SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stent, Coronary

Device Trade Name: Orsiro Sirolimus Eluting Coronary Stent System (Orsiro Stent System)

Device Procode: NIQ

Applicant's Name and Address: BIOTRONIK, Inc.
6024 Jean Road
Lake Oswego, OR 97035

Date(s) of Panel Recommendation: N/A

Premarket Approval Application (PMA) Number: P170030

Date of FDA Notice of Approval: February 22, 2019

II. INDICATIONS FOR USE

Orsiro is indicated for improving coronary luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, non-ST elevation myocardial infarction or documented silent ischemia due to atherosclerotic lesions in the native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm and a lesion length of $\leq$ 36 mm.

III. CONTRAINDICATIONS

Orsiro is contraindicated for use in patients with:

- A known hypersensitivity or allergy to the stent and/or stent coating materials such as amorphous silicon carbide, PLLA polymer, L-605 cobalt chromium alloy (including the major elements cobalt, chromium, tungsten and nickel), sirolimus or its derivatives.

Coronary artery stenting is contraindicated for use in the following patients:

- Patients who have contraindications for antiplatelet and/or anticoagulation therapy.
- Patients who are judged to have a lesion that would be likely to prevent complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Orsiro Stent System labeling.

V. DEVICE DESCRIPTION

A. Device Component Description

The Orsiro Stent System consists of a balloon-expandable drug-eluting stent pre-mounted on a fast-exchange delivery system (Figure 1). The stent is intended as a permanent implant. It is made from a cobalt chromium alloy (L-605), covered with a thin layer of amorphous silicon carbide (proBIO™), and further coated with BIOlute™, a bioabsorbable drug matrix consisting of a drug substance (i.e., sirolimus) and a polymer (i.e., PLLA).

The delivery system is a fast-exchange percutaneous transluminal coronary angioplasty (PTCA) catheter with a usable length of 140 cm and has two radiopaque markers to facilitate in the placement of the stent during fluoroscopy. Orsiro is compatible with 0.014 inch (0.36 mm) guidewires and guiding catheters with a minimum inner diameter of 0.056 inch (1.42 mm). The stent is crimped on various sizes of delivery catheter balloons, which range from 2.25 mm to 4.0 mm.

Figure 1: Orsiro Sirolimus Eluting Coronary Stent System

There are two different stent designs: small (2.25 - 3.0 mm in diameter) and medium (3.5 - 4.0 mm in diameter). See Table 1 below.

Table 1: Stent Parameters

			Stent Length (mm)								
Stent Design	**Maximum Labeled Diameter for Post-dilation (mm)**	**Nominal Stent Diameter (mm)**	9	13	15	18	22	26	30	35	40
Small	Ø max= 3.5 mm	Ø2.25	✓	✓	✓	✓	✓	✓	✓		
		Ø2.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
		Ø2.75	✓	✓	✓	✓	✓	✓	✓	✓	✓
		Ø3.0	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medium	Ø max= 4.5 mm	Ø3.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
		Ø4.0	✓	✓	✓	✓	✓	✓	✓	✓	✓

B. Drug Component Description

Orsiro is circumferentially coated with a bioabsorbable coating. The Orsiro stent drug matrix is composed of a drug substance (sirolimus) and a bioabsorbable polymer carrier (poly-L-lactide (PLLA)).

1. Active Ingredient: Sirolimus

The active pharmaceutical ingredient utilized in Orsiro is sirolimus. Orsiro stents have a drug load of 1.4 μg/mm^2 of stent surface.

The sirolimus chemical name is:
23,27-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine, rapamycin deriv.; (-)-Rapamycin

The molecular formula of sirolimus is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2 g/mol. The chemical structure of sirolimus is shown in Figure 2.

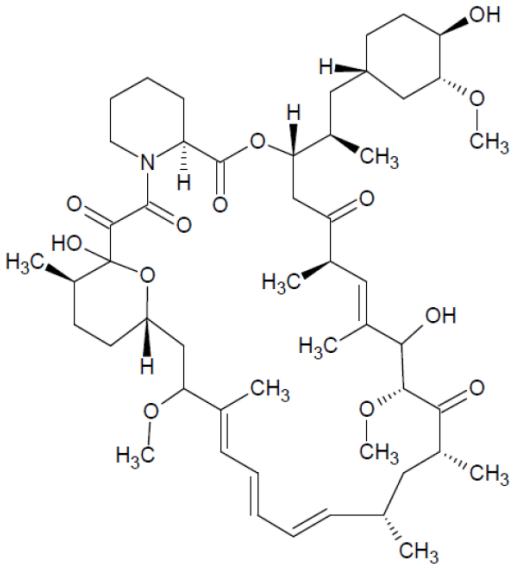

Figure 2: Chemical Structure of Sirolimus

The total nominal drug load of sirolimus per stent length/design is shown in Table 2.

Table 2: Total Nominal Drug Load of Sirolimus per Stent Length/Design

Stent design	Stent length (mm)	Total drug load (µg)
Small	9	55
Medium		70
Small	13	80
Medium		95
Small	15	93
Medium		113
Small	18	109
Medium		131
Small	22	134
Medium		162
Small	26	159
Medium		193
Small	30	184
Medium		224
Small	35	213
Medium		261
Small	40	247
Medium		298

2. **Inactive Ingredient: poly-L-lactide (PLLA)**
The PLLA is a high molecular weight bioabsorbable polymer, which acts as a drug carrier and provides a controlled release of sirolimus from the stent. The chemical name of PLLA is *S*,*S*-1,4-Dioxane-2,5-dione, 3,6-dimethyl-, *cis*-homopolymer and the chemical structure of the polymer is shown in Figure 3.

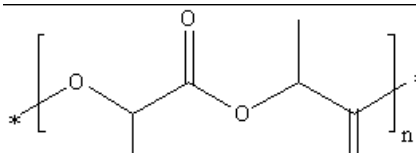

Figure 3: Chemical Structure of PLLA

C. Mechanism of Action

Sirolimus is a drug with potent anti-proliferative, anti-inflammatory and immunosuppressive effects. It acts by binding to the cytosolic receptor FK506-binding-protein-12 (FKBP-12).

The complex that is formed between sirolimus and FKBP-12 inhibits the activation of mammalian target of rapamycin (mTOR), which in turn causes cell cycle arrest (progression from phase G1 to S). In detail, the sirolimus-FKBP-12-mTOR complex inhibits the 70-kD S6 protein kinase p70S6K (the eukaryotic initiation factor binding protein eIF-4E-BP) and cell cycle progression through upregulation of p27kip1 (a cyclin dependent kinase inhibitor), which in turn inhibits the cell cycle controlling cyclin-dependent kinases (CDK) such as the CDK4 and CDK2.

A typical target cell is the activated T-lymphocyte, which undergoes G1 to S phase progression in response to antigenic and cytokine T-cell growth-promoting stimulation (Interleukin IL-2, IL-4, IL-7 and IL-15). In parallel, sirolimus inhibits antibody production.

Other target cells are the smooth muscle cells (SMC) and the endothelial cells. Sirolimus inhibits the proliferation and the migration of SMCs and shows an antiproliferative effect on endothelial cells. Sirolimus also inhibits several phases of the restenosis cascade such as inflammation, neointimal hyperplasia formation, total protein and collagen synthesis.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are multiple alternative options available to treat coronary artery disease, which may include: exercise, diet, smoking cessation, drug therapy, percutaneous coronary interventions (such as angioplasty and placement of bare metal stents, drug eluting stents, etc.), and coronary artery bypass graft surgery (CABG). A patient should fully discuss available alternatives with his/her physician to determine which method(s) are appropriate to best meet their clinical needs and lifestyle.

VII. MARKETING HISTORY

The Orsiro Stent System has been market released outside the United States (OUS) since 2011 with more than 1.5 million units sold worldwide through the end of 2018. In this time period, 1,204 complaints have been received resulting in an overall complaint rate of 0.077%. A list of countries where the Orsiro Stent System is distributed is provided in Table 3.

Table 3: List of Countries Where Orsiro Stent System is Distributed

Australia	Sri Lanka	Lebanon	Colombia
Bangladesh	Taiwan	Macedonia	Cuba
Hong Kong	Thailand	Montenegro	Dominican Republic
India	Vietnam	Russia	Guatemala
Indonesia	Japan	Saudi Arabia	Mexico
Malaysia	Bosnia and Herzegovina	Serbia	Panama
Myanmar	Egypt	Tajikistan	Paraguay
New Zealand	Iran	Turkey	Peru
Pakistan	Israel	Turkmenistan	Venezuela
Philippines	Jordan	Uzbekistan	Morocco
Singapore	Kazakhstan	Argentina	France
South Korea	Kyrgyzstan	Brazil	Switzerland
Germany	Spain	Netherlands	Italy
Poland	Belgium	Czech Republic	Austria
Bulgaria	Croatia	Denmark	Estonia
Finland	United Kingdom	Greece	Hungary
Cyprus	Latvia	Portugal	Romania
Slovakia	Sweden	Slovenia	Syria
Costa Rica			

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Orsiro Stent System. Adverse events (in alphabetical order) which may be associated with coronary stent use in native coronary arteries include, but are not limited to:

- Abrupt closure of coronary artery or stent
- Access site bleeding or hemorrhage
- Access site hematoma, pain
- Acute pulmonary edema
- Allergic reactions to contrast media, antiplatelets, anticoagulants, amorphous silicon carbide, L-605 cobalt chromium alloy, PLLA polymer matrix, sirolimus or sirolimus derivatives
- Aneurysm formation
- Angina
- Arteriovenous fistula formation
- Arrhythmias, including atrial fibrillation, bradycardia, palpitations, ventricular fibrillation, ventricular tachycardia
- Cardiac perforation
- Cardiac tamponade
- Cardiogenic shock
- Congestive heart failure
- Coronary artery rupture or spasm
- Death
- Delivery system balloon rupture or pinhole, inflation or deflation difficulties
- Dissection
- Distal embolization (air, tissue debris and thrombus)
- Embolization of catheter material
- Emergency cardiac surgery
- Failure to deliver stent to intended site
- Femoral nerve injury
- Hemorrhage requiring transfusion or other treatment
- Hypotension/hypertension
- Inadequate apposition or compression of stent/s
- Infection and sepsis
- Myocardial infarction (MI) or ischemia
- Perforation or dissection of coronary artery or aorta
- Pericardial effusion
- Peripheral ischemia
- Peripheral nerve injury
- Permanent (stroke) or reversible (TIA) neurologic event
- Pseudoaneurysm
- Renal failure
- Respiratory insufficiency or failure
- Restenosis of treated artery (greater than 50% of obstruction)

- Restenosis, thrombosis or occlusion of vessel
- Retroperitoneal hematoma
- Stent collapse
- Stent deformation
- Stent dislodgement from the delivery system
- Stent embolization
- Stent fracture
- Stent migration
- Stent misplacement
- Stent thrombosis or occlusion
- Vasospasm
- Vessel dissection or perforation
- Withdrawal difficulties

Potential adverse events related to oral administration of sirolimus include, but are not limited to:

- Abnormal liver function tests
- Anemia
- Arthralgia
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity (including anaphylactic/anaphylactoid type reactions)
- Hypertriglyceridemia
- Hypokalemia
- Infections
- Interstitial lung disease
- Thrombocytopenia
- Leukopenia
- Lymphoma and other malignancies

There may be other potential adverse events that are unforeseen at this time. For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. In Vitro Bench Testing

In vitro bench testing was performed to assess the functional characteristics of the Orsiro Stent System. Testing was conducted according to the guidelines provided in *the Food and Drug Administration (FDA) Guidance for Industry and FDA Staff - Non-clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* (April 18, 2010) and *Coronary Drug-Eluting Stents – Non-clinical and Clinical Studies – Draft Guidance for Industry and Food and Drug Administration Staff* (March 26, 2008).

Additionally, testing followed updated guidelines provided in *Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems - Guidance for Industry and Food and Drug Administration Staff* (August 18, 2015).

Table 4 below summarizes the engineering testing performed on the Orsiro Stent System. The test results are supportive of the device safety and effectiveness.

Table 4: Non-Clinical Engineering Tests of Stent and Delivery System

Test Performed	Test Purpose	Acceptance Criteria	Result
Material Identification & Characterization			
Identification of Delivery System Materials	To identify and list all components and their respective materials used in the construction of the delivery system.	All materials need to be identified.	Pass
Identification of Stent Materials	To identify and list all materials used in the construction of the stent body.	All materials need to be identified.	Pass
Characterization of Stent Raw Material	Characterization of the bare metal stent material according to raw material specification.	Characterization only.	Pass
Identification of DES-coating Materials	To identify and list all materials used for the a-SiC:H coating and BIOlute coating.	All materials need to be identified.	Pass
Characterization of Polymer (PLLA)	Characterization of the PLLA according to raw material specification extended by testing for elemental impurities according to ICH Q3D.	Characterization only.	Pass
Characterization of Drug Substance	Characterization of the sirolimus according to raw material specification extended by testing for elemental impurities according to ICH Q3D.	Characterization only.	Pass
Characterization of Drug Substance (manufacturing process changed)	Characterization of the sirolimus following change to manufacturing process (upscale of batch size) according to raw material specification extended by testing for elemental impurities according to ICH Q3D.	Characterization only.	Pass
Characterization of Solvents	Characterization of the solvents used in manufacturing according to raw material specification.	Characterization only.	Pass
Identification of Packaging Materials & Transfer of Packaging Validation	To identify the design and all materials used for the packaging.	All materials need to be identified.	Pass
Characterization of butylated hydroxytoluene (BHT)	Characterization of the BHT according to raw material specification extended by testing for elemental impurities according to ICH Q3D.	Characterization only.	Pass

Test Performed	Test Purpose	Acceptance Criteria	Result
Surface Characterization	Characterization of the stent surface and a-SiC:H coating.	• Homogeneity of a-SiC:H coating at different surface positions of stent. • Characterization of chemical composition of a-SiC:H coating.	Pass
Stent Corrosion Resistance	To determine resistance to galvanic and pitting corrosion potential.	• Demonstrate sufficient resistance to galvanic corrosion by a calculated penetration depth ≤ 0.001 mm/year. • Demonstrate sufficient resistance to pitting corrosion as determined by ASTM F2129.	Pass
Stent Dimensional and Functional Attributes			
Stent Dimensional Verification – Unexpanded Stent (Bare stent)	To inspect and measure the stent body dimensions before placement onto the delivery system.	Must meet specifications for strut dimensions.	Pass
Percent Surface Area of the Stent (Bare tent)	To determine the surface coverage of the bare stent in the vessel. Calculation has been performed for all stent sizes.	Stent to artery ratio at NP for all sizes: ≥11%.	Pass
Percent Surface Area of the Stent (Polymer/Drug coated)	To determine the surface coverage of the Polymer/Drug coated stent in the vessel. Calculation has been performed for all stent sizes.	Covered stent to artery ratio at NP for all sizes: ≥12%.	
Foreshortening	To determine the foreshortening of the stent.	Expansion to NP: ≤5%.	Pass
Recoil for Balloon Expandable Stents	To determine the amount of elastic recoil after deployment to determine the diameter of the stent in its deployed state.	Elastic Recoil: ≤ 7% after deployment to NP.	Pass
Stent Integrity	To determine the ability of the stent surface/coating to resist damage due to loading, tracking, and deployment.	Stent Coating Integrity: no flaking, delamination or other defects are permitted, according to ASTM F2743-11.	Pass
Radial Stiffness & Radial Strength	To determine the load/deformation characteristics of the stent while a radial load was applied.	Characterization only.	Pass
Stress / Strain and Fatigue Analysis (Overlapped)	To determine the stent durability due to worst case physiological loads and configuration by means of a Finite Element Analysis. Calculation of safety factor (SF).	The fatigue safety factor shall be greater or equal than one (≥1).	Pass
Accelerated Durability Testing	To determine the long-term integrity of the stent under cyclical loading conditions in an overlapping and bent configuration.	No failure due to fatigue after 10 years of simulated cyclical loading.	Pass

Test Performed	Test Purpose	Acceptance Criteria	Result
Magnetic Resonance Imaging (MRI) Safety and Compatibility	To determine the effect of Magnetic Resonance on the position and temperature of the Orsiro stent. Also to determine the extent of image artifact during MRI.	• The conditions in which the device can be used safely in 1.5 T and 3.0 T systems must be defined; • Displacement force and torque: ASTM F2052 – 06; • Image Artifact: Characterization only; • RF Heating: CEM43 (≤6°C for 15 minutes).	Pass
Radiopacity	To determine X-ray visibility (Bare Stent & Delivery System).	X-ray density shall be comparable to commercially available control devices of similar size.	Pass
Delivery System Dimensional and Functional Attributes			
Dimensional Verification	To inspect the physical and dimensional properties of the Stent System.	• Usable length 140 cm; • Shaft markers: brachial marker: 920 mm; femoral marker: 1020 mm; • Compatible with 0.014 inches (0.36 mm) guidewire; compatible with 0.056 inches (1.42 mm) guide catheter; • x-ray markers beyond the stent at each end < 0.18 mm (Diameter 2.25 to 3.00 mm), < 0.20 mm; • Catheter shaft outer diameter: Proximal (Hypotube): 2.0 F (0.67 mm), Distal for device sizes of 2.25 mm – 3.5 mm: 2.7F (0.91 mm), Distal for device size of 4.00 mm: 3.0F (0.99 mm); • Maximum Crossing Profile: For Stent Length 9 – 30 mm Ø 2.25 mm: 1.02 mm Ø 2.50 mm: 1.02 mm Ø 2.75 mm: 1.04 mm Ø 3.00 mm: 1.05 mm Ø 3.50 mm: 1.18 mm Ø 4.00 mm: 1.18 mm For Stent Length 35 – 40 mm Ø 2.25 mm: 1.02 mm Ø 2.50 mm: 1.02 mm Ø 2.75 mm: 1.04 mm Ø 3.00 mm: 1.08 mm Ø 3.50 mm: 1.19 mm Ø 4.00 mm: 1.20 mm	Pass

Test Performed	Test Purpose	Acceptance Criteria	Result
Delivery, Deployment and Retraction	To evaluate the performance of the stent system and if the delivery system can reliably deliver the stent to the intended location.	The delivery system should allow a safe and reliable delivery of the stent to the intended location according to the IFU and the stent should not be adversely affected by the guiding catheter, both during deployment and withdrawal.	Pass
Deflated Balloon Profile	To evaluate the largest deflated balloon diameter after stent deployment.	Deflated balloon system can be safely withdrawn into the recommended guide catheter size.	Pass
Rated Burst Pressure (RBP)	To determine the rated burst pressure (RBP) of the balloon when used with the stent.	RBP for all sizes ≥ 16.0 atm. with 95% confidence, at least 99.9% of balloons will not experience loss of integrity at or below the rated burst pressure.	Pass
Balloon Fatigue	To determine the ability of the balloon to withstand repeated inflation/ deflation cycles.	The balloon must resist 10 pressurization cycles to RBP. With 95% confidence, 90% of the catheters have no deformation or loss of pressure due to failure of the balloon, the shaft, the proximal or distal welding.	Pass
Balloon Compliance	To determine the relationship between the stent diameter and the balloon inflation pressure.	The stent sizing results must verify that the stent systems meet the labeled compliance values.	Pass
Balloon Inflation / Deflation Time	To determine the balloon inflation and deflation time.	Meet product specification across the range of stent diameters and lengths.	Pass
Catheter Bond Strength and Tip Pull Test	To determine the bond strength of the joint(s) and/or fixed connections, including the distal tip of the delivery system.	Catheter Bond Strength and Tip Pull Strength must meet the requirements according to ISO 10555-1.	Pass
Flexibility and Kink Test	To evaluate the flexibility and resistance to kink of the stent system.	The system shall neither kink nor the function be compromised.	Pass
Torque Strength	To demonstrate that the delivery system can withstand torsional forces that are typical of clinical use.	The function of the rotated system shall not be compromised after 1 rotation.	Pass
Coating Integrity	To evaluate the ability of catheters (delivery systems, balloon catheters) with coating to resist damage due to loading, tracking, deployment and delivery system withdrawal.	Characterization only.	Pass
Stent securement for unsheathed stents	To determine the force that will dislodge the stent from the delivery system after conditioning.	Stent retention force after pre-conditioning in distal and proximal direction meets the product specification.	Pass

B. Drug Coating Characterization Testing

The drug coating characterization testing conducted on the Orsiro stent coating is summarized in Table 5.

Table 5: Drug Coating Characterization Testing

Test Performed	Test Purpose	Acceptance Criteria	Results
Drug Coating Integrity	The coating integrity of the stent coating was assessed via a series of acute in vitro tests performed on the coated stent (baseline and simulated use).	Characterization only.	Pass
Particulate Evaluation	Particulate testing included assessment of baseline particulate (including overexpansion), simulated use particulate on the stent and delivery system.	Characterization only.	Pass
Chronic Particulate Evaluation and Coating Integrity	Particulate evaluation and coating integrity assessment of stents in bent overlapped configuration after exposure to pulsatile stresses and strains.	Characterization only	Pass
Chemical Identification of Particulates	Chemical identification of 90% of total particles on gold-coated filters with particles recovered after acute stent testing.	Characterization only.	Pass
Physical Microstructure of the Coating	Analysis of microstructure of the coating surface and cross sections by means of scanning electron microscopy.	Characterization only.	Pass
Coating Thickness and Uniformity	Verification of the abluminal / sidewall coating thickness uniformity along the stent.	Coating thickness along the entire stent length < 25 μm.	Pass
In Vitro Degradation of the Polymer Coating	To establish the degradation profile of the polymer coating and characterize the intermediate degradants.	Characterization only.	Pass
Coating Adhesion and Cohesion	Coating adhesion and coating cohesion testing has been performed to assess the adhesive and cohesive properties of the stent coating.	Characterization only.	Pass
Physical Drug / Polymer Interaction	To identify drug/polymer interactions by comparative differential scanning calorimetry (DSC) measurements of pure PLLA and PLLA/Sirolimus/BHT coated films.	Characterization only.	Pass
Characterization of Polymer (PLLA)	Characterization of the polymer properties on the final stent (molar mass averages of the number (Mn) or weight (Mw), the polydispersity index (PDI), and crystallinity)	Characterization only.	Pass
Characterization of the Final Product – Elemental Impurities and Residual Monomer L-lactide	Testing is conducted to quantitatively verify the amount of elemental impurities and residual monomer remain below acceptable levels established for the finished product.	• Elemental impurities per ICH Q3D or EMEA/CHMP/SWP/4446/2000; • Residual L-lactide per ASTM F1925-09.	Pass

Test Performed	Test Purpose	Acceptance Criteria	Results
Drug/Polymer Distribution along Stent Length	Testing is conducted to verify homogeneous drug distribution within the coating along the stent length.	Characterization only.	Pass
Sirolimus and BHT Content Uniformity over Stent Length	Analysis of the homogeneity of the distribution of the drug substance sirolimus and the presence of antioxidant BHT along the length of the Orsiro drug-eluting stent.	• Maximum deviation of ± 20% of the sirolimus content/stent mass for individual stent segments related to the mean sirolimus content/stent mass of all segments; • BHT greater than limit of quantitation in each stent segment.	Pass
Drug loading density	Analysis of the homogeneity of the distribution of the drug substance sirolimus along the length of the Orsiro drug-eluting stent.	Characterization only.	Pass

C. Chemistry Manufacturing Control (CMC) Release Testing

Where applicable, International Conference on Harmonization (ICH) guidelines were followed for the testing routinely performed on the Orsiro stents as part of CMC. This testing is summarized in Table 6.

Table 6: Chemistry Manufacturing Control (CMC) Release Testing

Test Performed	Test Purpose	Acceptance Criteria
Drug Identity	To verify the identity of the drug substance in the finished stent.	According to internal specifications
BHT Identity	To verify the identity of butylated hydroxytoluene in the finished stent.	According to internal specifications
BHT Content	Testing is conducted to verify that the amount of BHT is within the specifications established for the finished product.	According to internal specifications
Drug Content	Testing is conducted to verify that the amount of the drug substance is within the specifications established for the finished product.	According to internal specifications
Content Uniformity	To verify the uniformity of the drug content between individual stents is within the specifications established for the finished stent	According to internal specifications
Impurities and Degradation Products	Testing is conducted to verify that the amount of impurities and degradation products are within the specifications established for the finished product.	According to internal specifications
Drug Release	Testing is conducted to verify that the in vitro release of the drug substance is within the specifications established for the finished product.	According to internal specifications
Residual Solvents	Testing is conducted to quantitatively verify the amount of chloroform remaining is within the specification established for the finished product.	According to internal specifications
Particulates	To verify that particulate counts are below acceptable levels for the finished product	According to internal specifications

Test Performed	Test Purpose	Acceptance Criteria
Molecular Weight and PDI	To verify the weight average molecular weight and polydispersity index of the polymer in the drug coating	According to internal specifications
Bacterial Endotoxins	To verify that endotoxin levels are within specifications established for the finished product	According to internal specifications
Sterility	To verify the sterility of the finished product	According to internal specifications

D. Biocompatibility

As per ISO 10993, the stent and delivery system separately were subjected to the biocompatibility tests identified in Table 7.

Table 7: Summary Biocompatibility Testing

Test Performed	Test Purpose	Stent	Delivery S.	Results
Cytotoxicity (ISO 10993-5)	To determine potential for cytotoxicity of the test article extract	X	X	Non-cytotoxic
Sensitization (Magnusson/Kligman) (ISO 10993-10)	To evaluate the allergenic potential or potential for sensitization of the test article extracts	X	X	Non-sensitizing
Irritation / Intracutaneous Reactivity (ISO 10993-10)	To screen test article extracts for potential to produce irritation	X	X	Non-irritant
Acute Systemic Toxicity (ISO 10993-11)	To screen test article extracts for potential systemic toxic effects	X	X	Non-toxic
Material Mediated Pyrogenicity (ISO 10993-11)	To evaluate the potential of the test article extract to produce a pyrogenic response	X	X	Non-pyrogenic
Hemolysis (ISO 10993-4)	To assess the potential hemolytic activity of the test article in direct and indirect contact with rabbit blood	X	X	Non-hemolytic
Complement Activation (C3a & SC5b-9) (ISO 10993-4)	To measure the potential complement activation as a result of human plasma exposure to the test article	X	X	Not a complement activator
Genotoxicity – Bacterial Reverse Mutation Assay (ISO 10993-3)	To evaluate the potential of the test article extracts to induce gene mutations	X	Justification provided	Non-mutagenic
Genotoxicity - Mouse Lymphoma Assay (ISO 10993-3)	To investigate the potential of the test article extracts to induce mutations (gene mutations and chromosomal damage)	X	Justification provided	Non-mutagenic
Genotoxicity – *In vivo* Micronucleus Assay (ISO 10993-3)	To investigate the potential of the test article extracts to induce clastogenic effects	X	Justification provided	Non-mutagenic

Test Performed	Test Purpose	Stent	Delivery S.	Results
Implantation Short Term (14 days) (ISO 10993-6)	To determine the local tissue effects after test article implantation	X	n/a	Non-irritant
Implantation Long Term (90, 180 days) (ISO 10993-6)	To determine the local tissue effects after test article implantation	X	n/a	Non-irritant
Chemical Characterization and Toxicological Risk Assessment				
Gas chromatography–mass spectrometry (GC-MS); Liquid chromatography–mass spectrometry (LC-MS); Inductively coupled plasma- mass spectrometry (ICP-MS) (ISO 10993-18)	To identify possible volatile, semi-volatile and nonvolatile substances released from the test article via multiple instrumental methods and the subsequent toxicological evaluation of these substances.	X	X	Extractables / leachables not of toxicological concern for applicable endpoints

Chronic and sub-chronic systemic toxicity testing on the Orsiro stent was omitted based on a chemical characterization and toxicological risk assessment, which showed no toxicological concern for these endpoints. Carcinogenicity assessment was based on the negative results of genotoxicity testing as well as chemical characterization and toxicological risk assessment, which showed no toxicological concern for this endpoint.

Thrombogenicity of the delivery system and stent was assessed in the large animal Good Laboratory Practice (GLP) safety studies (as described in Section G below). In addition to the implantation assessments per ISO 10993-6, the implantation endpoint was also assessed in the large animal GLP safety studies.

A toxicological risk assessment was conducted on the degradants from the stent PLLA coating and was found to be acceptable.

Genotoxicity testing on the delivery system was omitted as the delivery system materials have been used in FDA approved devices in contact with circulating blood.

E. Sterilization

The Orsiro Stent System is sterilized with ethylene oxide (EtO) gas to a sterility assurance level (SAL) of $1x10^{-6}$. The sterilization processes are in compliance with ISO 11135:2014. The sterilization processes and the worst case representative product at BIOTRONIK AG (Bülach) are re-reviewed and/or re-qualified yearly.

F. Packaging and Product Shelf Life

Packaging verification testing was performed to demonstrate that the design of the Orsiro Stent System packaging can withstand the hazards of the distribution environment and that the sterility of the device is maintained throughout the labeled

shelf life. BIOTRONIK has conducted bench testing after aging of the devices according to FDA's drug eluting stent (DES) guidance in order to support a 24-month shelf life at 25 ˚C. The 24-month shelf life claim is based on data acquired from an 18-month real time and 6-month accelerated stability for drug properties, 12-month real time for particulate matter, packaging integrity and sterility, 2-year real time for polymer coating properties, 2-year real time data for packaging, and 92-day accelerated aging for the relevant engineering attributes of the stent and delivery system.

G. **Animal Studies**

An extensive series of animal studies has been conducted to evaluate the overall safety and acute performance of the Orsiro Stent System. The majority of the animal studies utilized earlier iterations of the Orsiro Stent manufactured from a previous version of the BIOlute Coating formulation. The in vivo animal studies included implantation of the earlier iteration of Orsiro Stent into study animals to evaluate its safety and acute performance covering follow-up time points from 3 days to 6 years.

An additional recent animal study utilizing the final finished iteration of the Orsiro Stent manufactured from the final BIOlute coating formulation was conducted in the PMA phase. The in vivo animal studies included implantation of the final iteration of the Orsiro Stents into study animals to evaluate its safety, pharmacokinetics, and polymer degradation covering follow-up time points from 1 day to 3 years.

To assess the safety, acute performance and certain biocompatibility endpoints of the Orsiro stent and delivery system, the animal studies were conducted to evaluate the inflammation, neointimal proliferation, endothelialization, necrosis, thrombogenicity, embolism, pharmacokinetics, polymer degradation, device deliverability and radiopacity. The animal studies also included overdose and overlap evaluations, and an endothelialization study. For all safety studies, stents were implanted in the coronary and internal thoracic arteries, and angiography, gross evaluation, quantitative histomorphometry, histopathology, quantitative analysis were performed. All Orsiro stents that were successfully implanted remained structurally intact for the duration of implantation.

All animal studies were conducted using healthy pigs and rabbits and were performed in accordance with the Good Laboratory Practice (GLP) for Non-clinical Laboratory Studies requirements outlined in 21 CFR Part 58, unless otherwise stated in Table 8. The results of the animal studies support the safety and performance of the device. A description of the studies and results is provided in Table 8.

Table 8: Summary of Animal Testing Conducted on Orsiro Stent System

Study Type	# of Stents	Testing Summary	Acceptance Criteria
Overall Safety Assessment (GLP)	N=50	In three safety studies, stents were implanted in coronary and mammary arteries of Yucatan miniature swine. Histological analysis was performed at 28, 90, 180 days, 1, 2, 3, 4, 5 and 6 years. The pathologist concluded that the overall safety profile of the Orsiro stent, as assessed by histopathology, was similar to that seen with the bare metal stent PRO-Kinetic Energy at all time points evaluated.	Safety of the subject stent shall be ensured, which is confirmed by the study pathologist. The safety assessment is based on but not restricted to inflammation, endothelialization, necrosis and thrombus formation.
GLP Safety Study	N=29	Stents were implanted in the coronary arteries of Yucatan miniature swine for safety evaluation after 28, 90 and 180 days of implantation by angiography, histomorphometry and histopathology. Based on the comparison of the results to the acceptance criteria, the subject device fulfills the predetermined specifications for this safety study. The results show that the device design meets its intended purpose.	Study focus is the collection of histology data to assess safety of the subject device. Based on the pathologist's judgement, the subject device shall not show any severe safety issues.
GLP Safety Study: Overdose Arm	N=11	The test is performed to demonstrate a safety margin with regard to higher drug and polymer dosages. The safety of overdose stents, nominal dose stents, the bare metal stent PRO-Kinetic Energy and PRO-Kinetic Energy with polymer coating only were assessed by angiography, histomorphometry and histopathology at 28 days after implantation. The overdose group fulfills the predetermined acceptance criteria for safety 28 days after implantation.	No severe safety issues of the subject device overdose may occur after 28d follow-up in comparison to the subject device (nominal dose). The safety assessment is based on but not restricted to: inflammation, endothelialization, necrosis and thrombus formation.
GLP Safety of Overlapping Stents Study I	N=18 (9 pairs)	Stents were implanted in coronary arteries of Yucatan miniature swine. The purpose of this preclinical study was to evaluate the safety of overlapping subject devices at 28 days. The safety assessment was focused on histopathology, macroscopic evaluation of the myocardium, histomorphometry, angiography and X-ray analysis. Based on the comparison of the results to the acceptance criteria subject devices fulfill the predetermined specifications for the overlap study. The results show that the device design meets its intended purpose.	Based on the pathologist's judgment, the overlap sections shall not show any severe safety issues. The safety assessment is based on but not restricted to: inflammation, endothelialization, thrombus formation and stent integrity.

Study Type	# of Stents	Testing Summary	Acceptance Criteria
GLP Safety of Overlapping Stents Study II	N=24 (12 pairs)	Stents were implanted in coronary arteries of Yucatan miniature swine. The purpose of this preclinical study was to evaluate the safety of overlapping Orsiro stents at 180 days. The safety assessment focused on histopathology, macroscopic evaluation of the myocardium, histomorphometry, angiography and X-ray analysis. Based on the comparison of the results to the acceptance criteria, Orsiro products fulfill the predetermined specifications for safety of overlapping stents in the porcine model. The results show that the device meets its intended purpose.	Safety of overlapping Orsiro stents at 180 days based on the judgment of the study pathologist. The safety assessment is based on but not restricted to: inflammation, endothelialization, necrosis, thrombus formation and evaluation of stent integrity.
Non-GLP Pharmacokinetic Study (Short-term)	N=34	The purpose of this study was to characterize sirolimus pharmacokinetics of the Orsiro. Stents were implanted in coronary arteries of hybrid farm pigs. Pharmacokinetic evaluation of tissue, organs and drug remaining on stent was performed at 1, 3, 8, 28 and 90 days. Whole blood sirolimus concentrations were measured at 5, 15 minutes, 0.5, 1, 2, 4, 6 hours, 1, 3, 8 and 14 days. Sirolimus was quantified by HPLC-MS/MS.	No acceptance criteria were applicable. For characterization only.
GLP Pharmacokinetic Study (Long-term)	N=49	Orsiro stents were implanted in the coronary arteries of Yucatan miniature pigs. The remaining amount of sirolimus on stent, and sirolimus concentrations in vessels and organs were measured at 28, 60, 90, 180, 270, 360, 720, and 1080 days after implantation. Blood samples were collected for analysis of sirolimus concentrations before implantation and after 1, 4 hours, 1, 3, 5, 7, 14, 21, 28, 60, 90, 180, 270, 360, and 720 days. Sirolimus was quantified by standard tandem mass spectrometry HPLC-MS/MS.	No acceptance criteria were applicable. For characterization only.
Evaluation of Coating Degradation (non-GLP)	N=104	The purpose of the analyses was to characterize the polymer coating within a similar timeframe to the three safety and the long-term pharmacokinetic studies. The polymer coating was evaluated by histology, confocal Raman microscopy and gel permeation chromatography. Polymer degradation profiles were characterized after stent implantation.	No acceptance criterion was applicable. For characterization only.

Study Type	# of Stents	Testing Summary	Acceptance Criteria
GLP Endotheliali-zation Study	N=7	Orsiro stents were implanted in iliac arteries of New Zealand White rabbits. 28 days after implantation endothelialization was evaluated using scanning electron microscopy. Based on the comparison of the results to the acceptance criteria, Orsiro products fulfill the predetermined specifications for endothelialization in the rabbit model. The device design meets its intended purpose.	Analysis and comparison of the extent of re-endothelialization 28 days after implantation of Orsiro and approved DES. The above strut re-endothelialization rate of Orsiro shall be non-inferior compared to the approved DES.
GLP Subacute Thrombogenicity Study	N=9	Orsiro stents and the bare metal stent PRO-Kinetic Energy were implanted into coronary arteries of hybrid farm pigs. The presence of thrombus formation, inflammation and endothelial coverage were evaluated at 3 days using scanning electron microscopy analysis and light microscopy. Based on the comparison of the results to the acceptance criteria, Orsiro products fulfill the predetermined specifications for subacute thrombogenicity.	The subacute thrombosis risk at 3 days shall be non-inferior compared to PRO-Kinetic Energy based on the study pathologist's judgment.
Evaluation of Deliverability (GLP)	N=393	The evaluation was performed in 5 porcine studies. All test articles functioned as expected. Based on the comparison of the results to the acceptance criteria, Orsiro products fulfill the predetermined specifications for deliverability in the porcine model.	The deliverability was judged by the interventionalist.

Study Type	# of Stents	Testing Summary	Acceptance Criteria
GLP Chronic Study for the Evaluation of Myocardial Changes, Pharmacokinetics, Polymer Degradation and Local Biological Response*	N=372	The purpose of this test was to evaluate the local biological response and myocardial changes, and, to characterize the drug release and the polymer degradation of the Orsiro Stent, in order to develop an *in vitro*/*in vivo* correlation (IVIVC) in a porcine model (Yucatan miniature pig). The final follow-up will be at 3 years. • Histopathological examination of myocardium sections was performed at 1 day, 3, 7, 14, 28, 42, 60, 90, 180, 270 and 365 days, to evaluate relevant changes in the myocardium associated with the downstream vasculature. • Histopathological evaluation of stented arteries for local biological response was conducted in one animal at 2-year timepoint. There is a pending evaluation for local biological response of stented coronary arteries in one animal at 3-year timepoint. • Pharmacokinetics was evaluated for three different Orsiro stent formulations (slow, nominal, fast drug release) of coronary artery implants up to 1-year timepoint. • Polymer degradation of the thoracic and coronary stents explanted from the animal was analyzed for molecular weight by Gel Permeation Chromatography at 1 day, 3, 7, 14, 28, 42, 60, 90, 180, 270 and 365 days. There is a pending polymer degradation analysis at 3-year timepoint.	Characterization of pharmacokinetics and polymer degradation. No occurrence of marked myocardial changes according to the pathologist.

*Several iterations (slow, nominal, fast drug release) of the Orsiro stents have been evaluated, including the final iteration of Orsiro stent manufactured from the final BIOlute coating formulation; a total of 161 Orsiro stents manufactured from the final coating formulation were used.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study (BIOFLOW-V) to establish a reasonable assurance of safety and effectiveness of improving coronary luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, non-ST elevation myocardial infarction or documented silent ischemia due to atherosclerotic lesions in the native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm and a lesion length of ≤ 36 mm in the United States (US) under investigational device exemption (IDE) # G140078. Data from this clinical study, as well as pooled data from previously conducted outside the United States (OUS) clinical trials (BIOFLOW-II and BIOFLOW-IV) (Table 9), were the basis for the PMA approval decision. These three clinical studies utilized earlier iterations of the Orsiro Stent manufactured from a previous version of the BIOlute Coating formulation. A summary of the pivotal clinical study (BIOFLOW-V) is presented below. Please also see Section XI below for further information for BIOFLOW-II and BIOFLOW-IV clinical trials.

A. Study Design

Patients were treated between May 8, 2015 and March 31, 2016. The database for this Premarket approval (PMA) reflected data collected through May 23, 2017 and included 1334 patients. There were 90 investigational sites.

The BIOFLOW-V study is a prospective, international, multicenter, randomized controlled trial (RCT) designed to evaluate the safety and effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System compared to the Xience Everolimus-Eluting Coronary Stent System for the treatment of atherosclerotic lesions ≤ 36 mm in length in native coronary arteries of 2.25 mm to 4.0 mm in diameter (by visual estimate)[i]. The Xience DES is a legally marketed alternative with similar indications for use.

The BIOFLOW-V study was designed to test the hypothesis that the rate of 12-month target lesion failure (TLF) in patients treated with an Orsiro stent was non-inferior to the rate of 12-month TLF in patients treated with a Xience stent. TLF is defined as all cardiac death, target vessel Q-wave or non–Q-wave myocardial infarction (MI), or clinically driven target lesion revascularization (TLR). The analysis of the primary endpoint of 12-month TLF was a non-inferiority analysis combining data from BIOFLOW-V patients with data from historical BIOFLOW-II and BIOFLOW-IV patients employing a Bayesian approach.

Table 9: Overview of the Clinical Studies of the Orsiro Stent System

Study	BIOFLOW-V RCT*	BIOFLOW-II RCT	BIOFLOW-IV	
			RCT	PK*
Purpose	Evaluation of safety and effectiveness in native *de novo* and PTCA only	Evaluation of safety and effectiveness in native *de novo* coronary lesions	Evaluation of safety and effectiveness in native *de novo* coronary lesions	Measurement of whole blood sirolimus concentrations and

Study	BIOFLOW-V RCT*	BIOFLOW-II RCT	BIOFLOW-IV	
			RCT	PK*
	restenotic coronary lesions			determination of PK parameters
Study Design	Prospective, randomized, controlled, multi-center non-inferiority to Xience IDE* Trial	Prospective, randomized, controlled, multi-center non-inferiority to Xience Regulatory trial	Prospective, randomized, controlled, multi-center non-inferiority to Xience Regulatory trial	Prospective, multicenter, non-randomized PK sub-study
Devices	2:1 Orsiro vs. Xience	2:1 Orsiro vs. Xience	2:1 Orsiro vs. Xience	Orsiro
Primary Endpoint	12-month TLF*	9-month Late Lumen Loss	12-month TVF*	N/A
Secondary/ Long-term Endpoints	TLF: cardiac death, target vessel Q-wave or non-Q wave MI*, clinically driven TLR* (including CABG*); ST*	TLF: cardiac death, target vessel Q-wave or non-Q wave MI, emergent CABG, clinically driven TLR; ST	TLF: cardiac death, target vessel Q-wave or non-Q wave MI, emergent CABG, clinically driven TLR; ST	N/A
Number of Patients (ITT*)	1334 Orsiro: 884 Xience: 450	452 Orsiro: 298 Xience: 154	575 Orsiro: 385 Xience: 190	21 Orsiro
Target lesion criteria	≤ 3 *de novo*/ PTCA* restenotic lesions/ 2 target vessels Native arteries 50 to <100% stenosis	1-2 *de novo* lesions Native arteries 50 to <100% stenosis	≤ 2 *de novo* lesions Native arteries 50 to <100% stenosis	
Lesion criteria: Vessel Diameter (by visual estimate), mm	RVD* 2.25 - 4.0	RVD 2.25 - 4.0	RVD 2.5 – 3.75	
Lesion criteria: Lesion Length (by visual estimate), mm	LL* ≤ 36	LL ≤ 26	LL ≤ 26	
Follow-up	1, 6 and 12 months, annually 2-5 years	1, 6, 9 and 12 months, annually 2-5 years	1, 6 and 12 months, annually 2-5 years	

*Definitions: RCT, random controlled trial; PK, pharmacokinetics; ITT, intention to treat; IDE, investigational device exemption; TLF, target lesion failure; TVF, target vessel failure; TLR, target vessel revascularization; MI, myocardial infarction; CABG, coronary artery bypass grafting; ST, stent thrombosis; PTCA, percutaneous transluminal coronary angioplasty; RVD, reference vessel diameter; and LL, late loss.

A total of 1,334 patients (884 Orsiro and 450 Xience) were randomized at 90 clinical sites in 13 countries in North America, Europe, Israel and the Asia-Pacific regions. Of the 1,334 patients included in the intent-to-treat (ITT) analysis set, a total of 1260 patients (833 Orsiro and 427 Xience) were evaluable for the 12 month primary endpoint[ii]. The follow-up schedule includes clinical assessments at 30 days, 6, 12 months and 2, 3, 4 and 5 years post index procedure.

The study utilized an independent angiographic core laboratory and an independent clinical events committee (CEC) to evaluate and adjudicate study primary endpoint data. The core laboratories and CEC were composed of experts in their field.

1. Clinical and Angiographic Inclusion and Exclusion Criteria

Enrollment in the BIOFLOW-V study was limited to patients who met the following inclusion criteria provided in Table 10.

Table 10: Inclusion Criteria, BIOFLOW-V

Clinical Inclusion Criteria	• Subject is ≥18 years or the minimum age required for legal adult consent in the country of enrollment. • Subject is an acceptable candidate for Percutaneous coronary intervention (PCI). • Subject is an acceptable candidate for CABG. • Subject has clinical evidence of ischemic heart disease, stable or unstable angina pectoris or documented silent ischemia. • Subject is eligible for dual anti-platelet therapy treatment with aspirin plus either, clopidogrel, prasugrel, ticagrelor or ticlopidine. • Subject has provided written informed consent. • Subject is willing to comply with study follow-up requirements.
Angiographic Inclusion Criteria	• Subject has up to three target lesions in up to two separate target vessels (two target lesions in one vessel and one target lesion in a separate vessel). • Target lesion must be *de novo* or restenotic lesion in native coronary artery; restenotic lesion must have been treated with a standard PTCA only. • Target lesion must be in major coronary artery or branch (target vessel). • Target lesion must have angiographic evidence of ≥ 50% and < 100% stenosis (by operator visual estimate). If the target lesion is < 70% stenosed, there should be clinical evidence of ischemia such as a positive functional study (e.g. exercise treadmill test, thallium stress test, single photon emission computed tomography (SPECT), or stress echo), cardiac computed tomography (CT), electrocardiography, fractional flow reserve, or post infarct angina. • Target vessel must have a Thrombolysis in Myocardial Infarction (TIMI) flow > 1. • Target lesion must be ≤ 36 mm in length by operator visual estimate. • Target vessel must have a reference vessel diameter of 2.25–4.0 mm by operator visual estimate • Target lesion must be amenable to treatment with a maximum of two overlapping stents.

Patients were not permitted to enroll in the BIOFLOW-V study if they met any of the following exclusion criteria listed in Table 11:

Table 11: Exclusion Criteria, BIOFLOW-V

Clinical Exclusion Criteria	• Subject has clinical symptoms and/or ECG changes consistent with acute ST-segment elevation myocardial infarction (STEMI) within 72 hours prior to the index procedure. o *Note: Hemodynamically stable non-STEMI (NSTEMI) subjects are eligible for study enrollment.* • Subject is hemodynamically unstable. • Subject is pregnant and/or breastfeeding or intends to become pregnant during the duration of the study. • Subject has a known allergy to contrast medium that cannot be adequately pre-medicated, or any known allergy to thienopyridine, aspirin, both heparin and bivalirudin, L-605 cobalt-chromium (Co-Cr) alloy or one of its major elements (cobalt, chromium, tungsten and nickel), acrylic, fluoropolymers, silicon carbide, PLLA, sirolimus or everolimus. • Revascularization of any target vessel within 9 months prior to the index procedure or previous PCI of any non-target vessel within 30 days prior to the index procedure. • Planned treatment of a lesion not meeting angiographic inclusion and exclusion criteria during the index procedure or after the index procedure. • Planned surgery within 6 months of index procedure unless dual antiplatelet therapy can be maintained throughout the peri-surgical period. • History of a stroke or transient ischemic attack (TIA) within 6 months prior to the index procedure. • Subjects with active bleeding disorders, active coagulopathy, or any other reason, who are ineligible for DAPT. • Subject will refuse blood transfusions. • Subject has documented left ventricular ejection fraction (LVEF) < 30% as evaluated by angiography, echocardiogram, radionuclide ventriculography or any non-invasive imaging method within 90 days prior to the index procedure. • Subject is dialysis-dependent. • Subject has impaired renal function (i.e., blood creatinine > 2.5 mg/dL or 221 μmol/L determined within 7 days prior to the index procedure). • Subject has leukopenia (i.e. < 3,000 white blood cells/mm^3), thrombocytopenia (i.e. < 100,000 platelets/mm^3) or thrombocytosis (i.e. > 700,000 platelet/mm^3). • Subject is receiving oral or intravenous immunosuppressive therapy (inhaled steroids are permitted) or has known life-limiting immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematosus; diabetes mellitus is permitted). • Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent). • Subject has life expectancy of < 1 year.

	• Subject is participating in another investigational (medical device or drug) clinical study. Subjects may be concurrently enrolled in a post-market study, as long as the post-market study device, drug or protocol does not interfere with the investigational treatment or protocol of this study. • In the investigator's opinion, subject will not be able to comply with the follow-up requirements.
Angiographic Exclusion Criteria (Visual Estimate)	• Target lesion is located within a saphenous vein graft or arterial graft. • Target lesion is a restenotic lesion that was previously treated with a bare metal or drug eluting stent (in-stent restenosis). • Target lesion has any of the following characteristics: o Lesion location is within the left main coronary artery, or within 3 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX). o Involves a side branch of > 2.0 mm in diameter. o *Note: Lesions within 3 mm of the origin of the right coronary artery may be treated.* • Target vessel/lesion is excessively tortuous/angulated or is severely calcified, that would prevent complete inflation of an angioplasty balloon. This assessment should be based on visual estimation. • Target vessel has angiographic evidence of thrombus. • Target lesion is totally occluded (100% stenosis). • Target vessel was treated with brachytherapy any time prior to the index procedure.

2. Follow-up Schedule, BIOFLOW-V

Following enrollment/baseline and the index procedure, all randomized subjects had planned follow-up visits at 1 month, 6 months and 12 months and will be followed annually up to 5 years post index procedure. Dual antiplatelet therapy (DAPT) was recommended for a minimum of 6 months and highly recommended for 12 months in subjects not at a high risk of bleeding. Aspirin therapy was recommended for the duration of study participation. The study primary endpoint follow-up was completed on May 10, 2017 after all evaluable subjects completed a 12-month follow-up visit.

3. Clinical Endpoints

3 (i) Primary Endpoint

The primary endpoint for the BIOFLOW-V study was TLF rate at 12 months post index procedure. TLF is defined as all cardiac death, target vessel Q-wave or non–Q-wave MI, or clinically driven target lesion revascularization (TLR).

All clinical data was analyzed based upon the pre-defined analysis populations. The primary endpoint, TLF, was evaluated on an intent-to-treat basis.

Non-inferiority of the Orsiro stent compared to the Xience stent in the BIOFLOW-V study was assessed using a Bayesian approach employing hierarchical models to formally incorporate data from the BIOFLOW-II and BIOFLOW-IV trials. This approach used Binomial analysis for the presence of a TLF event and a Bayesian model that allowed for bias between the TLF event rates of the BIOFLOW-II and BIOFLOW-IV trials and the TLF event rates of the BIOFLOW-V trial in both the Orsiro and Xience groups.

The assumptions for this analysis were:

- True 12-month TLF rate = 7.0% in both treatment groups ($\pi_X^V = \pi_O^V$).
- Power = 89%.
- Absolute non-inferiority margin = 3.85% (relative non-inferiority margin = 55%).
- The results of the BIOFLOW-IV data were discounted by 20% and the BIOFLOW-II data by 30%.
- Standard deviation of the bias terms between the odds of BIOFLOW-II TLF 12-month rates and odds of BIOFLOW-V 12-month rates = 0.3.
- Standard deviation of the bias terms between the odds of BIOFLOW-IV TLF 12-month rates and odds of BIOFLOW-V 12-month rates = 0.3.
- Non-inferiority assessment was assessed using the posterior probability of the alternative hypothesis as specified above, where $\pi^* = 0.975$

A Kaplan-Meier survival analysis was also performed as a supporting analysis to evaluate the time to first failure for all subjects in the intention-to-treat population.

3 (ii) Secondary Endpoints

The secondary endpoints in the BIOFLOW-V study were analyzed using frequentist methods. For each endpoint, the proportion and sample size were calculated and reported for the Orsiro group and for the Xience group. Fisher's exact test was used to test the difference between the groups. Analyses of secondary endpoints were carried out on the ITT, Modified ITT and PP (Per Protocol) analysis sets for BIOFLOW-V. There was no direct imputation of missing data.

Secondary Endpoints included the following measures:

- Device success
- Lesion success
- Procedure success

BIOFLOW-V utilized the % residual stenosis, as assessed by the investigator, for evaluating angiographic success for the aforementioned secondary endpoints. If investigator assessment of % residual stenosis was not available, the in-stent final % diameter stenosis, as assessed by the angiographic core-laboratory was used.

For the analysis of procedure success, the primary analysis definition of major adverse cardiac event (MACE) was used. Treatment group difference (Orsiro minus Xience) in the success rates and the two-sided 95% confidence intervals of the difference are presented.

The following secondary clinical endpoints were evaluated prior to discharge, at 1-, 6- and 12-months and will be evaluated annually thereafter through 5 years of follow-up:

- Death
- Protocol-defined MI
- Cardiac death or protocol-defined MI
- MACE and individual MACE components
- TLF and individual TLF components
- TVF and individual TVF components
- Stent thrombosis according to Academic Research Consortium (ARC) criteria

Included in the analysis are subjects experiencing the event or subjects with adequate follow-up (e.g., at least 23 days for the 1-month time point, at least 166 days for the 6-month time point, and at least 330 days for the 12-month time point).

3 (iii) Exploratory Analyses

In addition to the secondary endpoint assessments, pre-specified covariates were examined to determine potential relationships with the primary study endpoint or its components.

Subgroups for the primary endpoint (TLF at 12-Months) using Bayesian analysis for the BIOFLOW-V study included:

- Reference vessel diameter ≤ 2.75 mm versus RVD > 2.75 mm: Subjects with at least one target lesion ≤ 2.75 mm were classified with the small vessel subgroup.
- Subjects > 75 years of age versus subjects ≤ 75 years of age
- Women versus men
- Subjects with diabetes versus subjects without diabetes
- Lesion length >26 mm versus lesion length ≤ 26 mm in length: subjects with at least one target lesion >26 mm were included with the long lesion group.
- Single stents versus overlapping stents for lesion lengths > 26 mm
- Subjects with baseline acute coronary syndrome (ACS) versus subject without ACS: ACS was defined as subjects with unstable angina or Braunwald Class IIB or any elevated cardiac enzymes at baseline.

Treatment group difference (Orsiro minus Xience) in the primary endpoint rate and the two-sided 95% credible interval of the difference are presented within each subgroup. Only BIOFLOW-V data were included in these analyses. A test of interaction on the primary endpoint was performed to formally assess heterogeneity of treatment effect on the primary endpoint across subgroups was performed. The purpose of these analyses was not to formally assess non-inferiority within each subgroup, but simply to assess consistency of results across the various subgroups. Subjects with an event or with appropriate follow-up were included in these analyses.

B. Accountability of PMA Cohort: BIOFLOW-V RCT Study

A total of 1,334 patients (884 Orsiro and 450 Xience) were randomized at 90 clinical sites in 13 countries in North America, Europe, Israel and the Asia-Pacific regions from May 8, 2015 to March 31, 2016. There were 665 subjects enrolled from North America (among them 6 from Canada) and 669 from the other countries listed. Of the 1,334 patients included in the intent-to-treat (ITT) analysis set, a total of 1260 patients (833 Orsiro and 427 Xience) were evaluable for the 12 month primary endpoint.

At the time of database lock, of the 1334 patients enrolled in the BIOFLOW-V study (intent to treat population), 97.1% (1295/1334) of patients were actively enrolled at the time of the 12-month primary endpoint study visit. Of these, 1257 subjects completed a 12-month study visit. Seventeen subjects withdrew consent and eight were lost to follow up (Table 12).

Table 12: BIOFLOW-V RCT Subject Disposition, ITT Analysis Set

	Orsiro	Xience	Total
Number of Subjects Randomized	884	450	1334
Number of Subjects Active at 12-Months[a]	97.3% (860/884)	96.7% (435/450)	97.1% (1295/1334)
Follow-up Compliance at 12-Months[b]	97.2% (836/860)	96.8% (421/435)	97.1% (1257/1295)
No 12-Month Follow-up Performed[c]	48	29	77
Prematurely Discontinued	24	15	39
Withdrew Consent	10	7	17
Death	7	6	13
Lost to Follow-up	6	2	8
Other Reasons[d]	1	0	1
Missed 12-Month Visit	24	14	38
Primary Endpoint Evaluable Subjects:[e] At least 330 days of follow-up or an endpoint event	94.2% (833/884)	94.9% (427/450)	94.5% (1260/1334)

Numbers are n or % (count/sample size).
a: Subjects who were actively enrolled and had not been exited from the study.
b: Subjects who completed the 12-month visit out of the number of subjects that were actively enrolled at 12 months.
c: Subjects with early exit or missed 12-month visit.
d: Site discontinued ITT subject in error as no study stent was implanted.
e. Subjects that had follow-up through 330 days or an event prior to 360 days.

C. Study Population Demographics and Baseline Parameters

Table 13 and Table 14 present the baseline demographics and baseline risk factors respectively for the ITT population (N=1334) at the time of the enrollment/baseline visit. The demographics of the study population are typical for a coronary stent study performed in the US.

Table 13: Baseline Demographics, BIOFLOW-V ITT population

Demographics	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
Age (years)[1]			
Mean±SD (N)	64.5±10.32 (884)	64.6±10.67 (450)	64.5±10.44 (1334)
Median (Q1,Q3)	65.0 (57.0,72.0)	65.0 (57.0,73.0)	65.0 (57.0,72.0)
Range (min,max)	(34,90)	(29,89)	(29,90)
Female Sex	25.34% (224/884)	27.11% (122/450)	25.94% (346/1334)
Race			
American Indian or Alaska Native	0.00% (0/884)	0.00% (0/450)	0.00% (0/1334)
Asian	3.28% (29/884)	2.89% (13/450)	3.15% (42/1334)
Black or African American	2.71% (24/884)	2.89% (13/450)	2.77% (37/1334)
Native Hawaiian or other Pacific Islander	0.11% (1/884)	0.44% (2/450)	0.22% (3/1334)
White	89.59% (792/884)	90.22% (406/450)	89.81% (1198/1334)
Other	1.24% (11/884)	0.22% (1/450)	0.90% (12/1334)
Did not provide response	3.05% (27/884)	3.33% (15/450)	3.15% (42/1334)
Ethnicity			
Hispanic or Latino	3.96% (35/884)	2.89% (13/450)	3.60% (48/1334)
Non-Hispanic or non-Latino	91.86% (812/884)	92.67% (417/450)	92.13% (1229/1334)
Did not provide response	4.19% (37/884)	4.44% (20/450)	4.27% (57/1334)

[1]Age is presented as a whole number as only the year of birth was allowed to be collected for OUS subjects due to data privacy laws.

Table 14: Baseline Medical History and Risk Factors - BIOFLOW-V ITT population

Medical History and Risk Factors	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
History of MI	27.39% (238/869)	25.90% (115/444)	26.88% (353/1313)
History of Stroke or TIA	5.54% (49/884)	4.46% (20/448)	5.18% (69/1332)
Smoking Habits			
Never Smoked	38.80% (343/884)	40.22% (181/450)	39.28% (524/1334)
Ex-Smoker	37.56% (332/884)	37.11% (167/450)	37.41% (499/1334)
Current Smoker	23.64% (209/884)	22.67% (102/450)	23.31% (311/1334)
Renal Disease	7.93% (70/883)	7.56% (34/450)	7.80% (104/1333)
Hepatic Disease	1.58% (14/884)	2.22% (10/450)	1.80% (24/1334)
Respiratory Disease	13.49% (119/882)	11.36% (51/449)	12.77% (170/1331)
Hypertension	79.73% (696/873)	80.45% (354/440)	79.97% (1050/1313)
Hyperlipidemia	78.89% (695/881)	82.41% (370/449)	80.08% (1065/1330)
Diabetes	33.98% (300/883)	36.97% (166/449)	34.98% (466/1332)

Medical History and Risk Factors	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
Treatment			
Insulin[1]	10.42% (92/883)	11.14% (50/449)	10.66% (142/1332)
Oral Agents[1]	25.93% (229/883)	27.62% (124/449)	26.50% (353/1332)
Diet Alone	1.36% (12/883)	3.12% (14/449)	1.95% (26/1332)
No Treatment	1.47% (13/883)	0.89% (4/449)	1.28% (17/1332)
Congestive Heart Failure	7.72% (68/881)	6.47% (29/448)	7.30% (97/1329)
NYHA Class			
NYHA I	1.48% (13/881)	0.89% (4/448)	1.28% (17/1329)
NYHA II	3.29% (29/881)	3.13% (14/448)	3.24% (43/1329)
NYHA III	1.59% (14/881)	1.34% (6/448)	1.50% (20/1329)
NYHA IV	0.23% (2/881)	0.22% (1/448)	0.23% (3/1329)
Unknown	1.14% (10/881)	0.89% (4/448)	1.05% (14/1329)
Peripheral Vascular Disease	8.56% (75/876)	7.16% (32/447)	8.09% (107/1323)
History of Cancer	10.10% (89/881)	13.33% (60/450)	11.19% (149/1331)
Previous Coronary Revascularization	41.05% (360/877)	37.08% (165/445)	39.71% (525/1322)
History of PCI	36.83% (323/877)	33.03% (147/445)	35.55% (470/1322)
History of CABG	7.07% (62/877)	5.17% (23/445)	6.43% (85/1322)

[1] A total of seventy-four subjects received both Insulin and oral agents for the treatment of diabetes at baseline.

The majority of subjects reported current or past smoking history, concurrent diagnoses of hypertension and hyperlipidemia. Prevalence of diabetes was similar and consistent with recent prospective trials.

As presented in Table 15 below, baseline ischemic status was similar between the two study groups with no significant differences in the distribution of ischemic symptoms or the presence of elevated cardiac enzymes at baseline. Overall, one half of the subjects presented with acute coronary syndrome. Table 16 presents the baseline lesion characteristics.

Table 15: Ischemic Status at Baseline – BIOFLOW-V – ITT Population

Ischemic Status	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
Ischemic Status			
Stable Angina	48.42% (428/884)	47.44% (213/449)	48.09% (641/1333)
Unstable Angina	39.25% (347/884)	38.98% (175/449)	39.16% (522/1333)
Documented Silent Ischemia	12.33% (109/884)	13.59% (61/449)	12.75% (170/1333)
CCS Classification[1]			
I	7.92% (70/884)	5.57% (25/449)	7.13% (95/1333)
II	21.27% (188/884)	23.39% (105/449)	21.98% (293/1333)
III	16.52% (146/884)	16.70% (75/449)	16.58% (221/1333)
IV	2.71% (24/884)	1.78% (8/449)	2.40% (32/1333)
Braunwald Classification[2]			
IA	2.49% (22/884)	2.67% (12/449)	2.55% (34/1333)

Ischemic Status	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
IIA	2.49% (22/884)	2.23% (10/449)	2.40% (32/1333)
IIIA	1.92% (17/884)	2.00% (9/449)	1.95% (26/1333)
IB	7.92% (70/884)	8.46% (38/449)	8.10% (108/1333)
IIB	5.54% (49/884)	6.01% (27/449)	5.70% (76/1333)
IIIB-Tneg	7.58% (67/884)	6.68% (30/449)	7.28% (97/1333)
IIIB-Tpos	9.73% (86/884)	10.02% (45/449)	9.83% (131/1333)
IC	0.11% (1/884)	0.00% (0/449)	0.08% (1/1333)
IIC	0.90% (8/884)	0.22% (1/449)	0.68% (9/1333)
IIIC	0.57% (5/884)	0.67% (3/449)	0.60% (8/1333)
Baseline Cardiac Enzymes[3]			
CK above Normal Range	12.08% (87/720)	14.32% (53/370)	12.84% (140/1090)
CKMB above Normal Range	10.86% (66/608)	14.61% (45/308)	12.12% (111/916)
Troponin above Normal Range	33.65% (178/529)	33.45% (93/278)	33.58% (271/807)
Acute coronary syndrome[4]	51.36% (454/884)	49.56% (223/450)	50.75% (677/1334)

[1] Canadian Cardiovascular Society (CCS) classification was used for stable angina subjects only.
[2] Braunwald classification was used for unstable angina subjects only.
[3] Denominators for baseline cardiac enzymes include all subjects with reported values for the specific enzyme. Creatine kinase–MB isoenzyme (CK-MB), or troponin if CK-MB was not available, were required. Creatine kinase (CK) was optional.
[4] Acute coronary syndrome was defined as subjects with unstable angina or any elevated cardiac enzymes at baseline (any pre-procedure CK, CKMB or Troponin above normal range).

Table 16: Baseline Lesion Characteristics - BIOFLOW-V ITT Population

Measure- QCA* Analysis	Orsiro (N = 884 Subjects N = 1051 Lesions)	Xience (N = 450 Subjects N = 561 Lesions)	All Subjects (N = 1334 Subjects N = 1612 Lesions)
Number of Target Lesions (per subject)			
Mean±SD* (N)	1.19±0.43 (881)	1.26±0.50 (447)	1.21±0.46 (1328)
Vessel Location			
RCA*	32.45% (341/1051)	32.80% (184/561)	32.57% (525/1612)
LAD*	41.01% (431/1051)	41.18% (231/561)	41.07% (662/1612)
LCX*	26.55% (279/1051)	26.02% (146/561)	26.36% (425/1612)
ACC/AHA* Lesion Characterization			
B2/C	72.60% (763/1051)	75.94% (426/561)	73.76% (1189/1612)
Calcification			
Moderate or severe	23.98% (252/1051)	26.74% (150/561)	24.94% (402/1612)
Bifurcation Lesion	14.84% (156/1051)	14.97% (84/561)	14.89% (240/1612)
Lesion Length, mm			
Mean±SD (N)	13.28±7.58 (1044)	13.20±7.70 (555)	13.26±7.62 (1599)
Pre-procedure Reference Vessel Diameter (mm) (proximal-distal)			
Mean±SD (N)	2.59±0.54 (1041)	2.60±0.58 (558)	2.59±0.56 (1599)
Minimal Lumen Diameter (mm)			
Mean±SD (N)	1.14±0.40 (1043)	1.14±0.41 (552)	1.14±0.40 (1595)

*Definitions: QCA, quantitative coronary angiography; RCA, right coronary arteries; LAD, left anterior descending; LCX, left circumflex; ACC/AHA, American College of Cardiology and the American Heart Association; SD, standard deviation.

D. Safety and Effectiveness Results

1. Safety and Effectiveness Results

The analysis of safety and effectiveness was based on the primary endpoint and secondary endpoints outcomes.

Primary Endpoint

- The BIOFLOW-V, BIOFLOW-II and BIOFLOW-IV combined ITT population had a Bayesian estimate of the mean 12-month TLF of 6.32% in the Orsiro group compared to 8.90% in the Xience group (difference -2.58%, 95% Credible Interval of -5.47% to 0.13%). The posterior probability that the difference in the rate of 12-month TLF between Orsiro and Xience was less than the pre-specified margin of 3.85% is 100.0%, which is greater than 97.5% pre-specified criteria for success, demonstrating non-inferiority of Orsiro versus Xience with regards to 12-month TLF (Table 17).

Table 17: Primary Endpoint - TLF at 12 Months: Bayesian Analysis - BIOFLOW-V - ITT Population

Bayesian Analysis BIOFLOW-V, BIOFLOW-IV, BIOFLOW-II	**Orsiro N=1466**	**Xience N=742**	**Rate Difference**	**Posterior Probability** Non-inferiority Margin = 3.85%
Target-lesion failure at 12 Months, Posterior Mean (estimate of SD), %, 95% Credible Interval (Lower, Upper)	6.3 ± 0.8 (4.9, 7.9)	8.9 ± 1.2 (6.7, 11.4)	-2.6 ± 1.4 (-5.5, 0.1)	100.0%

- Given the primary hypothesis of non-inferiority was met, a post-hoc Bayesian superiority analysis was performed. The superiority hypothesis was evaluated by computing the posterior probability of the superiority alternative hypothesis and compared against the same threshold that was pre-specified for the non-inferiority test (97.5%). When assessed on BIOFLOW-V ITT subjects incorporating BIOFLOW-II and BIOFLOW-IV Bayesian analysis populations, the Bayesian posterior probability that Orsiro is superior to Xience with respect to 12-month TLF was 96.90%, which is below the pre-specified threshold of 97.5%.

- The 12-month TLF rate was principally driven by a higher rate of target vessel MI observed in the Xience group (TV-MI rate of 4.69% in the Orsiro group compared to 8.25% in the Xience group, p=0.0155). The rates of cardiac death and clinically-driven revascularization were similar, but numerically lower in the Orsiro group as compared to the Xience group.

- As a secondary analysis of the primary endpoint, a frequentist analysis was performed on the BIOFLOW-V ITT population evaluating the 12-month TLF rate and its components. The primary endpoint rate of 12-month TLF was ~~significantly~~ lower in the Orsiro group compared to the Xience group: 6.24% (52/833) compared to 9.60% (41/427) ~~(p=0.0399)~~.

- The observed TLF rate supports the safety and effectiveness of the Orsiro Stent System in treating coronary atherosclerotic lesions.

Secondary Endpoints

- BIOFLOW-V ITT lesion and device success rates were high and were similar in both study groups. Procedural success was higher in the Orsiro group (93.87%) as compared to the Xience group (90.11%). This was principally driven by a higher rate of in-hospital MI observed in the Xience group (in-hospital target vessel MI rate of 3.85% in the Orsiro group compared to 6.68% in the Xience group).

- Death: The BIOFLOW-V rates of all-cause death and cardiac death were numerically lower among Orsiro ITT subjects compared to Xience ITT subjects at all time points through 12 months.

- Target Vessel MI: Among BIOFLOW-V ITT subjects, lower rates of protocol-defined target-vessel MI with Orsiro compared to Xience were observed at all time points through 12 months. At 1 month, the rate of protocol-defined target vessel MI was 4.10% (36/878) in the Orsiro group and 6.70% (30/448) in the Xience group. At 12 months, the rate was 4.69% (39/831) in the Orsiro group compared to 8.25% (35/424) in the Xience group.

- Clinically-driven TLR: At 12 months, the rate of clinically-driven TLR was 2.04% (17/832) in the Orsiro group and 2.37% (10/422) in the Xience group

- Stent thrombosis: The rates of definite/probable stent thrombosis were low (acute, sub-acute, early, late or cumulative) and were similar in the two groups (Definite/Probable 12-month 0.48% [4/831] in Orsiro vs. 0.71% [3/422] in Xience). A lower rate of any ARC (definite/probable/possible) late stent thrombosis was observed in the Orsiro group (0.12% [1/830]) as compared to the Xience group (0.94% [4/424]).

- The results of the secondary endpoints at 12 months support the safety and effectiveness of the Orsiro stent.

Adverse effects that occurred in the PMA clinical study:

Adverse events (AE) that occurred in the PMA clinical study are reported in Table 18 and Table 19. Only categories of adverse events occurring at a rate of ≥1.0% in either treatment group are reported.

No unanticipated adverse device effects (UADEs) have been reported during the course of the BIOFLOW-V study. There have been 2750 adverse events, including 912 serious adverse events. Overall rates of device/procedure-related AEs were similar across the study groups. The frequency and nature of adverse events observed in the BIOFLOW-V trial were similar to those observed for other drug-eluting stents approved in the United States.

Table 18: All Site Reported Adverse Events by Type

Adverse Events to 360 Days	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
Any Adverse Event	**73.64% (651/884)**	**73.78% (332/450)**	**73.69% (983/1334)**
Blood and lymphatic system disorders	**3.62% (32/884)**	**4.00% (18/450)**	**3.75% (50/1334)**
Anemia	1.36% (12/884)	1.11% (5/450)	1.27% (17/1334)
Increased tendency to bruise	1.36% (12/884)	1.56% (7/450)	1.42% (19/1334)
Cardiac disorders	**28.39% (251/884)**	**30.89% (139/450)**	**29.24% (390/1334)**
Acute myocardial infarction	1.24% (11/884)	2.00% (9/450)	1.50% (20/1334)
Angina pectoris	10.52% (93/884)	12.44% (56/450)	11.17% (149/1334)
Angina unstable	3.73% (33/884)	2.89% (13/450)	3.45% (46/1334)
Atrial fibrillation	3.05% (27/884)	2.22% (10/450)	2.77% (37/1334)
Bradycardia	1.13% (10/884)	1.33% (6/450)	1.20% (16/1334)
Cardiac failure congestive	1.02% (9/884)	1.33% (6/450)	1.12% (15/1334)
Coronary artery disease	1.58% (14/884)	2.22% (10/450)	1.80% (24/1334)
Coronary artery dissection	3.51% (31/884)	5.56% (25/450)	4.20% (56/1334)
Coronary artery stenosis	2.26% (20/884)	2.44% (11/450)	2.32% (31/1334)
Myocardial infarction	0.57% (5/884)	1.33% (6/450)	0.82% (11/1334)
Palpitations	1.58% (14/884)	1.33% (6/450)	1.50% (20/1334)
Eye disorders	**1.24% (11/884)**	**1.56% (7/450)**	**1.35% (18/1334)**
Gastrointestinal disorders	**9.73% (86/884)**	**9.11% (41/450)**	**9.52% (127/1334)**
Abdominal pain	1.02% (9/884)	0.67% (3/450)	0.90% (12/1334)
Diarrhoea	0.57% (5/884)	1.56% (7/450)	0.90% (12/1334)
Gastrointestinal haemorrhage	1.36% (12/884)	0.22% (1/450)	0.97% (13/1334)
Nausea	1.02% (9/884)	1.33% (6/450)	1.12% (15/1334)
General disorders and administration site conditions	**24.21% (214/884)**	**23.56% (106/450)**	**23.99% (320/1334)**
Asthenia	1.02% (9/884)	1.78% (8/450)	1.27% (17/1334)
Catheter site haematoma	1.47% (13/884)	1.56% (7/450)	1.50% (20/1334)
Chest pain	3.05% (27/884)	1.11% (5/450)	2.40% (32/1334)
Fatigue	2.94% (26/884)	4.67% (21/450)	3.52% (47/1334)
Non-cardiac chest pain	12.90% (114/884)	12.22% (55/450)	12.67% (169/1334)

Adverse Events to 360 Days	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
Oedema peripheral	1.13% (10/884)	1.56% (7/450)	1.27% (17/1334)
Vascular stent restenosis	0.79% (7/884)	1.11% (5/450)	0.90% (12/1334)
Infections and infestations	**8.71% (77/884)**	**7.11% (32/450)**	**8.17% (109/1334)**
Pneumonia	1.47% (13/884)	0.89% (4/450)	1.27% (17/1334)
Urinary tract infection	1.24% (11/884)	1.11% (5/450)	1.20% (16/1334)
Injury, poisoning and procedural complications	**4.41% (39/884)**	**6.22% (28/450)**	**5.02% (67/1334)**
Investigations	**22.74% (201/884)**	**23.78% (107/450)**	**23.09% (308/1334)**
Blood creatine phosphokinase MB increased	0.79% (7/884)	1.33% (6/450)	0.97% (13/1334)
Myocardial necrosis marker increased	19.34% (171/884)	20.00% (90/450)	19.57% (261/1334)
Troponin increased	1.02% (9/884)	1.11% (5/450)	1.05% (14/1334)
Metabolism and nutrition disorders	**3.17% (28/884)**	**2.00% (9/450)**	**2.77% (37/1334)**
Musculoskeletal and connective tissue disorders	**8.94% (79/884)**	**13.33% (60/450)**	**10.42% (139/1334)**
Arthralgia	0.57% (5/884)	1.56% (7/450)	0.90% (12/1334)
Back pain	1.36% (12/884)	2.44% (11/450)	1.72% (23/1334)
Myalgia	1.58% (14/884)	1.78% (8/450)	1.65% (22/1334)
Pain in extremity	1.24% (11/884)	1.11% (5/450)	1.20% (16/1334)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2.15% (19/884)**	**3.33% (15/450)**	**2.55% (34/1334)**
Nervous system disorders	**9.95% (88/884)**	**9.33% (42/450)**	**9.75% (130/1334)**
Dizziness	3.51% (31/884)	3.11% (14/450)	3.37% (45/1334)
Headache	2.15% (19/884)	1.56% (7/450)	1.95% (26/1334)
Syncope	1.47% (13/884)	1.11% (5/450)	1.35% (18/1334)
Psychiatric disorders	**1.02% (9/884)**	**1.56% (7/450)**	**1.20% (16/1334)**
Renal and urinary disorders	**3.51% (31/884)**	**2.89% (13/450)**	**3.30% (44/1334)**
Acute kidney injury	1.13% (10/884)	0.67% (3/450)	0.97% (13/1334)
Haematuria	0.57% (5/884)	1.11% (5/450)	0.75% (10/1334)
Respiratory, thoracic and mediastinal disorders	**15.61% (138/884)**	**12.22% (55/450)**	**14.47% (193/1334)**
Cough	1.36% (12/884)	0.22% (1/450)	0.97% (13/1334)
Dyspnoea exertional	1.92% (17/884)	1.56% (7/450)	1.80% (24/1334)
Dyspnoea	8.03% (71/884)	6.67% (30/450)	7.57% (101/1334)
Epistaxis	1.24% (11/884)	1.33% (6/450)	1.27% (17/1334)
Skin and subcutaneous tissue disorders	**3.73% (33/884)**	**2.89% (13/450)**	**3.45% (46/1334)**
Dermatitis allergic	1.47% (13/884)	1.33% (6/450)	1.42% (19/1334)
Vascular disorders	**8.71% (77/884)**	**6.67% (30/450)**	**8.02% (107/1334)**
Hypertension	2.60% (23/884)	2.00% (9/450)	2.40% (32/1334)
Hypotension	2.04% (18/884)	1.78% (8/450)	1.95% (26/1334)

Table 19: All Serious Site Reported Adverse Events by Type

Serious Adverse Events to 360 Days	Orsiro (N = 884 Subjects)	Xience (N = 450 Subjects)	All Subjects (N = 1334 Subjects)
Any Serious Adverse Event	**34.73% (307/884)**	**35.78% (161/450)**	**35.08% (468/1334)**
Blood and lymphatic system disorders	**1.13% (10/884)**	**1.11% (5/450)**	**1.12% (15/1334)**
Cardiac disorders	**15.84% (140/884)**	**18.44% (83/450)**	**16.72% (223/1334)**
Acute myocardial infarction	1.02% (9/884)	1.56% (7/450)	1.20% (16/1334)
Angina pectoris	5.09% (45/884)	4.44% (20/450)	4.87% (65/1334)
Angina unstable	3.05% (27/884)	2.67% (12/450)	2.92% (39/1334)
Atrial fibrillation	1.47% (13/884)	1.33% (6/450)	1.42% (19/1334)
Coronary artery disease	0.68% (6/884)	1.33% (6/450)	0.90% (12/1334)
Coronary artery dissection	2.49% (22/884)	4.67% (21/450)	3.22% (43/1334)
Coronary artery stenosis	2.04% (18/884)	2.22% (10/450)	2.10% (28/1334)
Gastrointestinal disorders	**3.96% (35/884)**	**2.44% (11/450)**	**3.45% (46/1334)**
Gastrointestinal haemorrhage	1.02% (9/884)	0.22% (1/450)	0.75% (10/1334)
General disorders and administration site conditions	**8.82% (78/884)**	**7.56% (34/450)**	**8.40% (112/1334)**
Chest pain	1.58% (14/884)	0.22% (1/450)	1.12% (15/1334)
Non-cardiac chest pain	6.56% (58/884)	4.89% (22/450)	6.00% (80/1334)
Vascular stent restenosis	0.68% (6/884)	1.11% (5/450)	0.82% (11/1334)
Infections and infestations	**3.62% (32/884)**	**4.44% (20/450)**	**3.90% (52/1334)**
Injury, poisoning and procedural complications	**1.58% (14/884)**	**2.22% (10/450)**	**1.80% (24/1334)**
Investigations	**1.02% (9/884)**	**0.44% (2/450)**	**0.82% (11/1334)**
Musculoskeletal and connective tissue disorders	**1.81% (16/884)**	**3.56% (16/450)**	**2.40% (32/1334)**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**1.36% (12/884)**	**2.22% (10/450)**	**1.65% (22/1334)**
Nervous system disorders	**2.49% (22/884)**	**3.11% (14/450)**	**2.70% (36/1334)**
Renal and urinary disorders	**1.81% (16/884)**	**1.11% (5/450)**	**1.57% (21/1334)**
Respiratory, thoracic and mediastinal disorders	**4.07% (36/884)**	**2.89% (13/450)**	**3.67% (49/1334)**
Dyspnoea	1.58% (14/884)	0.89% (4/450)	1.35% (18/1334)
Vascular disorders	**2.60% (23/884)**	**2.00% (9/450)**	**2.40% (32/1334)**

2. Additional Analyses of Safety and Effectiveness Results

A 'frequentist' analysis of the key safety and effectiveness outcomes for the BIOFLOW-V ITT cohort of 1334 patients is presented below in Table 20.

Table 20: Safety and Effectiveness Endpoints – ITT Population

BIOFLOW-V	Orsiro (N = 884)	Xience (N = 450)
Target-lesion failure	6.2% (52/833)	9.6% (41/427)
Cardiac death	0.1% (1/831)	0.7% (3/425)
Target-vessel myocardial infarction	4.7% (39/831)	8.3% (35/424)
Clinically-driven target-lesion revascularization	2.0% (17/832)	2.4% (10/422)

BIOFLOW-V	Orsiro (N = 884)	Xience (N = 450)
Death from any cause	0.8% (7/837)	1.4% (6/428)
Any myocardial infarction	4.9% (41/832)	8.7% (37/425)
Q-wave	0.1% (1/831)	1.0% (4/422)
Non-Q-wave	4.8% (40/831)	8.0% (34/425)
Cardiac death or any myocardial infarction	5.0% (42/833)	9.1% (39/427)
Major adverse cardiac events	7.0% (59/839)	10.3% (44/429)
Target-vessel failure	7.2% (60/834)	10.5% (45/427)
Cardiac Death	0.1% (1/831)	0.7% (3/425)
Target-vessel myocardial infarction	4.7% (39/831)	8.3% (35/424)
Clinically-driven target-vessel revascularization	3.2% (27/833)	3.6% (15/422)
ARC Stent Thrombosis	0.5% (4/831)	1.2% (5/424)
Definite/Probable	0.5% (4/831)	0.7% (3/422)
Definite	0.5% (4/831)	0.7% (3/422)
Probable	0.0% (0/830)	0.0% (0/422)

3. Subgroup Analyses

To assess the consistency of the treatment effect, the primary endpoint was analyzed among BIOFLOW-V ITT subjects using Bayesian analysis in subgroups defined according to pre-specified factors: vessel diameter (RVD ≤ 2.75 mm vs. RVD > 2.75 mm), age (> 75 years vs. ≤ 75 years), gender (male vs. female), diabetes (diabetics vs. non-diabetics), lesion length (> 26 mm vs. ≤ 26 mm), overlapping stents vs. single stent in lesions > 26 mm in length and acute coronary syndrome status (unstable angina or elevated cardiac enzymes at baseline vs. none). Consistency was assessed using a test of interaction at the 0.15 level of significance.

Among BIOFLOW-V ITT subjects, results were consistent across all subgroups. Numerically lower 12-month TLF rates were observed for the Orsiro stent compared to the Xience stent in each of the subgroups with the exception of the subgroup of subjects older than 75 years. None of the interactions were significant (p for interaction < 0.15). Any numerical trends should be interpreted with caution due to the smaller number of subjects within subgroups.

Primary Endpoint Evaluation in the Diabetes Sub-group

An additional post hoc analysis of the diabetes subgroups was conducted according to the same statistical methods used for the primary endpoint analysis. The subjects included in this analysis were the subgroup of those included in the primary analysis of the primary endpoint that were identified by site investigators as having baseline diabetes on the electronic case report forms.

The analysis populations in the subgroup analyses were:

- BIOFLOW-V Intent-to-Treat (ITT) diabetes subgroup: 466 subjects (300 Orsiro, 166 Xience);
- BIOFLOW-IV Bayesian Analysis diabetes subgroup: 166 subjects (110 Orsiro, 56 Xience); and
- BIOFLOW-II Bayesian Analysis diabetes subgroup: 120 subjects (78 Orsiro, 42 Xience).

For the purpose of a sensitivity analysis of the primary Bayesian estimate of 12-month TLF, the BIOFLOW-II and BIOFLOW–IV ITT diabetic subgroups were used (including subjects regardless of subjects satisfying BIOFLOW-V eligibility criteria) instead of the corresponding Bayesian analysis of the diabetes subgroup populations.

Of the 1334 subjects in the BIOFLOW-V ITT population, 466 (34.9%) were identified as having diabetes at baseline and were included in the BIOFLOW-V diabetes subgroup.

Overall, subjects in the BIOFLOW-V ITT diabetes subgroup had a mean±SD age of 64.7±9.5 years; 71.7% of subjects were male and 86.7% of subjects were white. Medical history (% of subjects) included hypertension (87.4%), hyperlipidemia (85.3%), renal disease (9.5%), smoking (20.2% current/40.1% former), prior myocardial infarction (MI) (28.3%), prior percutaneous coronary artery intervention (PCI) (40.6%), and prior coronary artery bypass graft (CABG) (8.0%). At baseline, 45.1% of subjects had stable angina and 50.6% of subjects had acute coronary syndrome. At baseline, 30.5% of diabetic subjects were taking insulin. There were no statistically significant differences between the Orsiro and Xience groups with respect to any demographics, medical history or risk factors.

The primary analysis of the 12-month TLF rate was a Bayesian non-inferiority analysis using data from BIOFLOW-V subjects and the prior studies, BIOFLOW-II and BIOFLOW-IV. The primary analysis was carried out on all BIOFLOW-V ITT subjects with baseline diabetes who experienced TLF within 360 days of follow-up or at least 330 days of follow-up, and on the diabetes subgroups of the Bayesian analysis populations for BIOFLOW-II and BIOFLOW-IV. A total combined Bayesian analysis population of 719 subjects (468 Orsiro subjects and 251 Xience subjects) was included in the analysis of 12-month TLF rate. Among diabetic subjects, the Bayesian estimate of the mean 12-month TLF rate was 6.94% in the Orsiro group compared to 9.06% in the Xience group (difference of -2.12%, 95% credible interval of -6.97% to 2.32%). The posterior probability that the difference in the rate of 12-month TLF between Orsiro and Xience is less than the margin of 3.85% is 99.61%, demonstrating non-inferiority of Orsiro versus Xience with regards to 12-month TLF.

A frequentist analysis was performed on 12-month TLF and its components using only BIOFLOW-V data. Among BIOFLOW-V ITT diabetic subjects, the 12-month TLF rate was 6.43% in the Orsiro group compared to 9.80% in the Xience group (difference of -3.38% [95% confidence interval (CI): -9.57% to 1.77%]; p=0.255 for superiority). A lower rate of target vessel MI was observed

in the Orsiro group but was not statistically significant: 4.30% compared to 7.95% (difference of -3.65% [95% CI: -9.37% to 0.89%]; p=0.127).

A sensitivity analysis was performed by including all BIOFLOW-II and BIOFLOW-IV randomized subjects with baseline diabetes who had sufficient follow-up data (at least 330 days of follow-up or experienced TLF within 360 days post-procedure) whether or not the subjects satisfied the BIOFLOW-V inclusion/exclusion criteria. The Bayesian estimate of mean 12-month TLF in this population was 7.11% in the Orsiro group compared to 8.96% in the Xience group (difference of -1.85%, 95% credible interval of -6.70% to 2.58%) with a posterior probability of non-inferiority of 99.44%.

A second sensitivity analysis included the assessment of the 12-month TLF rate among the Bayesian ITT population of the 3 trials using the ARC definition for the target vessel MI component of TLF was performed. When the definition of TLF was extended to include ARC-defined target vessel MI, the Bayesian estimate of mean 12-month TLF was 11.81% in the Orsiro group compared to 15.81% in the Xience group (difference of -4.00%, 95% credible interval of -10.17% to 1.83%) with a posterior probability of non-inferiority of 99.67%. The rate of 12-month ARC-defined target vessel MI was 9.61% (27/281) in the Orsiro group compared to 13.91% (21/151) in the Xience group (difference of -4.30%, 95% CI of -11.35% to 1.82%). Similarly, the rate of 12-month TLF in the frequentist analysis was 11.70% (33/282) in the Orsiro group compared to 15.69% (24/153) in the Xience group (difference of -3.98%, 95% CI of -11.33% to 2.53%).

Overall rates of the primary endpoint and its components observed for Orsiro were similar to those observed for the comparator Xience within and between diabetic and non-diabetic cohorts. The overall 12-month TLF rate in the insulin-dependent diabetic cohort was 8.13% (10/123) for Orsiro and 13.16% (10/76) for Xience, with a mean difference of -5.03% and 95%CI [-15.11%, 3.49%]. Non-diabetics had a 12-month TLF rate of 6.02% (60/997) in Orsiro, versus 8.16% (40/490) in Xience, with a mean difference of -2.15%, 95% CI [-5.20%, 0.54%]. Medically-treated diabetic patients had a 12-month TLF rate of 7.22% (32/443) for Orsiro compared to 7.69% (18/234) for Xience, with a mean difference of -0.47%, 95% CI [-5.09%, 3.47%].

Results for measures of acute success and for rates of clinical endpoints (including death, MI, composites of cardiac death/MI, MACE, TVF and their components, and stent thrombosis) were similar in the Orsiro and Xience groups among diabetic subjects.

The results of the Bayesian analysis in the BIOFLOW-V ITT diabetes subgroup demonstrated the non-inferiority of Orsiro versus Xience with regard to 12-month TLF rate. These results support the non-inferiority in safety and effectiveness of the Orsiro stent compared to the Xience stent in a population of subjects with baseline diabetes undergoing percutaneous coronary intervention.

4. Pediatric Extrapolation

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

E. Financial Disclosure

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 BIOFLOW-V pivotal clinical study included 512 investigators of which none were full-time or part-time employees of the sponsor and eight had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 8
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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

A. BIOFLOW-II Clinical Trial

Primary Objective: The primary objective of the BIOFLOW-II trial was to evaluate the angiographic efficacy of the Orsiro Sirolimus Eluting Coronary Stent System compared to the Xience Prime Everolimus-Eluting Coronary Stent System for the treatment of atherosclerotic lesions ≤ 26 mm in length by visual estimate in native coronary arteries of 2.25 mm to 4.00 mm in diameter (by visual estimate).

Design: Patients aged 18 years or older with stable or unstable angina pectoris, silent ischemia, or clinical evidence of myocardial ischemia undergoing planned stent implantation in a single *de novo* native coronary lesion were eligible for enrollment. Angiographic inclusion criteria included a reference vessel diameter between 2.25 and 4.0 mm with lesion length ≤ 26 mm by visual estimation. Principal angiographic exclusions included chronic total occlusions, bifurcations involving a side branch with diameter >2.0 mm, bypass graft stenoses and in-stent

restenosis. Further exclusion criteria included thrombus in the target vessel, unprotected left main coronary artery disease (stenosis > 50%), evidence of myocardial infarction within 72 hours prior to the index procedure, heavily calcified lesions, ostial target lesions within 5.0 mm of vessel origin, and target lesions in or supplied by an arterial or venous bypass graft were also excluded. The protocol recommended antiplatelet therapy for a minimum of 6 months unless contraindicated.

The BIOFLOW-II study was designed to test the hypothesis that the in-stent late lumen loss at 9 months in patients treated with the Orsiro Stent was non-inferior to the in-stent late lumen loss at 9 months in patients treated with the Xience Prime control.

A total of 452 patients (298 Orsiro and 154 Xience Prime) were randomized and enrolled at 24 clinical sites in Europe. Of the 452 patients included in the intent-to-treat analysis set, a total of 438 (288 Orsiro and 150 Xience Prime) completed the 9-month follow-up visit. Angiography was completed for 85% of patients (383 total; 252 Orsiro and 131 Xience Prime) for evaluation of the 9-month primary endpoint. A total of 435 patients (287 Orsiro and 148 Xience Prime) were evaluable at the 12-month (379 days) interval. Follow-up included clinical assessments at 30 days, 6, 9, 12 months and 2, 3, 4 and 5 years post index procedure. An OCT substudy was performed at 6 of 24 sites in 65 patients at baseline and an intravascular ultrasound (IVUS) substudy was performed at 5 of 24 sites in 66 patients at baseline.

Demographics: Patients were well-matched for baseline demographics. Average age was 62.7±10.4 and 64.8±9.2 in the Orsiro and Xience Prime groups, respectively. Approximately 78.2% of patients in the Orsiro Stent group and 74.7% of patients in the Xience Prime Stent group were male, and 28.2% of patients in the Orsiro group and 28.6% in the Xience Prime group had diabetes.

Baseline lesion characteristics: Mean reference vessel diameter (RVD) was 2.78±0.49 mm and 2.75±0.49 mm for the Orsiro and Xience Prime, respectively. The percent diameter stenosis was 66.7±14.3 and 65.3±14.5 for the Orsiro and Xience Prime, respectively.

Results: The mean in-stent late lumen loss at 9 months was 0.10±0.32 mm for Orsiro as compared to 0.11±0.29 mm for the Xience Prime™ (Table 21). The non-inferiority hypothesis was confirmed with a p value <0.0001. At 12 months, the TLF Kaplan Meier estimate was 6.5% (95% CI [4.2%, 10.0%]) in the Orsiro group compared to 8.0% (95% CI [4.6%, 13.7%]) in the Xience Prime™ group (Table 22).

Table 21: BIOFLOW-II Primary Endpoint – Late Lumen Loss - Angiographic Follow-Up Results at 9 Months

Angiographic Outcomes			Difference	
	Orsiro (n=278 lesions)	Xience (n=149 lesions)	Estimate (95% CI)	p Value
Late lumen loss, mm (Mean±SD)				
In-stent	0.10±0.32	0.11±0.29	0.0006 (−0.06 to .07)	0.98
In-segment	0.09±0.35	0.09±0.33	0.007 (−0.07 to 0.08)	0.86

Mean±SD or counts (%) are reported for each randomized arm. Two-sided p values from superiority tests, differences, odds ratios, and 95% CIs are based on models; differences are the mean of the Orsiro arm minus the mean of the Xience arm. Continuous and categorical outcomes were analyzed at lesion level with mixed effects linear regression models or mixed effects logistic regression models that account for the nonindependence of multiple lesions within patients. Late loss is defined as minimal lumen diameter at the baseline post procedure minus minimal lumen diameter at 9 months of follow-up. CI indicates confidence interval.

Table 22: BIOFLOW-II Kaplan-Meier Estimates of Endpoints at 12 Months, Intent-to-Treat Patients

Endpoints	Orsiro (n=298)	Xience (n=154)
EFFICACY		
Target lesion failure (TLF)	6.5%	8.0%
Cardiac death	0.7%	0.7%
Clinically indicated TLR	3.5%	4.7%
TV MI	2.7%	2.6%
Target vessel failure (TVF)	9.3%	10.1%
Cardiac death	0.7%	0.7%
Clinically indicated TVR	6.6%	6.7%
TV MI	2.7%	2.6%
SAFETY		
Death	1.0%	0.7%
Cardiac death or MI	3.7%	3.3%
Cardiac death	0.7%	0.7%
MI*	3.1%	2.6%
TV MI	2.7%	2.6%
Definite Stent Thrombosis	0.0%	0.0%
Probable Stent Thrombosis	0.0%	0.0%

Number of events (Kaplan–Meier–based incidence rates [%]) are reported. No coronary artery bypass grafting revascularization events were reported. Target lesion failure is the composite of cardiac death, target-vessel myocardial infarction, coronary artery bypass grafting, or clinically driven TLR. Target vessel failure is the composite of cardiac death, target-vessel myocardial infarction, coronary artery bypass grafting, or clinically driven TVR. CI indicates confidence interval; MI, myocardial infarction; TLR, target-lesion revascularization; TV, target vessel; and TVR, target-vessel revascularization.

*Event rates for myocardial infarction in the table are reported according to the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force universal definition of myocardial infarction.

B. BIOFLOW-IV Clinical Trial

Primary Objective: The primary objective of the BIOFLOW-IV trial was to evaluate the safety and effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System compared to the Xience Prime™ or Xience Xpedition™ Everolimus-Eluting Coronary Stent System for the treatment of patients with up to two *de novo* atherosclerotic coronary artery lesions with lesion length ≤26 mm and vessel diameters ≥ 2.50 mm and ≤ 3.75 mm by visual estimate.

Design: Eligible patients aged 18 years to ≤ 80 years old with ischemic heart disease undergoing planned stent implantation in a single *de novo* native coronary lesion in up to two coronary arteries were eligible for enrollment. Angiographic inclusion criteria included a reference vessel diameter between 2.5 and 3.75 mm with lesion length ≤ 26 mm by visual estimation and TIMI flow ≥ 2. Principal angiographic exclusions included target lesions in the left main, lesions located in or supplied by an arterial or venous bypass graft, heavy calcification, and bifurcations involving a side branch with diameter >2.0 mm. Multiple focal stenosis were considered a single lesion if they could be completely covered with a single stent. Clinical exclusion criteria included patients with recent (<72 hours) ST-segment elevation myocardial infarction, left ventricular ejection fraction <30%, those currently on immunosuppressive therapy, impaired renal function, target vessel(s) or side branch treated with any type of PCI within 12 months prior to the index procedure, target lesion requiring any treatment with a device other than a pre-dilatation balloon prior to stent placement, planned intervention of the target vessel after the index procedure, three-vessel coronary artery disease at time of procedure, and those unlikely to adhere to dual antiplatelet therapy (DAPT) were also excluded. The protocol recommended antiplatelet therapy for a minimum of 6 months and highly recommended for 12 months for patients who were not at a high risk of bleeding.

The BIOFLOW-IV study was designed to test the hypothesis that the rate of 12-month TVF in patients treated with the Orsiro Stent was non-inferior to the rate of 12-month TVF in patients treated with the Xience control. TVF was defined as the composite rate of any clinically-driven revascularization of the target vessel, target vessel Q-wave or non-Q-wave myocardial infarction, emergent CABG, or cardiac death. The analysis of the primary endpoint of 12-month TVF was evaluated for all patients who were randomized to a study stent.

A total of 579 patients (387 Orsiro and 192 Xience) were randomized and enrolled at 46 clinical sites in Japan, Europe, and Australia. Of the 579 patients enrolled, 575 patients (385 Orsiro and 190 Xience) were included in the intent-to-treat analysis set. A total of 557 patients (374 Orsiro and 183 Xience) were evaluable for the 12-month primary endpoint. Follow-up included clinical assessments at 30 days, 6, 12 months and 2, 3, 4 and 5 years post index procedure.

Demographics: The average patient age was 64.8±9.6 and 64.4±9.8 in the Orsiro and Xience groups, respectively. Approximately 72.7% of patients in the Orsiro Stent group and 76.8% of patients in the Xience Stent group were male, and 30.4% of patients in the Orsiro group and 31.1% in the Xience group had diabetes.

Baseline lesion characteristics: Average lesion length was 13.7±6.1 mm and 13.4±6.3 mm for the Orsiro and Xience Stent groups, respectively. Mean lesion diameter stenosis was 66.3% and 65.2% for the Orsiro and Xience groups, respectively.

Results: The 12-month TVF rate in the ITT population, based on the MI Universal Definition, was 5.1% in the Orsiro group compared to 6.6% in the Xience group, with a difference of -1.5% [95% CI: -5.7%, 2.7%] and the primary endpoint was met (p=0.0003, for non-inferiority) (Table 23).

Table 23: BIOFLOW-IV, Kaplan Meier Estimates of Secondary Endpoints at 12 Months.

Endpoints	Orsiro N=385 Rate, % (n)	Xience N=190 Rate, % (n)
TVF (MI Universal Definition)	5.5% (19)	7.5% (12)
TVF (MI Extended Historical Definition)	4.0% (13)	4.9% (7)
Clinically driven (CD) TVR	3.7% (12)	3.9% (5)
TLF (MI Universal Definition)	4.2% (14)	5.4% (8)
TLF (MI Extended Historical Definition)	2.6% (8)	2.8% (3)
TLR (CD)	2.1% (6)	1.8% (1)
MI (Universal Definition)	3.7% (14)	3.2% (6)
MI (Extended Historical Definition)	1.8% (7)	0.5% (1)
Death (all-cause)	1.6% (6)	2.9% (4)
Death (Cardiac)	0.0% (0)	0.5% (1)
Death (Non-cardiac)	1.6% (6)	2.4% (3)
Stent thrombosis (Definite/Probable)	0.8% (3)	0.0% (0)

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 Circulatory Systems 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 principal safety and effectiveness information for the Orsiro Sirolimus Eluting Coronary Stent System is derived from preclinical studies and from the BIOFLOW-V clinical trial. The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

Non-clinical testing performed during the design and development of the Orsiro Sirolimus Eluting Coronary Stent System confirmed the product design characteristics, specifications, and intended use.

The in vitro engineering testing conducted on the stent and delivery system demonstrated that the performance characteristics met the product specifications. The biocompatibility evaluation and in vivo animal studies demonstrated that the acute and chronic in vivo performance characteristics of the Orsiro Sirolimus Eluting Coronary Stent System provide reasonable assurance of safety and acceptability for clinical use. The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The shelf life testing has established acceptable performance for the labeled shelf life of two years.

A. Effectiveness Conclusions

The BIOFLOW-V multi-center randomized controlled clinical trial evaluated the safety and effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System compared to the Xience stent system.

The primary endpoint was TLF at 12 months, defined as the composite of cardiovascular death, target vessel-related MI or clinically-driven TLR.

For the analysis of the primary endpoint, the trial employed a Bayesian design to incorporate data from two prior randomized trials (the BIOFLOW-II and BIOFLOW-IV trials), which reduced the sample size needed for the trial. The pooled analysis included 2208 subjects. The study statistical plan included a 12-month TLF target rate of 7.0% and pre-specified a 3.85% non-inferiority margin, with 97.5% posterior probability success criteria.

The 12-month Bayesian population TLF rate estimate was 6.3 ± 0.8% for Orsiro versus 8.9 ± 1.2% for Xience, which resulted in a mean estimate difference of -2.6± 1.4%, 95% Credible Interval (-5.5% to 0.1%) and a posterior probability of 100.0%.

Therefore, the primary endpoint was met, with the treatment difference demonstrating unequivocal non-inferiority of Orsiro to Xience, which exceeded the pre-defined 97.5% criteria for success.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The biocompatibility, in vivo pharmacokinetics, and in vivo performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

As noted above, the primary endpoint of the BIOFLOW-V study was met, and the study satisfactorily demonstrated the safety of the Orsiro Sirolimus Eluting Coronary Stent System. Individual components of the TLF composite rates of cardiac death, target-vessel myocardial infarction and ischemia-driven TLR at 12 months were 0.1%, 4.7%, and 2.0%, respectively in the Orsiro BIOFLOW-V ITT population as compared to with 0.7%, 8.3% and 2.4% in the Xience. In addition, the 12-month rate of definite/probable stent thrombosis according to ARC definitions for the BIOFLOW-V ITT cohort was 0.5% in Orsiro versus 0.7% for Xience.

No UADEs occurred during the BIOFLOW-V study. There have been 2750 adverse events, including 912 serious adverse events reported for the BIOFLOW-V study through 360 days. Overall rates of device/procedure-related AEs were similar across the study groups. The overall adverse event profile and frequency of events observed was similar to those previously reported for US-marketed drug eluting stents.

Long-term evaluations at 2, 3, 4 and 5 years require additional data collection and analysis due to the small number of evaluations completed. However, available data from BIOFLOW-II[iii, iv] and BIOSCIENCE[v] trials, as well as the SCAAR[vi] registry support long-term safety of the Orsiro Sirolimus Eluting Coronary Stent System.

C. Benefit-Risk Determination

The probable benefits of the Orsiro Sirolimus Eluting Coronary Stent System are based on data collected in the clinical study conducted in support of PMA approval as described above.

The Orsiro Sirolimus Eluting Coronary Stent System has been shown to be beneficial for improving luminal diameter in patients with symptomatic coronary artery disease. In the pivotal IDE BIOFLOW-V trial, Orsiro demonstrated unequivocal non-inferiority compared with the approved Xience stent system for TLF at 12-months, a meaningful and clinically important assessment of both safety and effectiveness.

The patients treated in the BIOFLOW-V study represent a standard PCI population, and the results can be applied to the general population of patients with coronary artery disease.

These benefits outweigh the risks when used as intended according to the Instructions for Use, as determined by the product risk analysis. No new risks were identified in

the BIOFLOW-V study and the overall risks were similar to those observed for other US marketed drug-eluting stents.

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

In summary, the available data support the conclusion that the probable benefits outweigh the risks for the use of Orsiro Sirolimus Eluting Coronary Stent System for improving coronary luminal diameter in patients, including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, non-ST elevation MI or documented silent ischemia due to atherosclerotic lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm and a lesion length of ≤ 36 mm.

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. Although the majority of clinical and non-clinical studies used earlier iterations of the Orsiro Stent manufactured from a previous version of the BIOlute Coating formulation, the results are reasonably representative of the performance of the approved version of the Orsiro stent to support marketing along with the conditions of approval described below.

XIV. CDRH DECISION

CDRH issued an approval order on February 22, 2019. The final conditions of approval cited in the approval order are described below.

1. You will conduct an additional real time *in vitro* polymer degradation study (3 lots and 6 samples/lot) on the Orsiro stent system, produced according to the approved manufacturing conditions, using different raw material batches (e.g., different lots of polymer and solvent). The degradation study will include characterizing the mass loss, molecular weight change and degradation products with sufficient time points covering all stages of the degradation process.

2. You will conduct a real time *in vitro* degradation study monitoring the polymer characteristics during the full degradation process for each incoming lot of solvent until alternative measures are approved.

3. You will conduct a post-approval study (PAS) to confirm that the clinical performance of the Orsiro stent, produced according to the approved manufacturing conditions, is similar to the clinical performance observed for the Orsiro stent studied in the IDE pivotal trial. The PAS will be a single-arm study, and the primary endpoint will be Target Lesion Failure (TLF) at 1-year, defined as Cardiac Death, Target Vessel Myocardial Infarction or Target Lesion Revascularization. The study

will enroll at least 500 on-label subjects, and the TLF rate will be compared with a statistically valid performance goal that is based on the TLF rate observed in patients treated with Orsiro stents in the BIOFLOW V pivotal trial. You will collect and report clinical outcomes to FDA through at least 5 years post-procedure on patients enrolled in the Biotronik ORSIRO PAS.

~~3.~~4. You will continue follow-up of the BIOFLOW-V Clinical Study, which was initiated prior to device approval. The BIOFLOW-V study (G140078) is a prospective, international, multicenter, randomized controlled trial (RCT) designed to evaluate the safety and effectiveness of the Orsiro Sirolimus Eluting Coronary Stent System compared to the Xience Everolimus-Eluting Coronary Stent System for the treatment of atherosclerotic lesions ≤36 mm in length in native coronary arteries of 2.25 mm to 4.0 mm in diameter (by visual estimate). The BIOFLOW-V study was designed to test the hypothesis that the rate of 12-month target lesion failure (TLF) in patients treated with an Orsiro stent was non-inferior to the rate of 12-month TLF in patients treated with a Xience stent. You will collect and annually report clinical outcomes to FDA through 5 years post-procedure on patients enrolled in the BIOFLOW-V Clinical Study.

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.

XVI. REFERENCES

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