=1101)	American Indian or Alaska Native (N=9)	Asian (N=17)	Black or African American (N=110)	Hispanic or Latino (N=41)	Native Hawaiian or Pacific Islander (N=4)
Major Bleeding (BARC 3-5)	2.6% (38/1438)	0.0% (0/11)	0.0% (0/36)	2.2% (2/92)	4.4% (2/45)	0.0% (0/5)	4.5% (47/1053)	0.0% (0/8)	0.0% (0/15)	4.0% (4/101)	5.4% (2/37)	0.0% (0/4)
All Stroke	1.3% (19/1435)	0.0% (0/11)	0.0% (0/36)	2.2% (2/90)	2.2% (1/45)	0.0% (0/5)	0.6% (2/313)	0.0% (0/1)	0.0% (0/6)	0.0% (0/27)	0.0% (0/8)	0.0% (0/2)
Ischemic Stroke	1.3% (18/1435)	0.0% (0/11)	0.0% (0/36)	1.1% (1/90)	2.2% (1/45)	0.0% (0/5)	0.6% (2/313)	0.0% (0/1)	0.0% (0/6)	0.0% (0/27)	0.0% (0/8)	0.0% (0/2)
Hemorrhagic Stroke	0.1% (1/1435)	0.0% (0/11)	0.0% (0/36)	1.1% (1/90)	0.0% (0/45)	0.0% (0/5)	NA	NA	NA	NA	NA	NA
Clinically-indicated Target Lesion Revascularization (CI-TLR)	1.0% (15/1478)	0.0% (0/11)	0.0% (0/36)	1.1% (1/95)	0.0% (0/45)	0.0% (0/5)	1.4% (15/1076)	0.0% (0/9)	6.7% (1/15)	0.9% (1/106)	2.7% (1/37)	0.0% (0/4)
Clinically-indicated Target Vessel Revascularization (CI-TVR)	1.7% (25/1478)	0.0% (0/11)	0.0% (0/36)	1.1% (1/95)	0.0% (0/45)	0.0% (0/5)	2.8% (30/1076)	0.0% (0/9)	6.7% (1/15)	3.8% (4/106)	2.7% (1/37)	0.0% (0/4)
Target Lesion Failure (TLF)	4.1% (60/1478)	0.0% (0/11)	0.0% (0/36)	5.3% (5/95)	6.7% (3/45)	0.0% (0/5)	3.6% (39/1076)	11.1% (1/9)	6.7% (1/15)	6.6% (7/106)	8.1% (3/37)	0.0% (0/4)
Target Vessel Failure (TVF)	4.3% (64/1478)	0.0% (0/11)	0.0% (0/36)	5.3% (5/95)	6.7% (3/45)	0.0% (0/5)	4.5% (48/1076)	11.1% (1/9)	6.7% (1/15)	8.5% (9/106)	8.1% (3/37)	0.0% (0/4)

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

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

(2) XIENCE 28 USA and XIENCE 28 Global Clinical Trials

A. Study Design

The XIENCE 28 analysis was conducted on the combined populations from XIENCE 28 USA and XIENCE 28 Global trials, as pre-specified in the XIENCE 28 USA SAP. Both trials are prospective, single arm, multi-center, open label trials to evaluate the safety of 1-month (as short as 28 days) DAPT in subjects at high risk of bleeding undergoing PCI with the approved XIENCE family of stents. Subjects were considered to be high bleeding risk if, in the opinion of the referring physician, the risk of major bleeding with >1-month DAPT outweighed the benefit and they met one or more of the same HBR criteria listed in XIENCE 90. Subjects were prescribed DAPT ($P2Y_{12}$ inhibitor + aspirin) between 0-1 month post-procedure. Subjects were considered as "1-month clear" and were to discontinue $P2Y_{12}$ inhibitor at 1 month if they were compliant with the prescribed DAPT and were free from events between 0-1 month (myocardial infarction, repeat coronary revascularization, stroke, or stent thrombosis). Subjects that discontinued $P2Y_{12}$ inhibitor at 1 month were prescribed aspirin through the end of the study.

For the primary endpoint of all death or all MI and the secondary endpoint of BARC 2-5 bleeding, the primary analysis population for the XIENCE 28 analysis is the 1-month clear subjects. The 1-month clear population, combined from XIENCE 28 Global and XIENCE 28 USA, was compared with the 1-month clear population of the historical control of non-complex HBR subjects treated with DAPT duration of up to 12 months from the XIENCE V USA Study. For these primary and secondary endpoints, the comparison with the 1-month clear population of the historical control was done after propensity score adjustment.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the XIENCE 28 trials was limited to subjects who met the inclusion criteria listed in **Table 17**. Subjects were not permitted to enroll in the XIENCE 28 trials if they met any of the exclusion criteria in **Table 17**.

Table 17. XIENCE 28 Trials Enrollment Inclusion and Exclusion Criteria

General Inclusion Criteria	1. Subject is considered at high risk for bleeding, defined as meeting one or more of the criteria previously listed in **Table 5** at the time of registration and in the opinion of the referring physician, the risk of major bleeding with > 1-month DAPT outweighs the benefit: 2. Subject must be at least 18 years of age. 3. Subject must provide written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site prior to any trial related procedure. 4. Subject is willing to comply with all protocol requirements, including agreement to stop taking $P2Y_{12}$ inhibitor at 1 month, if eligible per protocol.

	5. Subject must agree not to participate in any other clinical trial for a period of one year following the index procedure, except for cases where subject is transferred to the XIENCE 90 study after the 1-month visit assessment.
General Exclusion Criteria	1. Subject with an indication for the index procedure of acute ST-segment elevation MI (STEMI). 2. Subject has a known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, $P2Y_{12}$ inhibitors (clopidogrel/prasugrel/ticagrelor), everolimus, cobalt, chromium, nickel, tungsten, acrylic and fluoro polymers or contrast sensitivity that cannot be adequately pre-medicated. 3. Subject with implantation of another drug-eluting stent (other than XIENCE) within **12** months prior to index procedure. 4. Subject has a known left ventricular ejection fraction (LVEF) <30%. 5. Subject judged by physician as inappropriate for discontinuation from $P2Y_{12}$ inhibitor use at 1 month, due to another condition requiring chronic $P2Y_{12}$ inhibitor use. 6. Subject with planned surgery or procedure necessitating discontinuation of $P2Y_{12}$ inhibitor within 1 month following index procedure. 7. Subject with a current medical condition with a life expectancy of less than 12 months. 8. Subject intends to participate in an investigational drug or device trial within 12 months following the index procedure. Transferring to the XIENCE 90 study will not be an exclusion criterion. 9. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 7 days prior to the index procedure per site standard test. Note: Female subjects of childbearing potential should be instructed to use safe contraception (e.g., intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches, hormonal vaginal devices, injections with prolonged release.) It is accepted, in certain cases, to include subjects having a sterilized regular partner or subjects using a double barrier contraceptive method. However, this should be explicitly justified in special circumstances arising from the trial design, product characteristics, and/or trial population. 10. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results. 11. Subject is currently participating in another clinical trial that has not yet completed its primary endpoint.

Angiographic Inclusion Criteria	Identical to XIENCE 90, except target lesions ≤32 mm in length by visual estimation were not listed as inclusion criteria.
Angiographic Exclusion Criteria	1. Target lesion is in a left main location. 2. Target lesion is located within an arterial or saphenous vein graft. 3. Target lesion is restenotic from a previous stent implantation. 4. Target lesion is a **chronic** total occlusion (CTO, defined as lesion with TIMI flow 0 for at least 3 months). 5. Target lesion is implanted with overlapping stents, whether planned or for bailout.

2. Follow-up Schedule

All patients were scheduled to have follow-up examinations at the following time points: 1, 3, 6, and 12 months post index procedure. Study follow-up through 6 months is complete. Per study design, the primary endpoint was to be evaluated at 6 months.

Preoperatively, laboratory assessments were conducted per SOC to determine subject's eligibility for PCI and confirm eligibility for the study. Post-procedure, ECG and cardiac enzyme collection were performed per SOC. Use and compliance of protocol required antiplatelet medication and adverse events and complications were recorded at all visits.

The key time points are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Primary Endpoint

The primary endpoint is a composite rate of all death or all myocardial infarction (MI, modified ARC) from 1 to 6 months post index procedure.

Major Secondary Endpoint

The major secondary endpoint is major bleeding rate (BARC type 2-5) from 1 to 6 months.

Other Secondary Endpoints

The following endpoints were assessed from 1 to 6 months:

- Stent thrombosis (ARC definite/probable, ARC definite)
- All death, cardiac death, vascular death, non-cardiovascular death
- All MI (modified ARC) and MI attributed to target vessel (TV-MI, modified ARC)

- Composite of cardiac death or MI (modified ARC)
- Composite of all death or all MI (modified ARC)
- All stroke, ischemic stroke and hemorrhagic stroke
- CI-TLR
- CI-TVR
- TLF, (composite of cardiac death, TV-MI and CI-TLR)
- TVF, (composite of cardiac death, TV-MI and CI-TVR)
- Major bleeding defined by BARC type 3-5

B. Accountability of PMA Cohort

Between February 9, 2018 and April 22, 2019 (XIENCE 28 Global), and between February 25, 2019 and February 7, 2020 (XIENCE 28 USA), a total of 1605 subjects were enrolled in XIENCE 28, 642 from the US and Canada and 963 from Europe and Asia, at 110 sites. Of the 1605 subjects, 1392 subjects met the 1-month clear criteria and are the primary analysis group. A total of 154 subjects did not meet the 1-month clear criteria and these subjects were not included in the primary analysis population. At 6 months, 1375 of the 1-month clear subjects completed their visit (98.8%). The subject enrollment and disposition up to 6 months for XIENCE 28 are shown below in **Figure 4**.

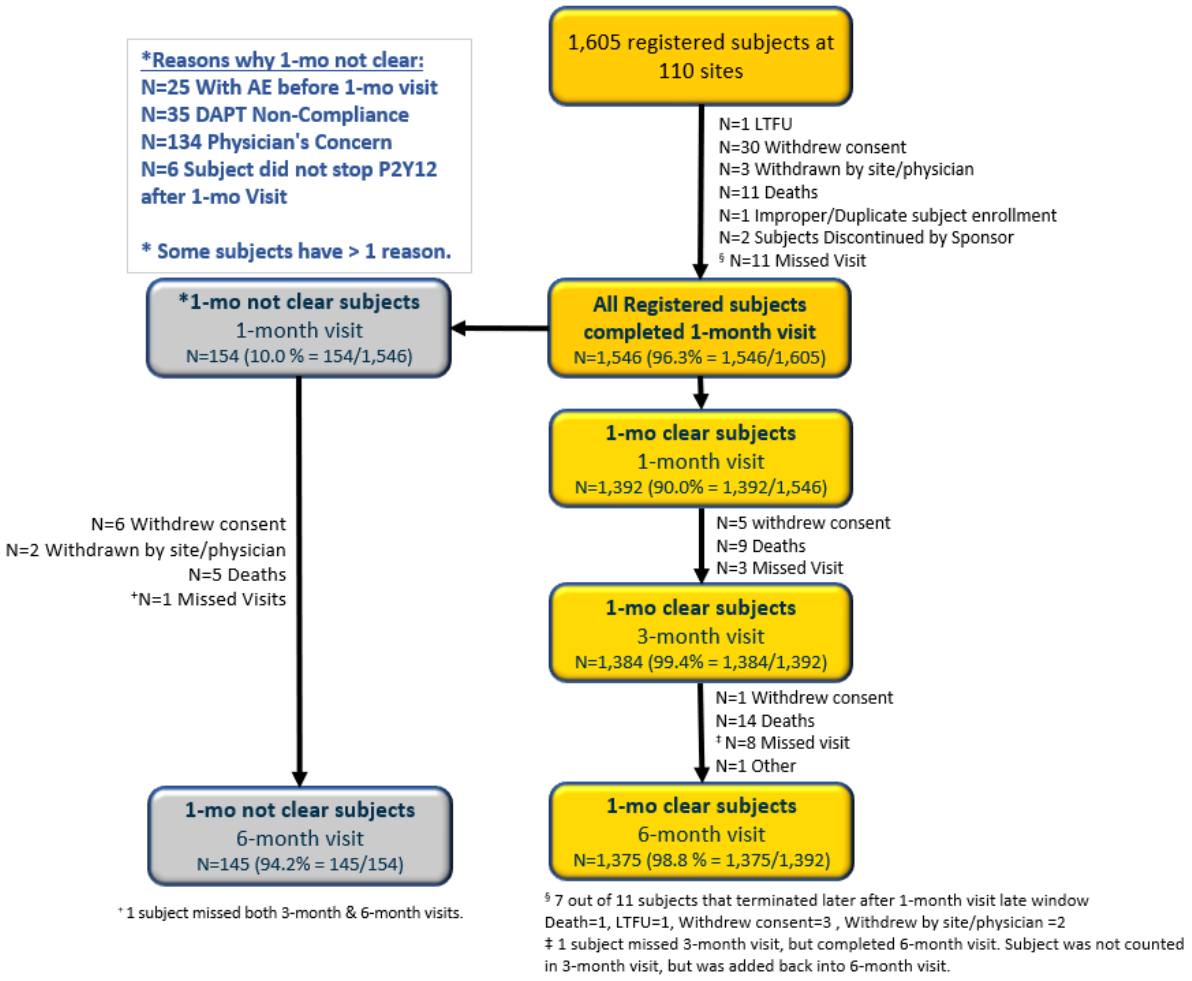

Figure 4. XIENCE 28 Subject Enrollment and Disposition

Note: LTFU = Lost to Follow Up

C. Study Population Demographics and Baseline Parameters

Table 18 presents demographics for the primary analysis group (XIENCE 28 1-month clear subjects) and the historical control group (XIENCE V USA 1-month clear subjects). The mean age in the XIENCE 28 1-month clear subjects was 75.97 years and 32.5% were female. Subjects were majority white (at least 58.0%; race data not available for nearly a third of XIENCE 28 subjects) and overweight (mean BMI 28.32).

Table 18. XIENCE 28 1-Month Primary Analysis Demographics

	XIENCE 28 1-Month Clear Subjects (N=1392)	XIENCE V USA 1-Month Clear Subjects (N=1411)
Age (years)	75.97 ± 8.37 (1392) (40.0, 96.0)	72.56 ± 10.42 (1411) (34.9, 100.4)

Gender		
Male	67.5% (939/1392)	59.2% (835/1411)
Female	32.5% (453/1392)	40.8% (576/1411)
Race		
American Indian or Alaska Native	0.1% (2/1392)	0.8% (11/1411)
Asian	9.1% (126/1392)	1.3% (19/1411)
Black or African American	2.6% (36/1392)	8.2% (115/1411)
Hispanic or Latino	9.9% (138/1392)	3.0% (42/1411)
Native Hawaiian or Pacific Islander	0.0% (0/1392)	0.3% (4/1411)
White	58.0% (807/1392)	86.7% (1224/1411)
Did not wish to disclose	2.5% (35/1392)	NA
Not available	27.7% (386/1392)	0.3% (4/1411)
BMI (kg/m^2)	28.32 ± 5.94 (1390) (13.9, 104)	29.53 ± 6.33 (1396) (13.7, 82.1)

Table 19 shows the baseline clinical characteristics and medical history for the primary analysis group (1-month clear subjects). Of the 1392 XIENCE 28 subjects that were 1-month clear, 36.8% had diabetes, 16.4% had prior MI, and 34.1% presented with an acute coronary syndrome. In general, baseline clinical characteristics were comparable between the XIENCE 28 and XIENCE V USA 1-month clear subjects. Any imbalances were mitigated after propensity score stratification.

Table 19. XIENCE 28 Primary Analysis Baseline Clinical Characteristics

	XIENCE 28 1-Month Clear Subjects (N=1392)	**XIENCE V USA 1-Month Clear Subjects (N=1411)**
Current/Recent Smoker*	14.7% (205/1392)	12.3% (164/1331)
Diabetes Mellitus	36.8% (512/1392)	42.1% (594/1411)
Diabetic (Medically Treated)	24.7% (344/1392)	26.6% (375/1411)
Diabetic (Insulin Dependent)	11.5% (160/1392)	16.1% (227/1411)
Dyslipidemia	67.5% (939/1392)	90.7% (1254/1383)
Hypertension	84.7% (1179/1392)	91.5% (1283/1402)
History of Major Bleeding	3.3% (46/1391)	2.6% (37/1411)
Chronic Kidney Disease (eGFR < 60 mL/min)	47.4% (631/1330)	44.0% (584/1327)
History of MI	16.4% (227/1382)	30.3% (393/1295)
Prior CABG	8.0% (112/1392)	14.8% (201/1355)
ACS at Presentation	34.1% (475/1392)	35.8% (472/1318)
NSTEMI	17.6% (245/1392)	11.5% (138/1195)
Unstable angina	16.5% (230/1392)	21.9% (287/1311)
History of Stroke	10.4% (145/1391)	12.5% (176/1411)
PARIS score	6.1 ± 2.3 (1392)	5.2 ± 2.2 (1404)
PRECISE-DAPT score	27.7 ± 11.3 (1295)	25.3 ± 10.9 (1276)

eGFR: estimated Glomerular Filtration Rate; CABG: Coronary Artery Bypass Graft; NSTEMI: Non-ST Elevation Myocardial Infarction

* In XIENCE 28, "current/recent smoker" is defined as actively smoking or quit < 1 year ago. In XIENCE V USA, "current/recent smoker" is defined as actively smoking or quit < 1 month ago.

Key Baseline Lesion Characteristics: In XIENCE 28 1-month clear subjects, visually estimated mean reference vessel diameter was 2.99 ± 0.50 mm, mean lesion length was 18.01 ± 8.43 mm, and mean percent diameter stenosis was 82.47 ± 10.8%. The target lesion location distribution is generally reflective of patients presenting for PCI with approximately 46% in the LAD, 24% in the LCX, and 30% in the RCA. Approximately one third of lesions were classified as complex (B2/C). Additional baseline lesion characteristics can be found in **Table 20**.

Table 20. XIENCE 28 Primary Analysis Baseline Lesion Characteristics

	XIENCE 28 1-Month Clear (N=1392 Subjects N=1700 Lesions)	XIENCE V USA 1-Month Clear (N=1411 Subjects N=1835 Lesions)
Pre-Procedure		
Target Lesion Location		
LAD	45.9% (781/1700)	41.8% (766/1834)
LCX	24.1% (409/1700)	25.1% (461/1834)
RCA	29.9% (509/1700)	32.7% (600/1834)
Left Main	0.1% (1/1700)	0.0% (0/1834)
Mean Lesion Length (mm)	18.01 ± 8.43 (1700)	14.31 ± 6.15 (1737)
Mean RVD (mm)	2.99 ± 0.50 (1700)	2.97 ± 0.44 (1751)
% Diameter Stenosis	82.47 ± 10.80 (1699)	83.15 ± 10.73 (1828)
TIMI flow		
0	0.5% (8/1700)	1.5% (27/1757)
1	2.9% (49/1700)	1.9% (33/1757)
2	7.7% (131/1700)	12.0% (211/1757)
3	88.9% (1512/1700)	84.6% (1486/1757)
B2/C lesion	33.9% (576/1697)	47.5% (744/1566)
Thrombus	3.6% (61/1700)	NA
Bifurcation	9.8% (167/1700)	8.6% (158/1832)
Post-Procedure		
TIMI Flow of 3	100.0% (1700/1700)	NA
% DS	0.60 ± 2.48 (1700)	0.87 ± 3.58 (1829)
Dissection	0.14% (2/1392)	NA
Perforation	0.0% (0/1392)	NA

Key Procedural Characteristics: The majority of the XIENCE 28 1-month clear subjects had 1 lesion treated (80.3%) and 1 vessel treated (88.2%). In addition, most subjects had 1 stent implanted (78.7%). Additional procedural characteristics can be found in **Table 21**.

Table 21. XIENCE 28 Primary Analysis Procedural Characteristics

	XIENCE 28 1-Month Clear Subjects (N=1392 Subjects N=1700 Lesions N=1734 Stents)	XIENCE V USA 1-Month Clear Subjects (N=1411 Subjects N=1835 Lesions N=2007 Stents)
Number of Lesions Treated/Subject	1.2 (1392)	1.3 (1411)
1	80.3% (1118/1392)	741.1% (1045/1411)
2	17.2% (240/1392)	21.8% (308/1411)
3 or more	2.4% (34/1392)	4.1% (58/1411)
Number of Vessels Treated/Subject	1.1 (1392)	1.1 (1411)
1	88.2% (1228/1392)	88.5% (1243/1404)
2	11.6% (162/1392)	11.3% (159/1404)
3	0.1% (2/1392)	0.1% (2/1404)
Number of Stents Placed/Subject	1.24 (1392)	1.42 (1411)
1	78.7% (1093/1389)	66.7% (941/1411)
2	17.9% (249/1389)	26.1% (368/1411)
3 or more	3.4% (47/1389)	7.2% (102/1411)
Stent Type		
XIENCE Sierra	62.2% (1079/1734)	0.0% (0/2007)
XIENCE Alpine	29.9% (518/1734)	0.0% (0/2007)
XIENCE Xpedition	7.9% (137/1734)	0.0% (0/2007)
XIENCE V		100.0% (2007/2007)
Total XIENCE Stent Length (mm)/Subject	21.8 ± 8.4 (1734)	17.6 ± 5.9 (2001)

HBR Characteristics of Patients Enrolled in XIENCE 28 trials: Table 22 below provides an overview of the study HBR criteria met by all registered subjects. The mean number of HBR criteria met per XIENCE 28 subject was 1.6 ± 0.8. The most common HBR criteria met were age ≥75 years (69.3% of all XIENCE 28 subjects) and the need for chronic or lifelong oral anticoagulation (43.9% of all XIENCE 28 subjects). Most of the HBR criteria in XIENCE 28 are comparable with the XIENCE V USA historical control arm, with the exception of "Clinical Indication for Chronic or Lifelong Anticoagulation Therapy" (43.9% for XIENCE 28 vs. 11.2% for XIENCE V USA control) and "Renal Insufficiency (Creatinine ≥ 2.0 mg/dl) or Failure (Dialysis Dependent)" (8.6% for XIENCE 28 vs. 30.5% for the XIENCE V USA control arm). These imbalances may reflect the PCI subject baseline demographic shift and the change in site standard of care over time since the XIENCE V USA study was completed in 2012. The imbalances in baseline characteristics were mitigated after the subjects were stratified based on their propensity scores.

Table 22. XIENCE 28 Subjects Meeting One or More of the HBR Inclusion Criteria

HBR Inclusion Criteria	XIENCE 28 All Registered (N = 1605)	XIENCE 28 1-Month Clear (N = 1392)	XIENCE V USA 1-Month Clear (N=1411)
Patients satisfying one or more of the following criteria:			
≥ 75 Years of age	69.3% (1112/1605)	68.2% (950/1392)	54.9% (775/1411)
≥ 75 Years of age only (and no other criteria met)	35.1% (563/1605)	35.1% (488/1392)	38.0% (536/1411)
Clinical indication for chronic or lifelong anticoagulation therapy	43.9% (704/1605)	44.3% (617/1392)	13.0% (184/1411)
History of major bleeding which required medical attention within 12 months of the index procedure	3.6% (57/1605)	3.3% (46/1392)	2.6% (37/1411)
History of stroke (ischemic or hemorrhagic)	10.8% (174/1605)	10.4% (145/1392)	12.5% (176/1411)
Renal insufficiency (creatinine ≥ 2.0 mg/dl) or failure (dialysis dependent)	8.6% (138/1605)	8.3% (116/1392)	29.8% (420/1411)
Systemic conditions associated with an increased bleeding risk	3.9% (63/1605)	4.0% (55/1392)	1.8% (25/1411)
Anemia with hemoglobin < 11 g/dl	15.2% (244/1605)	14.4% (201/1392)	16.2% (229/1411)
Number of HBR criteria met	1.6 ± 0.8 (1603)	1.5 ± 0.7 (1391)	1.3 ± 0.6 (1411)
One criterion met	57.8% (927/1603)	58.7% (816/1391)	74.4% (1050/1411)
≥ 2 criteria met	42.0% (674/1603)	41.3% (575/1391)	25.6% (361/1411)
≥ 3 criteria met	10.7% (172/1603)	9.3% (129/1391)	4.5% (64/1411)

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

Antiplatelet Medication Usage: Use of dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) at procedure, at discharge, 1 month, 3 months and 6 months are shown in **Table 23**. Clopidogrel was the predominant $P2Y_{12}$ inhibitor (86.5% usage) used at discharge. After 1 month, there were 8.4% (117/1392) of 1-month clear subjects who were $P2Y_{12}$ non-adherent (meaning subjects took $P2Y_{12}$ for a certain amount of time between 1-6 months when they should have stopped $P2Y_{12}$) and 7.3% (102/1392) who were aspirin non-adherent (did not continue to take aspirin for a certain amount of time between 1-6 months when they should have continued). There were 2.7% (37/1392) 1-month clear subjects who were medication non-adherent for both $P2Y_{12}$ and aspirin between 1-6 months.

Table 23. XIENCE 28 Antiplatelet Medication Usage

	XIENCE 28 1-Month Clear Subjects (N=1392)	XIENCE 28 Other Registered Subjects* (N=213)	XIENCE V USA 1-Month Clear Subjects (N=1411)
Procedure			
$P2Y_{12}$ Inhibitor	99.6% (1386/1392)	99.5% (212/213)	60.8% (858/1411)
Clopidogrel	83.0% (1156/1392)	81.7% (174/213)	59.6% (841/1411)
Prasugrel	3.2% (45/1392)	4.7% (10/213)	0.9% (13/1411)
Ticagrelor	17.1% (238/1392)	18.3% (39/213)	NA
Aspirin	94.6% (1317/1392)	93/9% (200/213)	58.8% (829/1411)
DAPT (Aspirin and $P2Y_{12}$)	94.3% (1312/1392)	93.9% (200/213)	39.8% (562/1411)
Discharge			
$P2Y_{12}$ Inhibitor	100.0% (1392/1392)	100.0% (213/213)	99.5% (1404/1411)
Clopidogrel	86.5% (1204/1392)	85.9% (183/213)	98.1% (1381/1408)
Prasugrel	1.0% (14/1392)	0.9% (2/213)	4.1% (17/412)
Ticagrelor	12.5% (174/1392)	13.1% (28/213)	NA
Aspirin	81.3% (1132/1392)	79.3% (169/213)	98.7% (1392/1411)
DAPT (Aspirin and $P2Y_{12}$)	81.3% (1132/1392)	79.3% (169/213)	98.7% (1389/1408)
Anticoagulant	45.6% (635/1392)	43.2% (92/213)	9.8% (137/1405)
Double Therapy (Anticoagulant and $P2Y_{12}$ Inhibitor)	18.5% (257/1392)	20.6% (44/213)	0.8% (11/1411)
Triple Therapy (Anticoagulant, Aspirin, and $P2Y_{12}$ Inhibitor)	27.2% (378/1392)	22.5% (48/213)	8.8% (124/1411)
1 month			
$P2Y_{12}$ Inhibitor	97.1% (1352/1392)	76.1% (162/213)	100.0% (1411/1411)
Clopidogrel	85.0% (1183/1392)	67.1% (143/213)	98.4% (1388/1411)

	XIENCE 28 1-Month Clear Subjects (N=1392)	XIENCE 28 Other Registered Subjects* (N=213)	XIENCE V USA 1-Month Clear Subjects (N=1411)
Prasugrel	1.1% (15/1392)	0.9% (2/213)	1.3% (18/1411)
Ticagrelor	11.2% (156 /1392)	8.5% (18/213)	NA
Aspirin	97.7% (1360/1392)	64.8% (138/213)	98.3% (1387/1411)
DAPT (Aspirin and $P2Y_{12}$)	96.9% (1349/1392)	73.2% (156/213)	98.3% (1387/1411)
3 months			
$P2Y_{12}$ Inhibitor	4.3% (60/1380)	85.2% (133/156)	99.4% (1383/1392)
Clopidogrel	4.1% (56/1380)	76.3% (119/156)	97.3% (1355/1392)
Prasugrel	0.1% (1/1380)	1.3% (2/156)	1.1% (16/1392)
Ticagrelor	0.2% (3/1380)	7.7% (12/156)	NA
Aspirin	96.2% (1327/1380)	64.1% (100/156)	96.9% (1349/1392)
DAPT (Aspirin and $P2Y_{12}$)	3.3% (45/1380)	52.6% (82/156)	96.4% (1342/1392)
6 months			
P2Y12 Inhibitor	5.0% (68/1358)	79.3% (115/145)	98.5% (1353/1374)
Clopidogrel	4.6% (62/1358)	71.0% (103/145)	96.7% (1329/1374)
Prasugrel	0.1% (1/1358)	1.4% (2/145)	0.9% (13/1374)
Ticagrelor	0.4% (5/1358)	6.9% (10/145)	NA
Aspirin	94.9% (1289/1358)	61.4% (89/145)	95.8% (1316/1374)
DAPT (Aspirin and P2Y12)	3.2% (44/1358)	46.2% (67/145)	94.7% (1301/1374)

Note:

- Medication usage at a specific follow-up visit requires a minimum of 1-day of use of the specific medication(s) during that specific visit window. For patients of XIENCE 28 on chronic anti-coagulant medication, aspirin may be skipped for the first month, according to physician's discretion
- *Includes all subjects not categorized as "3 month clear", including subjects with events prior to 3 months, subjects non-compliant with DAPT, losses to follow up, etc.
- NA, not available. Ticagrelor usage was not collected for the XIENCE V USA study, as Ticagrelor was not commercially available at that time.

D. Safety and Effectiveness Results

1. Study Results

The analysis of safety and effectiveness was based on the 1375 1-month clear patients evaluable at 6 months.

The primary study safety results between 1-6 months for the primary analysis population (1-month clear subjects) in XIENCE 28 are summarized in **Tables 24** and **25**. Additional supportive individual and composite safety and effectiveness endpoints are presented in **Table 26.**

Primary Endpoint (Safety):

The primary endpoint of all death/all MI was met. Non-inferiority of the primary endpoint of all death or all MI (modified ARC) from 1 to 6 months following XIENCE implantation in HBR subjects treated with 1-month DAPT compared to the XIENCE V USA historical control arm was demonstrated after propensity score adjustment (as pre-specified in the XIENCE 28 SAP). Propensity score stratification was performed by an independent statistician.

Based on the number of patients and observed rates in each stratum, the results show a non-inferiority p-value of 0.0005, meeting the pre-specified significance level of 0.025. The 1-6 months propensity score stratified mean rate for all death/all MI in 1-month clear patients was 3.5% in XIENCE 28 vs. 4.3% in the XIENCE V USA historical control (**Table 24**). This demonstrated that the 1-6 months composite rate of all death/ all MI following XIENCE implantation in HBR subjects treated with 1 month of DAPT was non-inferior to the historical control subjects treated with up to 6 months of DAPT.

Major Secondary Endpoint – Bleeding (Effectiveness):

The propensity score stratification method was also used to compare the XIENCE 28 patient population to the XIENCE V USA historical control for the major secondary endpoint of BARC 2-5 bleeding. Based on the number of patients and observed rates in each stratum, the results show a superiority p-value of 0.1888, which did not meet the pre-specified significance level of 0.025. Although the significance level was not met, the 1-6 months propensity score stratified mean rate of BARC 2-5 bleeding in 1-month clear patients was numerically lower in XIENCE 28 as compared to the historical control (4.9% vs 5.9%; **Table 24**).

Table 24. XIENCE 28 Primary Death/MI and Secondary Bleeding Endpoint Results.

	XIENCE 28 (N=1392)	XIENCE V USA (N=1411)	Difference [95% CI]	*p-value
All Death/All MI	3.5%	4.3%	-0.97% [-3.02%, 1.09%]	**0.0005

	XIENCE 28 (N=1392)	XIENCE V USA (N=1411)	Difference [95% CI]	*p-value
BARC 2-5 Bleeding	4.9%	5.9%	-1.07% [-3.45%, 1.31%]	***0.1888

*Stratified Farrington-Manning method is carried out using propensity score stratified data in each imputed dataset, and Rubin's combination rule is applied to integrate the final test results from each imputed dataset.
** The test is carried out with a non-inferiority margin of 2.5% against a one-sided significance level of 0.025.
*** The superiority test was carried out against a one-sided significance level of 0.025.
Note:
- Subjects are only counted once for each type of event in each time period.
- Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators.
- Subjects who are lost to follow-up without any DMR event (death, MI (modified ARC), revascularization) are excluded
- Subjects who are lost to follow-up without any bleeding event (BARC 1-5) are excluded.

In a post-hoc analysis, the propensity score stratification methodology was used to compare BARC 3-5 bleeding rates between XIENCE 28 and the XIENCE V USA historical control. The observed 1-6 months BARC 3-5 bleeding rate was 2.2% in XIENCE 28 subjects as compared to 4.5% in XIENCE V USA HBR subjects after propensity score adjustment.

Other supportive individual and composite safety and effectiveness endpoints between 1 and 6 months are listed in **Table 25**. Most adverse clinical events in the "not clear" population were higher than those in the overall "clear" population for the primary analysis time window (1-6 months). The values provided are without propensity score adjustment.

Table 25. XIENCE 28 Unadjusted Additional Secondary Endpoint Results 1-6 Months

	XIENCE 28 1-Month Clear Subjects (N=1392)	XIENCE 28 1-Month Not Clear Subjects Who Had a 1-Month Visit (N=154)	XIENCE V USA 1-Month Clear Subjects (N=1411)
Safety			
All Death/All MI (modified ARC)	3.3% (46/1380)	8.9% (13/146)	3.2% (45/1399)
All Death	1.7% (23/1380)	3.4% (5/146)	1.9% (27/1399)
Cardiac Death	0.9% (12/1380)	0.7% (1/146)	1.1% (15/1399)
Vascular Death	0.1% (2/1380)	0.0% (0/146)	0.3% (4/1399)
Non-cardiovascular Death	0.7% (9/1380)	2.7% (4/146)	0.6% (8/1399)
All MI (modified ARC)	1.7% (24/1380)	5.5% (8/146)	1.8% (25/1399)
Target Vessel MI (TV-MI, modified ARC)	1.5% (21/1380)	3.4% (5/146)	1.4% (19/1399)
Cardiac Death/All MI (modified ARC)	2.5% (35/1380)	6.2% (9/146)	2.4% (34/1399)
Stent Thrombosis (ARC definite/probable)	0.3% (4/1361)	0.7% (1/141)	0.3% (4/1387)
Major Bleeding (BARC 2-5)	5.3% (72/1362)	5.7% (8/141)	4.3% (60/1380)

	XIENCE 28 1-Month Clear Subjects (N=1392)	XIENCE 28 1-Month Not Clear Subjects Who Had a 1-Month Visit (N=154)	XIENCE V USA 1-Month Clear Subjects (N=1411)
Major Bleeding (BARC 3-5)	2.4% (33/1362)	2.8% (4/141)	3.6% (49/1380)
All Stroke	0.3% (4/1357)	1.4% (2/142)	0.2% (3/1373)
Ischemic Stroke	0.2% (3/1357)	1.4% (2/142)	0.2% (3/1373)
Hemorrhagic Stroke	0.1% (1/1357)	0.0% (0/142)	0.0% (0/1373)
Effectiveness			
Clinically-indicated Target Lesion Revascularization (CI-TLR)	0.7% (10/1380)	1.4% (2/146)	1.4% (20/1399)
Clinically-indicated Target Vessel Revascularization (CI-TVR)	1.0% (14/1380)	1.4% (2/146)	1.7% (24/1399)
Safety and Effectiveness			
Target Lesion Failure (TLF)	2.5% (35/1380)	4.1% (6/146)	3.2% (45/1399)
Target Vessel Failure (TVF)	2.8% (38/1380)	4.8% (7/146)	3.3% (46/1399)

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

2. Results by Subgroups

The following preoperative characteristics were evaluated for potential association with outcomes:

Sex/Gender
Although not powered to evaluate safety or effectiveness of the XIENCE family of stents in gender-specific subgroups, outcomes for male and female subjects from XIENCE 28 are available (**Table 26**).

The composite rate of all death/all MI in the 1-month clear XIENCE 28 subjects between 1-6 months was 3.3% in male subjects and 3.3% in female subjects.

The BARC 2-5 bleeding rate was 5.4% in male subjects and 5.1% in female subjects.

Table 26. XIENCE 28 Unadjusted Primary and Secondary Endpoints By Sex/Gender

	XIENCE 28 1-Month Clear Subjects (N=1392)		XIENCE V USA 1-Month Clear Subjects (N=1411)	
	Male (N=939)	**Female (N=453)**	**Male (N=835)**	**Female (N=576)**
All Death/All MI*	3.3% (31/927)	3.3% (15/453)	3.9% (32/827)	2.3% (13/572)
BARC 2-5 Bleeding**	5.4% (49/915)	5.1% (23/447)	4.1% (33/812)	4.8% (27/568)
All Death	1.6% (15/927)	1.8% (8/453)	2.5% (21/827)	1.0% (6/572)
Cardiac Death	0.9% (8/927)	0.9% (4/453)	1.5% (12/827)	0.5% (3/572)
Vascular Death	0.1% (1/927)	0.2% (1/453)	0.4% (3/827)	0.2% (1/572)
Non-cardiovascular Death	0.6% (6/927)	0.7% (3/453)	0.7% (6/827)	0.3% (2/572)
All MI (modified ARC)	1.7% (16/927)	1.8% (8/453)	1.9% (16/827)	1.6% (9/572)
Target Vessel MI (TV-MI, modified ARC)	1.5% (14/927)	1.5% (7/453)	1.5% (12/827)	1.2% (7/572)
Cardiac Death/All MI (modified ARC)	2.6% (24/927)	2.4% (11/453)	2.9% (24/827)	1.7% (10/572)
Major Bleeding (BARC 3-5)	2.7% (25/915)	1.8% (8/447)	3.2% (26/812)	4.0% (23/568)
All Stroke	0.4% (4/912)	0.0% (0/445)	0.4% (3/807)	0.0% (0/566)
Ischemic Stroke	0.3% (3/912)	0.0% (0/445)	0.4% (3/807)	0.0% (0/566)
Hemorrhagic Stroke	0.1% (1/912)	0.0% (0/445)	0.0% (0/807)	0.0% (0/566)
Clinically-indicated Target Lesion Revascularization (CI-TLR)	0.5% (5/927)	1.1% (5/453)	1.1% (9/827)	1.9% (11/572)
Clinically-indicated Target Vessel Revascularization (CI-TVR)	0.5% (5/927)	2.0% (9/453)	1.5% (12/827)	2.1% (12/572)
Target Lesion Failure (TLF)	2.5% (23/927)	2.6% (12/453)	3.4% (28/827)	3.0% (17/572)
Target Vessel Failure (TVF)	2.5% (23/927)	3.3% (15/453)	3.5% (29/827)	3.0% (17/572)

	XIENCE 28 1-Month Clear Subjects (N=1392)		XIENCE V USA 1-Month Clear Subjects (N=1411)	
	Male (N=939)	**Female (N=453)**	**Male (N=835)**	**Female (N=576)**
Stent Thrombosis (ARC definite/probable)	0.2% (2/915)	0.4% (2/446)	0.4% (3/818)	0.2% (1/569)

Note: Subjects are only counted once for each type of event.

* Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators. Subjects who are lost to follow-up without any DMR event (death, MI (modified ARC), revascularization) are excluded.

**Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators. Subjects who are lost to follow-up without any bleeding event (BARC 1-5) are excluded.

The overall conclusions of the trial regarding the safety of the XIENCE family of stents when used with 1 months of DAPT in patients at high risk of bleeding can be generalized to males and females.

Age

Of the 1392 1-month clear subjects in XIENCE 28, 1251 were ≥65 years old at the time of registration. The rates of all death/all MI and BARC 2-5 bleeding between 1 and 6 months, in subjects age 65 or older were 3.2% and 5.2%, respectively. These rates were comparable to those observed in the overall 1-month clear population.

Race and Ethnicity

Outcomes by race in the 1392 1-month clear subjects from XIENCE 28 are presented in **Table 27**. 807 (58.0%) were white, while 164 (11.8%) subjects were non-white (identified as American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, or Other). Because XIENCE 28 was partially conducted in regions that do not permit the collection of racial demographic data, race data is not available for approximately 30% of subjects. The available race and ethnicity information is too limited to comment on any potential associations.

Table 27. XIENCE 28 Unadjusted Primary and Secondary Endpoints By Race as Compared to XIENCE V

	XIENCE 28 1-Month Clear Subjects (N=1392)						XIENCE V USA 1-Month Clear Subjects (N=1411)					
	White (N=807)	**American Indian or Alaska Native (N=2)**	**Asian (N=126)**	**Black or African American (N=36)**	**Hispanic or Latino (N=138)**	**Native Hawaiian or Pacific Islander (N=0)**	**White (N=1224)**	**American Indian or Alaska Native (N=11)**	**Asian (N=19)**	**Black or African American (N=115)**	**Hispanic or Latino (N=42)**	**Native Hawaiian or Pacific Islander (N=4)**
***All Death/All MI**	2.9% (23/802)	0.0% (0/2)	4.0% (5/125)	5.7% (2/35)	3.6% (5/138)	NA	3.3% (40/1213)	10.0% (1/10)	0.0% (0/19)	1.7% (2/115)	4.9% (2/41)	0.0% (0/4)

	XIENCE 28 1-Month Clear Subjects (N=1392)						XIENCE V USA 1-Month Clear Subjects (N=1411)					
	White (N=807)	**American Indian or Alaska Native (N=2)**	**Asian (N=126)**	**Black or African American (N=36)**	**Hispanic or Latino (N=138)**	**Native Hawaiian or Pacific Islander (N=0)**	**White (N=1224)**	**American Indian or Alaska Native (N=11)**	**Asian (N=19)**	**Black or African American (N=115)**	**Hispanic or Latino (N=42)**	**Native Hawaiian or Pacific Islander (N=4)**
****BARC 2-5 bleeding**	5.3% (42/795)	0.0% (0/2)	8.1% (10/124)	11.8% (4/34)	7.4% (10/136)	NA	4.7% (56/1196)	0.0% (0/9)	0.0% (0/19)	2.6% (3/114)	2.4% (1/41)	0.0% (0/4)
All Death	1.2% (10/802)	0.0% (0/2)	1.6% (2/125)	5.7% (2/35)	1.4% (2/138)	NA	2.1% (25/1213)	10.0% (1/10)	0.0% (0/19)	0.9% (1/115)	0.0% (0/41)	0.0% (0/4)
Cardiac Death	0.6% (5/802)	0.0% (0/2)	0.0% (0/125)	2.9% (1/35)	1.4% (2/138)	NA	1.1% (13/1213)	10.0% (1/10)	0.0% (0/19)	0.9% (1/115)	0.0% (0/41)	0.0% (0/4)
Vascular Death	0.1% (1/802)	0.0% (0/2)	0.8% (1/125)	0.0% (0/35)	0.0% (0/138)	NA	0.3% (4/1213)	0.0% (0/10)	0.0% (0/19)	0.0% (0/115)	0.0% (0/41)	0.0% (0/4)
Non-cardiovascular Death	0.5% (4/802)	0.0% (0/2)	0.8% (1/125)	2.9% (1/35)	0.0% (0/138)	NA	0.7% (8/1213)	0.0% (0/10)	0.0% (0/19)	0.0% (0/115)	0.0% (0/41)	0.0% (0/4)
All MI (modified ARC)	1.6% (13/802)	0.0% (0/2)	2.4% (3/125)	2.9% (1/35)	2.2% (3/138)	NA	1.7% (21/1213)	0.0% (0/10)	0.0% (0/19)	1.7% (2/115)	4.9% (2/41)	0.0% (0/4)
Target Vessel MI (TV-MI, modified ARC)	1.5% (12/802)	0.0% (0/2)	1.6% (2/125)	2.9% (1/35)	2.2% (3/138)	NA	1.2% (15/1213)	0.0% (0/10)	0.0% (0/19)	1.7% (2/115)	4.9% (2/41)	0.0% (0/4)
Cardiac Death/All MI (modified ARC)	2.2% (18/802)	0.0% (0/2)	2.4% (3/125)	2.9% (1/35)	3.6% (5/138)	NA	2.4% (29/1213)	10.0% (1/10)	0.0% (0/19)	1.7% (2/115)	4.9% (2/41)	0.0% (0/4)
Major Bleeding (BARC 3-5)	2.4% (19/795)	0.0% (0/2)	6.5% (8/124)	0.0% (0/34)	2.9% (4/136)	NA	3.8% (45/1196)	0.0% (0/9)	0.0% (0/19)	2.6% (3/114)	2.4% (1/41)	0.0% (0/4)
All Stroke	0.3% (2/792)	0.0% (0/2)	0.8% (1/123)	0.0% (0/33)	0.7% (1/136)	NA	0.3% (3/1189)	0.0% (0/9)	0.0% (0/19)	0.0% (0/114)	0.0% (0/41)	0.0% (0/4)
Ischemic Stroke	0.1% (1/792)	0.0% (0/2)	0.8% (1/123)	0.0% (0/33)	0.7% (1/136)	NA	0.3% (3/1189)	0.0% (0/9)	0.0% (0/19)	0.0% (0/114)	0.0% (0/41)	0.0% (0/4)
Hemorrhagic Stroke	0.1% (1/792)	0.0% (0/2)	0.0% (0/123)	0.0% (0/33)	0.0% (0/136)	NA	0.0% (0/1189)	0.0% (0/9)	0.0% (0/19)	0.0% (0/114)	0.0% (0/41)	0.0% (0/4)
Clinically-indicated Target Lesion Revascularization (CI-TLR)	0.6% (5/802)	0.0% (0/2)	0.8% (1/125)	2.9% (1/35)	1.4% (2/138)	NA	1.5% (18/1213)	0.0% (0/10)	0.0% (0/19)	0.9% (1/115)	2.4% (1/41)	0.0% (0/4)
Clinically-indicated Target Vessel Revascularization (CI-TVR)	0.7% (6/802)	0.0% (0/2)	0.8% (1/125)	2.9% (1/35)	2.9% (4/138)	NA	1.8% (22/1213)	0.0% (0/10)	0.0% (0/19)	0.9% (1/115)	2.4% (1/41)	0.0% (0/4)
Target Lesion Failure (TLF)	2.4% (19/802)	0.0% (0/2)	1.6% (2/125)	2.9% (1/35)	4.3% (6/138)	NA	3.2% (39/1213)	10.0% (1/10)	0.0% (0/19)	1.7% (2/115)	7.3% (3/41)	0.0% (0/4)
Target Vessel Failure (TVF)	2.5% (20/802)	0.0% (0/2)	1.6% (2/125)	2.9% (1/35)	5.1% (7/138)	NA	3.3% (40/1213)	10.0% (1/10)	0.0% (0/19)	1.7% (2/115)	7.3% (3/41)	0.0% (0/4)

	XIENCE 28 1-Month Clear Subjects (N=1392)						XIENCE V USA 1-Month Clear Subjects (N=1411)					
	White (N=807)	**American Indian or Alaska Native (N=2)**	**Asian (N=126)**	**Black or African American (N=36)**	**Hispanic or Latino (N=138)**	**Native Hawaiian or Pacific Islander (N=0)**	**White (N=1224)**	**American Indian or Alaska Native (N=11)**	**Asian (N=19)**	**Black or African American (N=115)**	**Hispanic or Latino (N=42)**	**Native Hawaiian or Pacific Islander (N=4)**
Stent Thrombosis (ARC definite/probable)	0.3% (2/795)	0.0% (0/2)	0.0% (0/123)	0.0% (0/33)	0.7% (1/137)	NA	0.3% (4/1201)	0.0% (0/10)	0.0% (0/19)	0.0% (0/115)	0.0% (0/41)	0.0% (0/4)

Note: Subjects are only counted once for each type of event in each time period.
Note: Subjects who are on or beyond the target day of follow-up visit (i.e., 180 days) at the time of data extraction are included in the denominators
NA: not applicable since no Native Hawaiian or Pacific Islander were enrolled in XIENCE 28.
* Denominator includes subjects with the DMR (Death, ARC MI and Revascularization) or subjects without the DMR who had 6m visit or had 180 days in the study (i.e., without early termination) Subjects who are lost to follow-up without any DMR event (death, MI (modified ARC), revascularization) are excluded.
** Denominator includes subjects with the major bleeding (BARC 2-5) or subjects without the major bleeding who had 6m visit or had 180 days in the study (i.e., without early termination)

3. Poolability Analyses

As XIENCE 28 combined subjects from Europe, Asia, Canada, and the US, poolability analyses for multiple geography effect and multiple center effect were pre-specified in the study SAP and performed. **Table 28** shows the results of the multiple geography analysis (p = 0.7602 by Fisher Exact test against a significance level of 0.15). No poolability issue was found between XIENCE 28 USA and XIENCE 28 Global. Similarly, results for the multiple center effect analysis (p = 0.3631 by Monte Carlo Estimates exact test against an alpha level of 0.05) shows no issue of poolability between investigational sites.

Table 28. XIENCE Evaluation of Poolability of Primary Endpoint Across Multiple Geographic Regions – Per Subject Analysis

	Percent of Subjects with Primary Endpoint Events (N=1392)	**p-value***
US	3.1% (17/552)	0.7602
OUS	3.5% (29/828)	
Total	3.3% (46/1380)	

*P-value is obtained from the Fisher Exact test. P-value to be compared with a significance level of 0.15.
Note: Subjects who have completed the required amount of follow-up at the time of data extraction are included in the denominators. Subjects who are lost to follow-up without any DMR event (death, MI (modified ARC), revascularization) are excluded
Note: XIENCE 28 USA Canadian sites are included in US group.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

(3) Financial Disclosure for XIENCE 90 and XIENCE 28

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 XIENCE 90 study included 704 investigators, none of which were full-time or part-time employees of the sponsor and 14 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: 0; none
- Significant payment of other sorts: 12
- Proprietary interest in the product tested held by the investigator: 1
- Significant equity interest held by investigator in sponsor of covered study: 1

The XIENCE 28 USA Study included 290 investigators, none of which were full-time or part-time employees of the sponsor and 5 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: 0; none
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: 0; none
- Significant equity interest held by investigator in sponsor of covered study: 1

The XIENCE 28 Global Study included 262 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f).

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplementary Safety and Effectiveness Analysis Using the ARC HBR Definition
The consensus definition (ARC) of high bleeding risk in patients undergoing PCI was published in 2019, after the initiation of the XIENCE 90 and XIENCE 28 studies.

Therefore, some of the variables needed to define HBR per the ARC criteria were not collected in XIENCE 90, XIENCE 28, or XIENCE V USA, the historical control. For XIENCE 28 Global, a case report form (CRF) was introduced mid-way through the trial to collect the additional variables needed. In XIENCE 28 USA, the additional variables needed were included in the CRF close to the start of the trial. Based on available data, 74.4% of the 3-month clear subjects in XIENCE 90 and 77.2% of the 1-month clear subjects in XIENCE 28 met the ARC HBR criteria. The same trends were observed for the key primary and secondary trial endpoints (all death/all MI, stent thrombosis, and BARC 3-5 bleeding) whether the HBR population was defined using the ARC HBR criteria or the HBR criteria of the XIENCE 90 and XIENCE 28 trials.

Supplementary Analysis of XIENCE 28 vs XIENCE 90

A pre-specified descriptive comparison between XIENCE 28 (1-month DAPT) and XIENCE 90 (3-month DAPT) was performed for definite/probable stent thrombosis, death/MI, and BARC 2-5/3-5 bleeding for different time periods. The purpose of this sensitivity analysis was to understand whether there was a difference between 1-month DAPT vs. 3-month DAPT for HBR patients in terms of clinical outcomes. To perform this comparison, programming was used to derive the "1-month clear" population from XIENCE 90. It should be noted that the "1-month clear" population from XIENCE 90 was on DAPT from 0-3 months, whereas the "1-month clear" population from XIENCE 28 was on DAPT from 0-1 month post-procedure.

For all death or all MI, 1-month DAPT compared to 3-month DAPT resulted in numerically lower rates between 31 to 90 days (1.5% vs. 1.7%), 31-180 days (3.3% vs. 4.1%), and 91-180 days (1.9% vs. 2.5%).

For BARC 2-5 bleeding, 1-month DAPT showed numerically lower rates between 31 to 90 days (2.9% vs. 4.4%) and 31-180 days (5.3% vs. 6.8%), but a numerically slightly higher rate for 91-180 days (2.8% vs. 2.6%). Similar to BARC 2-5, for BARC 3-5 bleeding, 1-month DAPT showed numerically lower rates between 31 to 90 days (1.2% vs. 2.1%) and 31-180 days (2.4% vs. 3.1%), but a numerically higher rate for 91-180 days (1.5% vs. 1.0%).

Stent thrombosis (ARC definite/probable) rates were very low for 1-month or 3-month DAPT at any analyzed time window.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Cardiovascular Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The XIENCE 90 and XIENCE 28 trials evaluated the safety and effectiveness of the XIENCE family of stents as compared to a historical control with the use of 3-months or 1-month of DAPT in non-complex high bleeding risk subjects. The studies met their primary endpoints of a composite of all death/all myocardial infarction from three months to one year (XIENCE 90) or one month to six months (XIENCE 28) in HBR patients treated with 1-3 months of DAPT and support the safety and effectiveness of the XIENCE family of stents.

A. Effectiveness Conclusion

The results from the XIENCE 90 and XIENCE 28 trials demonstrated that, in high bleeding risk patients judged by enrolling physicians to have risk of bleeding that outweighs the benefits of longer DAPT, there was no increase in ischemic risks when the XIENCE family of stents was used with shorter durations of DAPT (3 months or 1 month), as compared to duration of up to 12 months. Although the benefit of shorter duration of DAPT was not demonstrated for BARC 2-5 bleeding events (superiority was not met in either trial), BARC 2-5 bleeding rates were numerically lower with shorter DAPT durations. Additionally, post hoc analyses demonstrated numerical reductions in the more severe bleeds (BARC 3-5) in patients on short DAPT, as compared to patients on longer DAPT durations of 6 or 12 months post-PCI.

B. Safety Conclusions

The risks associated with use of the XIENCE family of stents have been evaluated in the clinical studies discussed above along with non-clinical laboratory, animal studies and clinical studies leveraged from the original PMA approval and associated supplements. The biocompatibility, in vivo pharmacokinetics and in vivo performance characteristics of the XIENCE family of stents provide a reasonable assurance of safety and acceptability for clinical use.

The XIENCE 90 and XIENCE 28 trials support the safety of the XIENCE family of stents when used with shorter DAPT duration (as short as 28 days) post-PCI for the treatment of patients at high bleeding risk.

As shown above, no increased risk of ischemic events has been identified in patients treated with XIENCE and receiving short durations of DAPT post-PCI:

- Both XIENCE 90 and XIENCE 28 met their primary endpoint of all death or all MI, demonstrating non-inferiority to historical controls with longer DAPT duration of 12 months (XIENCE 90) or 6 months (XIENCE 28). The 3-12 month death/MI rate in XIENCE 90 was 5.4% for both the 3-month and 12-month DAPT groups ($p_{\text{non-inferiority}} = 0.0063$). In XIENCE 28, the 1-6 month death/MI rate was 3.5% in the 1-month DAPT group, compared to 4.3% in the 6-month DAPT control group ($p_{\text{non-inferiority}} = 0.0005$).

- In XIENCE 90, the 3-12 month ARC definite/probable stent thrombosis rate was 0.2% in patients treated with 3 months of DAPT (upper limit of two-sided 95% confidence interval was 0.63% which was significantly less than the performance goal of 1.2%).

- In XIENCE 28, the 1-6 month ARC definite/probable stent thrombosis rate was 0.3% in both the 1-month DAPT group and the 6-month DAPT control group.

C. Benefit-Risk Determination

The probable benefits of the XIENCE stent when used with shorter DAPT durations (3 months or 1 month) in HBR patients are based on the data from the XIENCE 90 and XIENCE 28 trials. A numerical decrease in the rates of BARC 2-5 and BARC 3-5 bleeding was observed between 3-12 months (XIENCE 90) and between 1-6 months (XIENCE 28) in patients treated with short DAPT duration, as compared to patients treated with longer DAPT durations (12-month DAPT in XIENCE 90; 6-month DAPT in XIENCE 28).

The probable risks of the device are also based on the XIENCE 90 and XIENCE 28 trials. Data from these trials demonstrated that there was no increased risk of ischemic events (death or MI) in patients treated with shorter DAPT duration, as compared to patients treated with longer DAPT duration of up to 12 months. Additionally, the ARC definite/probable stent thrombosis rate was low in patients treated with shorter DAPT duration, and comparable to rates observed in patients treated with longer DAPT duration.

Additional factors to be considered in determining probable risks and benefits for the XIENCE stent include characterization of the disease, availability of alternative treatments, quality of the study design and conduct, robustness of analysis of study results, and risk mitigations. Coronary artery disease (CAD) can be accompanied by symptomatic chest pain or silent ischemia which affects patients' quality of life. CAD is treatable, but if left untreated, the condition can progress to further stenosis within the arteries, increased symptoms, and the need for revascularization. Available treatments for CAD include medical therapy, percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. When treatment for coronary artery disease beyond medications and lifestyle changes is warranted, patients often choose stent deployment over surgical revascularization due to shorter recovery times and the less invasive nature of PCI. The risks associated with use of drug eluting stents are already well established, and in comparison to medical therapy, PCI has been shown to reduce the incidence of angina and increase quality of life. Patient tolerance and clinical outcomes of the XIENCE family of stents in XIENCE 90 and XIENCE 28 are in line with expectations.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information provided above, the data support that for the improvement of coronary artery luminal diameter in patients, *including those at high risk for bleeding* and those with diabetes mellitus, 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, including the treatment of *de novo* chronic total coronary occlusions, the probable benefits outweigh the probable risks.

D. 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. Data from the XIENCE 90 and XIENCE 28 studies support the safety and effectiveness of the XIENCE family of stents for the treatment of patients at high risk of bleeding.

XIV. CDRH DECISION

CDRH issued an approval order on 6/25/2021.

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

XV. 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.