BIOFLOW-V:

BIOTRONIK – A Prospective Randomized Multicenter Study to Assess the Sa**F**ety and Effectiveness of the Orsiro Siro**L**imus Eluting Coronary Stent System in the Treatment **O**f Subjects **W**ith up to Three *De Novo* or Restenotic Coronary Artery Lesions – **V**

Clinical Investigational Plan

Final Version 4.0, February 11, 2016

IDE#G140078

Investigational Device	Orsiro Sirolimus Eluting Coronary Stent System
Sponsor and Manufacturer	BIOTRONIK, Inc. Vascular Intervention Clinical Studies 6024 Jean Road Lake Oswego, Oregon 97035 United States of America BIOTRONIK AG Center for Vascular Intervention Ackerstrasse 6 8180 Bülach Switzerland
Sponsor Contact	[redacted]
Protocol Development	Harvard Clinical Research Institute [redacted]

STUDY PRINCIPAL INVESTIGATORS SIGNATURE PAGE

IDE# G140078

I, the undersigned, have read and understood the Clinical Investigational Plan for the study entitled:

BIOFLOW-V:
BIOTRONIK – A Prospective Randomized Multicenter Study to Assess the Sa**F**ety and Effectiveness of the Orsiro Siro**L**imus Eluting Coronary Stent System in the Treatment **O**f Subjects **W**ith up to Three *De Novo* or Restenotic Coronary Artery Lesions – **V**

BIOTRONIK, Inc.
BIOTRONIK AG

And agree with its contents. I declare that I will comply with all the Clinical Investigational Plan's requirements. The Clinical Investigational Plan, the Investigator's Agreement and any additional information provided by BIOTRONIK will serve as a basis for cooperation in the clinical investigation

US Study Principal Investigator [redacted]

Investigator's Signature _____

Date _____

OUS Study Principal Investigator [redacted]

Investigator's Signature _____

Date _____

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

IDE# G140078

I have reviewed this protocol for the study entitled:

BIOFLOW-V:
BIOTRONIK – A Prospective Randomized Multicenter Study to Assess the Sa**F**ety and Effectiveness of the Orsiro Siro**L**imus Eluting Coronary Stent System in the Treatment **O**f Subjects **W**ith up to Three *De Novo* or Restenotic Coronary Artery Lesions – **V**

BIOTRONIK, Inc.
BIOTRONIK AG

The signature below documents the receipt and review of the BIOFLOW-V clinical study protocol and any attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US Federal Regulations, ISO 14155, ICH and GCP guidelines

Investigator Name (print or type) _____

Investigator's Signature _____

Date _____

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1. PROTOCOL SYNOPSIS

STUDY TITLE	BIOFLOW-V: **BIO**TRONIK – A Prospective Randomized Multicenter Study to Assess the Sa**F**ety and Effectiveness of the Orsiro Siro**L**imus Eluting Coronary Stent System in the Treatment **O**f Subjects **W**ith up to Three *De Novo* or Restenotic Coronary Artery Lesions – **V**.
INVESTIGATIONAL DEVICE	BIOTRONIK Orsiro Sirolimus Eluting Coronary Stent System.
OBJECTIVES	To assess the safety and efficacy of the Orsiro Sirolimus Eluting Coronary Stent System in the treatment of subjects with up to three native de *novo* or restenotic (standard PTCA only) coronary artery lesions compared to the Xience coronary stent system.
STUDY DESIGN	BIOFLOW-V is a prospective, multicenter, randomized, controlled trial combining data on the randomized subjects with data from two historical studies by employing a Bayesian approach. Subjects with coronary artery disease (CAD) that qualify for percutaneous coronary intervention (PCI) with stenting will be screened per the protocol inclusion and exclusion criteria to achieve a total of up to 1,400 randomized subjects. Eligible subjects will be randomized in a 2:1 ratio to undergo percutaneous coronary revascularization with either the Orsiro Sirolimus Eluting Stent System (treatment group) or the Xience Everolimus Eluting Stent System (control group). BIOFLOW-V randomized subjects will be combined with historical Orsiro, Xience Prime™ and Xience Xpedition™ randomized subjects from the BIOFLOW-II and BIOFLOW-IV trials by employing a Bayesian statistical approach. Only subjects that meet all clinical and angiographic eligibility criteria of the BIOFLOW-V trial will be included in the analysis.
SUBJECT POPULATIONS	Subjects with CAD due to *de novo* lesions or restenotic lesions from percutaneous transluminal coronary angioplasty (PTCA) in native coronary arteries with a reference vessel diameter of 2.25–4.0 mm and lesion length of ≤ 36 mm.
NUMBER OF SUBJECTS	Sufficient number of subjects will be provisionally enrolled in the trial to achieve a total of up to 1,400 randomized subjects (933 Orsiro: 467 Xience). It is expected that approximately 50% will be enrolled in the United States.
NUMBER OF CLINICAL SITES	Up to 100 clinical sites in the United States and 50 clinical sites outside of the United States.

CLINICAL INCLUSION CRITERIA	Subjects must meet all of the following criteria to participate in the trial: 1. Subject is ≥18 years or the minimum age required for legal adult consent in the country of enrollment. 2. Subject is an acceptable candidate for PCI. 3. Subject is an acceptable candidate for CABG. 4. Subject has clinical evidence of ischemic heart disease, stable or unstable angina pectoris or documented silent ischemia. 5. Subject is eligible for dual anti-platelet therapy treatment with aspirin plus either, clopidogrel, prasugrel, ticagrelor or ticlopidine. 6. Subject has provided written informed consent. 7. Subject is willing to comply with study follow-up requirements.
ANGIOGRAPHIC INCLUSION CRITERIA	Each target lesion/vessel must meet all of the following angiographic criteria for the subject to be eligible for the trial: 1. 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). 2. Target lesion must be *de novo* or restenotic lesion in native coronary artery; restenotic lesion must have been treated with a standard PTCA only. 3. Target lesion must be in major coronary artery or branch (target vessel). 4. 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, SPECT, or stress echo), cardiac computed tomography (CT), electrocardiography, fractional flow reserve, or post infarct angina. 5. Target vessel must have a Thrombolysis In Myocardial Infarction (TIMI) flow > 1. 6. Target lesion must be ≤ 36 mm in length by operator visual estimate. 7. Target vessel must have a reference vessel diameter of

	2.25–4.0 mm by operator visual estimate.
ANGIOGRAPHIC INCLUSION CRITERIA (CONT.)	8. Target lesion must be amenable to treatment with a maximum of two overlapping stents.
CLINICAL EXCLUSION CRITERIA	Subjects will be excluded from the trial if any of the following criteria are met: 1. Subject has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute ST elevation myocardial infarction (STEMI) within 72 hours prior to the index procedure. *Note: Hemodynamically stable non-STEMI (NSTEMI) subjects are eligible for study enrollment.* 2. Subject is hemodynamically unstable. 3. Subject is pregnant and/or breastfeeding or intends to become pregnant during the duration of the study. 4. 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. 5. 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. 6. Planned treatment of a lesion not meeting angiographic inclusion and exclusion criteria during the index procedure or after the index procedure. 7. Planned surgery within 6 months of index procedure unless dual antiplatelet therapy can be maintained throughout the peri-surgical period. 8. History of a stroke or transient ischemic attack (TIA) within 6 months prior to the index procedure. 9. Subjects with active bleeding disorders, active coagulopathy, or any other reason, who are ineligible for DAPT. 10. Subject will refuse blood transfusions. 11. 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.
CLINICAL EXCLUSION CRITERIA (CONT.)	12. Subject is dialysis-dependent. 13. 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). 14. 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). 15. 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). 16. Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent). 17. Subject has life expectancy of < 1 year. 18. 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. 19. In the investigator's opinion, subject will not be able to comply with the follow-up requirements.
ANGIOGRAPHIC EXCLUSION CRITERIA	Subjects will be excluded from the trial if any of the target lesions/vessels meets any of the following angiographic criteria: 1. Target lesion is located within a saphenous vein graft or arterial graft. 2. Target lesion is a restenotic lesion that was previously treated with a bare metal or drug eluting stent (in-stent restenosis). 3. Target lesion has any of the following characteristics: a. 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). b. Involves a side branch of > 2.0 mm in diameter. *Note: Lesions within 3 mm of the origin of the right coronary artery may be treated.*

	4. 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.
ANGIOGRAPHIC EXCLUSION CRITERIA (CONT.)	5. Target vessel has angiographic evidence of thrombus. 6. Target lesion is totally occluded (100% stenosis). 7. Target vessel was treated with brachytherapy any time prior to the index procedure.
PRIMARY ENDPOINT	Target lesion failure (TLF) rate at 12 months post–index procedure. 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).
SECONDARY ENDPOINTS	Secondary endpoints include the following measures: 1. Device success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only. *Note: Post-dilatation is allowed to achieve device success.* 2. Lesion success, defined as attainment of < 30% residual stenosis of the target lesion using any percutaneous method. 3. Procedure success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only without occurrence of in-hospital major adverse cardiac events (MACE; composite of all-cause death, Q-wave or non–Q-wave MI, and any clinically-driven TLR). The following secondary clinical endpoints will be evaluated prior to discharge, at 1, 6 and 12 months and annually thereafter through 5 years follow-up: 4. Death. 5. MI. 6. Cardiac death or MI. 7. MACE and individual MACE components (MACE: composite of all-cause death, Q-wave or non–Q-wave MI, and any clinically-driven TLR). 8. TLF and individual TLF components (TLF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and any clinically-driven TLR). 9. Target vessel failure (TVF) and individual TVF components

	(TVF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and any clinically-driven TVR).
SECONDARY ENDPOINTS (CONT.)	10. Stent thrombosis (all, definite, definite/probable, probable, possible) according to Academic Research Consortium (ARC) criteria for acute, subacute, late, very late and cumulative stent thrombosis.
SUBJECTS FOLLOW-UP	Randomized subjects will be followed through 5 years post–index procedure, with clinical follow-up at 1 month, 6 months, 12 months and annually thereafter through 5-years. An office visit is required for the 12-month follow-up. All visits except the 12-month visit may be performed by telephone interview.
TREATMENT STRATEGY	• Eligible subjects will be randomized in a 2:1 ratio to receive either the Orsiro Sirolimus Eluting Stent or the Xience Everolimus Eluting Stent. Randomization will be stratified by study center. • Subjects may receive treatment for up to three target lesions, one or two target lesions per target vessel, for a maximum of two target vessels. *Note: Concurrent treatment of non-target lesions during the index procedure is not allowed.* • All target lesions are to be treated with the assigned study stent per randomization. • All target lesions are to be treated during a single index procedure. Pre-dilatation of the target lesion(s) must be performed. Direct stenting of the target vessel(s) is not allowed. • Post-dilatation may be performed at the investigator's discretion. • Cardiac biomarkers CK and/or CKMB (CKMB is required [or troponin if CKMB is not available]) will be measured at 6–24 hours post index procedure. • Dual antiplatelet therapy (DAPT) is recommended for a minimum of 6 months and highly recommended for 12 months in subjects not at a high risk of bleeding. • All subjects will receive a minimum of 150 mg aspirin within 24 hours prior to the procedure and continued on a minimum of 75 mg aspirin daily indefinitely post-procedure. • Subjects will receive a loading dose of 600 mg clopidogrel, within 24 hours prior to the procedure or immediately post-procedure (within 30 minutes). Clopidogrel may be substituted with prasugrel at a loading dose of 60 mg or

	ticagrelor at a loading dose of 180 mg. No loading dose is required for subjects on chronic thienopyridine therapy. Following the procedure, subjects will receive treatment with the same thienopyridine agent for a minimum of 6 months, highly recommended for 12 months for subjects not at high risk for bleeding, as follows: **Clopidogrel:** 75 mg daily **Prasugrel:** 10 mg daily; a lower dose of 5 mg daily is allowed for subjects < 60 kg. **Ticagrelor:** 90 mg twice daily. **Ticlopidine:** 250 mg twice daily. OUS investigators may follow medication administration recommendations in accordance with the European Society of Cardiology (ESC) guidelines, national guidelines and/or hospital standard of care.

2. STUDY ADMINISTRATION

SPONSOR

BIOTRONIK, Inc.
Vascular Intervention Clinical Studies
6024 Jean Road
Lake Oswego, Oregon 97035
United States of America

[redacted]

BIOTRONIK AG
Center for Vascular Intervention
Ackerstrasse 6
8180 Bülach
Switzerland

[redacted]

US STUDY PRINCIPAL INVESTIGATOR

[redacted]

OUS STUDY PRINCIPAL INVESTIGATOR

[redacted]

STEERING COMMITTEE CHAIRPERSON

[redacted]

ELECTRONIC DATA CAPTURE VENDOR

MedNet Solutions, Inc.
110 Cheshire Lane
Minnetonka, Minnesota 55305

DATA COORDINATING CENTER	United States of America Harvard Clinical Research Institute 930 Commonwealth Ave Boston, Massachusetts 02215 United States of America [redacted]
STATISTICAL CENTER	Harvard Clinical Research Institute 930 Commonwealth Avenue Boston, Massachusetts 02215 United States of America
DATA MONITORING COMMITTEE CHAIRPERSON	[redacted]
CLINICAL EVENTS COMMITTEE	Harvard Clinical Research Institute 930 Commonwealth Avenue Boston, Massachusetts 02215 United States of America [redacted]
ANGIOGRAPHIC CORE LABORATORY	MedStar Health Research Institute CRI Angiographic Core Lab Washington Hospital Center 110 Irving St, NW, Suite 4B-1, Washington, District of Columbia 20010, USA United States of America [redacted]

MONITORING

Harvard Clinical Research Institute
930 Commonwealth Avenue
Boston, Massachusetts 02215
United States of America

[redacted]

[redacted]

BIOTRONIK AG
Center for Vascular Intervention
Ackerstrasse 6
8180 Bülach
Switzerland

BIOTRONIK, Inc.
Vascular Intervention Clinical Studies
6024 Jean Road
Lake Oswego, Oregon 97035
United States of America

3. INTRODUCTION

Each year, approximately 7.2 million people worldwide die from coronary artery disease (CAD),[1] with 11.1 million deaths per year projected by 2020.[2] Since the first percutaneous transluminal coronary angioplasty (PTCA), this procedure has become a widely accepted treatment modality for coronary artery disease. For the majority of patients with CAD, treatment with PTCA provides high initial procedural success, symptomatic relief, improvement in functional capacity, and survival rates similar to those of coronary artery bypass grafting (CABG). However, all percutaneous techniques, regardless of mode of intervention, have relatively high rates of repeat interventions at long-term follow-up, a limitation that is attributable to restenosis or angiographic re-narrowing of the vessel's lumen.[3] Distinct from atherosclerotic lesions, restenosis following conventional angioplasty results from elastic recoil, vessel contraction, thrombus formation, smooth muscle cell proliferation and excessive production of extracellular matrix. Depending on the subject population and angiographic diagnostic criteria, reported incidence of restenosis after PTCA ranges from 30% to 50%.[4] Such rates of recurrence have serious economic consequences.

The first type of stent used in percutaneous coronary intervention (PCI) was a bare metal stent (BMS), designed to address restenosis following PTCA.[5] BMS reduced the angiographic and clinical restenosis rates in *de novo* lesions compared with PTCA alone as well as decreased the need for CABG. BMS substantially reduced the incidence of abrupt artery closure, but restenosis still occurred in about 15% to 30% of cases, necessitating repeat procedures.[6,7,8,9]

The development of drug eluting stents (DES) significantly improved on the principle of BMS by adding an antiproliferative drug that is either directly immobilized on the stent surface or released from a polymer matrix, allowing for controlled drug release at the site of injury to inhibit neointimal hyperplasia. The introduction of DES greatly reduced incidence of restenosis and resulted in a better safety profile compared with BMS with systemic drug administration. These advantages and lower cost compared with surgical interventions made DES an attractive option for treating coronary artery disease.[10]

However, despite significant improvement in revascularization rates, certain clinical events were reported more frequently for DES compared with BMS,[11,12] especially late and very late stent thrombosis, a life-threatening complication that relates to occurrence of myocardial infarction (MI) and death.[13,14] The pathophysiology of very late stent thrombosis includes hypersensitivity, inflammatory infiltrates, delayed endothelialization, delayed vascular healing, malapposed and uncovered struts, and vessel remodeling due to inflammation and neoatherosclerosis, which are more common with DES than BMS.[15,16,17,18,19]

To address these limitations, newer technologies have been developed, including BMS with thinner struts of cobalt-chromium and passive coating, fully absorbable stents, second-generation DES with improved stent design and new limus analogues, and DES with biodegradable polymers. Unlike non-biodegradable polymers, which reside on the surface of the stent indefinitely, biodegradable polymers dissolve after a certain period

of time, leaving only the BMS platform in the vessel wall, which is designed to improve late clinical incomes by reducing inflammation burden and improving arterial healing.[20]

Several randomized controlled trials have demonstrated better late clinical outcomes among subjects receiving DES with biodegradable polymers compared with DES with conventional durable polymers.[21,22,23] Nine-month follow-up data from the LEADERS trial, involving 1,707 subjects randomized to a biolimus eluting stent with a biodegradable polymer or to a sirolimus eluting stent with a durable polymer, demonstrated no significant difference in the primary endpoint of major adverse cardiac events (MACE; includes cardiac death, MI or target-vessel revascularization; 9.2% vs. 10.5%).[24] Furthermore, an optical coherence tomography (OCT) sub-study at 9 months demonstrated a statistically significant lower rate of uncovered struts for subjects treated with a biolimus eluting stent with biodegradable polymer,[25] and 4-year data demonstrated superiority of the stent with biodegradable polymer with respect to MACE (18.7% vs. 22.6%).[26] A marked reduction of stent thrombosis was also observed (80% relative risk reduction of very late stent thrombosis), with a statistically significant (superiority) difference in definite stent thrombosis between 1 and 4 years (0.4% vs. 2.0%).

3.1. Investigational Device Description

The ORSIRO stent system is a drug eluting balloon expandable stent, mounted on a delivery system. It is a combination product comprised of two regulated components:

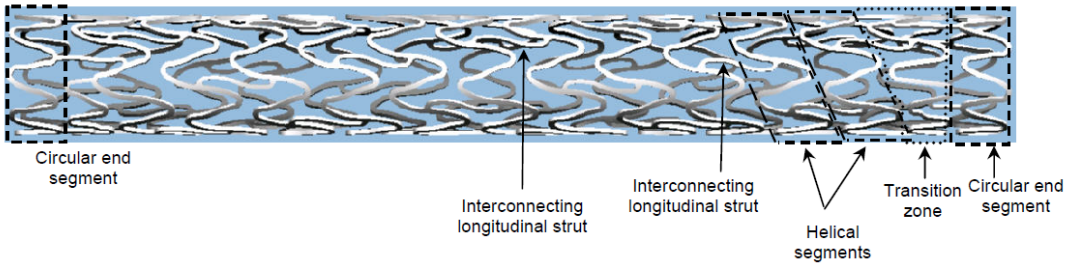
1. The device:
   - Bare Metal Stent: PRO-Kinetic Energy (PKE) Stent (IDE# G110147)
   - Delivery System: Fast-exchange with a Polyamide 12 semi-compliant balloon
2. The drug-polymer coating:
   - A formulation of the drug substance Sirolimus with
   - A bioresorbable Poly-L-lactic acid (PLLA) polymer excipient

Full details can be found in the Instructions for Use (IFU) that are provided with each system.

3.1.1. PRO-Kinetic Energy Stent

The backbone of the Orsiro stent system is the PRO-Kinetic Energy stent, the BMS platform of which is left in the vessel wall after the biodegradable polymer has dissolved. It is a tubular, balloon-expandable stent sculpted by laser from a single tube of L-605 Co-Cr alloy. As shown in Figure 3-1, the stent consists of circular segments at each end, followed by a transition zone and helicoidally arranged struts in the middle. Each loop of the helix is connected to the next loop by 3 longitudinal struts. The stent surface is fully coated with a layer of amorphous silicon carbide (PROBIO®).

Figure 3-1. Image of Orsiro/PRO-Kinetic Energy Stent



The PRO-Kinetic ENERGY stent received CE marking in September 2008. BIOTRONIK is conducting an investigational device exemption (IDE) study in the United States to evaluate the safety and efficacy of the PRO-Kinetic Energy stent (IDE #G110147).

Outside of the United States, BIOTRONIK conducted a multicenter, prospective, non-randomized observational registry (ENERGY Registry) to evaluate long-term safety and clinical performance of the Co-Cr PRO-Kinetic Energy Coronary Stent System in a large patient population. The primary endpoint for the ENERGY registry is 6-month MACE rate, which includes cardiac death, clinically-driven target lesion revascularization (TLR) and MI/acute MI (ST-elevated/non–ST-elevated). A total of 1,016 subjects with 1,074 lesions in 48 centers were enrolled from April to November 2010. Clinical follow-up was scheduled at 6 and 12 months. Six-month clinical data were available for 986 enrolled subjects and 12-month data were available for 916 subjects.

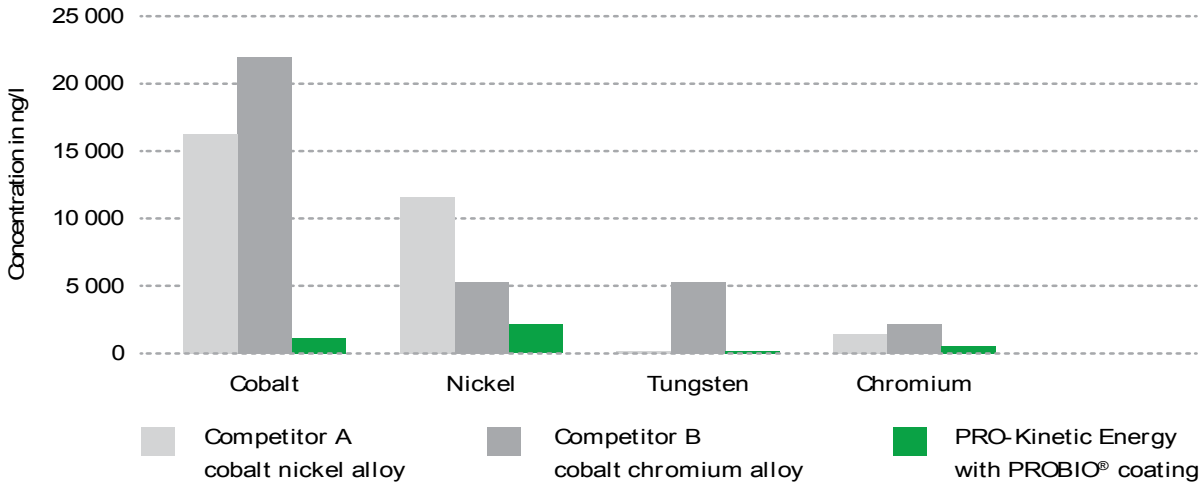
At 6 months, MACE rate was 6.3% (62/986), including a 3.7% (36/986) rate of TLR; no probable stent thrombosis; and a 0.9% (9/986) rate of definite and possible stent thrombosis. At 12 months, MACE rate was 8.8% (81/916), including a 4.6% (42/916) rate of TLR; no probable stent thrombosis; and a 1.1% (10/916) rate of definite and possible stent thrombosis. Major adverse cardiac events at 12 months in pre-defined subgroups included 11.4% (17/149) for subjects with diabetes, 7.0% (16/229) for small vessels, and 9.5% (40/419) for subjects with acute coronary syndrome. There was no statistically significant difference between these subgroups.

PROBIO® Coating

The entire surface of the underlying bare-metal stent is coated with amorphous silicon carbide that is saturated with hydrogen (a-SiC:H), referred to as PROBIO® coating, in a physical vapor deposition process. The coating has a transparent appearance with a thickness in the range of 100 nm. The a-SiC:H-coating material has been used since 2000 on all of BIOTRONIK's coronary stents, including the Rithron XR coronary stent system approved for commercial distribution in the United States on April 29, 2005 (P030037), the Astron, Astron Pulsar, and Pulsar-18 Nitinol stents being evaluated in an IDE clinical study (IDE#G100002), and the PRO-Kinetic Energy stent being evaluated in an IDE clinical study (IDE #G110147).

The silicon carbide material encapsulates the stent and minimizes interaction between the metal stent and surrounding tissue. Finally, the release of potentially allergenic ions from a silicon carbide–coated stent is reduced in comparison to an uncoated metal stent (Figure 3-2).

Figure 3-2. Metal Ion Release with PROBIO® Coating

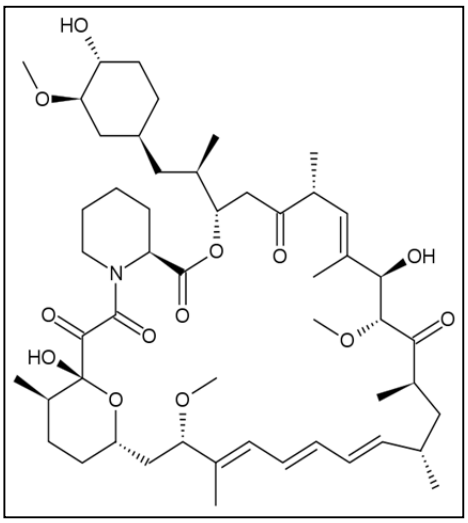


In vitro studies have shown up to 96% reduction of allergenic metal ions when the stent surface is coated with silicon carbide (data on file, BIOTRONIK AG).

3.1.2. Sirolimus

Sirolimus is the drug substance utilized in the Orsiro stent system. It is a natural macrocyclic lactone (Figure 3-3), first isolated from *Streptomyces hygroscopicus* in the mid-1970s. It was approved by the US Food and Drug Administration (FDA) for prophylaxis of renal transplant rejection in 1999. Sirolimus has potent antiproliferative, anti-inflammatory and immunosuppressive effects. It acts by inhibiting activation of mammalian target of rapamycin (mTOR), ultimately causing arrest of the cell cycle by preventing progression from phase G1 to S. The restenosis process is thus inhibited due to decreased proliferation of T cells as well as decreased proliferation and migration of smooth muscle cells.[27,28] Sirolimus eluting stents have been shown to reduce neointimal thickening compared with both BMS and polymer-coated stents, in a broad array of various animal models and clinical studies.[29,30,31,32,33]

Figure 3-3: Structural Formula of Sirolimus



The first DES to be approved for marketing was the Cypher® Sirolimus Eluting Stent System. The Cypher stent is associated with significant improvement in angiographic outcomes, including reduced rates of restenosis and need for revascularization compared with BMS,[10,34] with durable benefit for up to 5 years based on current clinical data. The efficacy of the Cypher and the improved Cypher Select+® Sirolimus Eluting Stent Systems (SESS) has been proven in populations ranging from highly selected subjects with single *de novo* lesions to unselected all-comers.[35,36,37,38] Since the preliminary results from the first-in-man feasibility clinical investigation were presented, the Cypher SESS has become available in more than 80 countries (including Europe, Japan and the United States), receiving CE marking in 2002 and FDA approval in 2003. It is one of the most studied drug eluting stents, having been evaluated in more than 200 clinical trials involving more than 155,000 subjects. It was used to treat more than 3 million patients with CAD[39] until sales were discontinued in 2011.

Like the Cypher stent, the Orsiro stent system also elutes Sirolimus. Both stents have similar drug loads of 1.4 µg/mm^2.

3.1.3. Poly-L-Lactic Acid

Poly-L-lactic acid (PLLA) is the polymer used as the excipient in the Orsiro stent system. The Orsiro stent body surface is completely coated by a matrix consisting of the carrier PLLA and the drug substance Sirolimus (BIOlute). The matrix has a maximal thickness on the ab-luminal surface of 25 µm. The largest stent design has a maximal coating mass of 42.6 µg per millimeter of stent length. PLLA is a highly biocompatible material. There is existing published experience with PLLA as a stent and stent coating material in humans.[46,40,41] Previously, this material was used in osteosynthesis and as suture material.

This highly biocompatible polymer gently degrades over 3 years, avoiding increased inflammation, and ultimately metabolizes into CO_2 and H_2O via the Krebs cycle. Studies in mini pigs have shown no residual PLLA and benign histology at 3 years.

The first successful in-human experience with a fully biodegradable stent was described by Tamai *et al*. in 2000.[42] The study included 15 subjects with 19 lesions treated with a monopolymer poly-L-lactic acid Igaki-Tamai stent with a zigzag helical coil pattern. No death, MI or stent thrombosis occurred for up to 6 months, and only one subject with two lesions underwent repeat revascularization.

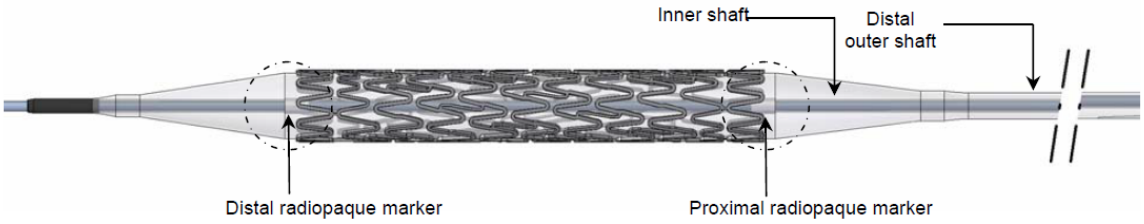
Another fully biodegradable stent using PLLA is the everolimus eluting ABSORB stent. Two-year outcomes of the first-generation, first-in-man trial involving 30 subjects were encouraging, with only one myocardial infarction and no cardiac death, stent thrombosis or ischemia-driven target lesion revascularization (TLR), resulting in a MACE rate of 3.6%.[43] For the second-generation ABSORB stent, the MACE rate at 12 months was 7.1% (7 of 101 subjects).[44] Other stent systems using poly-L-lactic acid as biodegradable polymers, such as the BioMATRIX and Nobori stent, have also been proven safe and effective.[45,46]

3.1.4. Delivery System

The delivery system of the Orsiro stent is a fast-exchange PTCA catheter compatible with a 5F guide catheter, with a working length of 140 cm. As shown in Figure 3-4, the stent is securely crimped on a nylon balloon situated at the distal tip of the catheter between two radiopaque markers made of a platinum-iridium alloy. The proximal shaft of the delivery system is a hypotube composed of polyamide-covered 304 or 304L stainless steel; it has a single luer port for connecting an inflation/deflation device to inflate/deflate the balloon.

The distal section of the catheter comprises the inflation/deflation (balloon) lumen and the 29-cm-long guide wire lumen, which starts at the catheter tip and ends at the guide wire exit port. It accepts guide wires of 0.014" diameter. The stent delivery system is compatible with guiding catheters with a minimal inner diameter of ≥ 0.056" (1.42 mm). Shaft exit markers are located on the hypotube 92 cm (brachial technique) and 102 cm (femoral technique) from the distal end of the catheter to indicate when the delivery system tip exits from the guiding catheter.

Figure 3-4. Orsiro Sirolimus Eluting Stent System



3.1.5. Investigational Device Matrix

Investigational device matrix for the BIOFLOW-V study is shown below in Table 3-1. Device sizes other than shown below cannot be used in this study.

Table 3-1. Orsiro Stent System – Device Matrix for the BIOFLOW-V Study

Orsiro		Nominal length [mm]								
Stent design	Nominal Ø [mm]	9	13	15	18	22	26	30	35*	40*
T6S	Ø 2.25	x	x	x	x	x	x	x		
	Ø 2.5	x	x	x	x	x	x	x	x	x
	Ø 2.75	x	x	x	x	x	x	x	x	x
	Ø 3.0	x	x	x	x	x	x	x	x	x
T6M	Ø 3.5	x	x	x	x	x	x	x	x	x
	Ø 4.0	x	x	x	x	x	x	x	x	x

* Orsiro LL

The 2.25 x 35 mm and 2.25 x 40 mm sizes of Orsiro may be available outside of the US, but are not permitted to be utilized in the BIOFLOW-V subjects.

3.2. Control Device Description

The Xience family of Everolimus Eluting Coronary Stent Systems (Xience V™, Xience nano™, Xience Prime™, Xience PRIME™ LL, Xience Xpedition™, Xience Xpedition™ SV, Xience Xpedition™ LL, Xience Alpine™ and Xience Pro / Xience Pro^X [will be used only outside of the United States]), manufactured and marketed by Abbott Vascular, will be used as a control device in this study.

Device description details of the different Xience stents can be found in the IFU provided with each system.

3.2.1. Control Device Matrix

Xience matrix for the BIOFLOW-V study is shown in Table 3-2 below.

Table 3-2. Xience Family of Stent Systems – Devices Matrix for the BIOFLOW-V Study

Xience	Nominal length [mm]							
Nominal Ø [mm]	8	12	15	18	23	28	33*	38*
Ø 2.25**	x	x	x	x	x	x		
Ø 2.5	x	x	x	x	x	x	x	x
Ø 2.75	x	x	x	x	x	x	x	x
Ø 3.0	x	x	x	x	x	x	x	x
Ø 3.25***	x	x	x	x	x	x	x	x
Ø 3.5	x	x	x	x	x	x	x	x
Ø 4.0	x	x	x	x	x	x	x	x

* Xience Prime™ LL and Xience Xpedition™ LL, Xience Alpine™, Xience Pro^X

** Xience nano™, Xience Xpedition™ SV, Xience Prime™, Xience Alpine™, Xience Pro^X

*** Xience Xpedition™, Xience Xpedition™ LL, Xience Alpine™, Xience Pro^X

3.3. Indications for Use

The Orsiro Sirolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in subjects with symptomatic ischemic heart disease due to discrete *de novo* lesions or restenotic lesions from PTCA in native coronary arteries with a reference vessel diameter of 2.25–4.0 mm and lesion length of ≤ 36 mm.

3.4. Contraindications

The Orsiro Sirolimus Eluting Coronary Stent System is contraindicated for use in subjects with:

- A known hypersensitivity or allergy to stent coating materials (amorphous silicon carbide or PLLA polymer), to L-605 cobalt chromium alloy (including the major elements cobalt, chromium, tungsten and nickel) and to Sirolimus or its derivatives.
- Subjects in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- A lesion judged to prevent complete inflation of an angioplasty balloon or proper placement of the stent or the stent system.
- Transplant patients.
- Subjects who would be considered unsuitable candidates for standard PCI.
- Treatment of in-stent restenosis.

3.5. Orsiro Clinical Data Summary

The Orsiro stent is investigational in the United States. However, the stent received CE Mark on February 23, 2011 and is currently approved for marketing in more than 55 countries worldwide with over 200,000 units distributed as of March 2014.

The development of the Orsiro stent system has been supported by an extensive clinical trial program designed to collect data on over 3,000 Orsiro-treated subjects in studies using the Xience Everolimus Eluting Stent System as a comparator. The Orsiro clinical trial program includes the BIOFLOW-I first-in-man study; the BIOFLOW-II international randomized study against the Xience Prime™ stent with intravascular ultrasound (IVUS) and optical coherence tomography (OCT) subsets; the BIOFLOW-III international all-comers registry; the BIOFLOW-IV international randomized study against the Xience Prime™/Xpedition™ stent with a pharmacokinetic subset, and the BIOSCIENCE international, randomized all-comers study against the Xience Prime™ stent.

Table 3-3 summarizes the key design elements of each Orsiro study. A brief description of the study, its status and results is provided in this section.

Table 3-3. Orsiro Clinical Trials Summary

	BIOFLOW-I	BIOFLOW-II	BIOFLOW-III	BIOFLOW-IV	BIOSCIENCE
Location	Romania	Europe	Europe, Chile	Europe, Japan	Switzerland
Design	• Prospective • Multi-center • Non-randomized • Single-arm	• Prospective • Multi-center • **Randomized** (2:1 vs Xience Prime)	• Prospective • Multi-center • Non-randomized • Single-arm • Open label	• Prospective • Multi-center • **Randomized** (2:1 vs Xience Prime/Xpedition)	• Prospective • Multi-center • **Randomized** (1:1 vs Xience Prime)
Primary Endpoint	Late lumen loss at 9 months	Late lumen loss at 9 months	Target lesion failure at 12 months	Target vessel failure at 12 months	Target lesion failure at 12 months
Number of subjects enrolled	30	452 (Orsiro: 298, Xience Prime: 154)	1,356	555 planned (Orsiro: 370, Xience: 185)	2,121* (Orsiro: 959, Xience Prime: 966) * Not all data sets validated yet
Lesion criteria	• Single, *de novo* lesion • Native artery • ≥50% and ≤100%	• 1 or 2 *de novo* lesions • Separate arteries • ≥50% and ≤100% • ≤ 26 mm • RVD ≥ 2.25 mm and ≤ 4.0 mm	All-comers	• 1 or 2 *de novo* lesions • Separate arteries • ≥50% and ≤100% • ≤ 26 mm • RVD ≥ 2.5 mm and ≤ 3.75 mm	All-comers
Follow-up	• 1 month and 1,2, 3 yrs: clinical • 4 and 9 months: clinical and angio • 4 and 9 months: IVUS (15 pts)	• 1, 6, 12 mos and 2-5 yrs: clinical • 9 months: clinical and angio • 9 months: OCT and IVUS (60 pts)	• 6, 12 mos and 3,5 yrs: clinical	• 1, 6, 12 mos and 2-5 yrs: clinical	• 1, 6, 12 mos and 2-5 yrs: clinical
Status (enrollment period)	Primary endpoint complete (Enrollment July 2009)	Primary endpoint complete (Enroll July '11–Mar '12)	Primary endpoint complete (Enroll Aug '11 - Mar '12)	First implants occurred September 30, 2013	Primary endpoint complete (Enroll Feb' 12 - Jun' 13)

BIOFLOW-I

BIOFLOW-I was a 30-subject feasibility study conducted at two sites in Romania. The purpose of the trial was to evaluate safety and efficacy of the Orsiro stent in treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5–3.5 mm and lesion length of ≤ 22 mm. The primary efficacy endpoint was late lumen loss measured at 9 months post–index procedure. The first subject was enrolled on July 2, 2009, and enrollment was completed on July 23, 2009.

The primary endpoint of in-stent late lumen loss at 9 months was 0.05 ± 0.22 mm. Secondary safety endpoints included a composite rate of cardiac death, target vessel MI and clinically-driven TLR of 6.7% (2/30) at 1 year[47] and 13.7% (4/30) at 2 years, and a composite rate of all-cause death, any MI and any revascularization of 16.7% (5/30) at 2 years (Kaplan-Meier estimate).

BIOFLOW-II

BIOFLOW-II is a prospective, multicenter, randomized, controlled, non-inferiority trial that enrolled 458 and randomized 452 evaluable subjects at 24 clinical centers in 8 European countries (clinicaltrials.gov identifier NCT01356888). The purpose of this trial was to compare the Orsiro SES with the Xience Prime™ Everolimus Eluting Stent (EES) in subjects with single *de novo* coronary artery lesions in up to two coronary arteries of 2.25–4.0 mm in diameter. Subjects were randomized in a 2:1 fashion to receive the Orsiro stent or the Xience Prime™ stent. All subjects underwent repeat angiography at 9 months post–index procedure. A subset of approximately 60 pre-specified subjects underwent IVUS examination at both baseline and 9 months. Another subset of approximately 60 pre-specified subjects underwent OCT examination at both baseline and 9 months. The primary efficacy endpoint was late lumen loss at 9 months post–index procedure. The first subject was enrolled in July 2011 and enrollment was completed in March 2012. Subjects continue in the follow-up phase of the trial.

Of the 452 enrolled subjects, 298 subjects were randomized to receive the Orsiro stent and 154 were randomized to receive the Xience Prime™ stent. Follow-up angiography was completed in 85% of subjects at 9 months post-procedure and demonstrated a mean in-stent late lumen loss of 0.10 ± 0.32 mm for the Orsiro stent compared to 0.11 ± 0.29 mm for the Xience Prime™ stent. The non-inferiority hypothesis was confirmed with a *P* value of < 0.0001 (delta = 0.16 mm).

At 12 months, clinical event rates were low, and there were no significant differences between the two arms. TLF, a composite measure of safety (target vessel MI, cardiac death) and stent efficacy (clinically-driven TLR and emergent CABG) was measured in the BIOFLOW-II trial. The TLF rate was evaluated, with Kaplan Meier estimates to be 6.5% in the Orsiro group compared to 8.0% in the Xience Prime™ group at 12-month follow-up (log-rank = 0.5832).

The BIOFLOW-II IVUS/OCT subset analyses showed comparable results between the Orsiro and Xience Prime™ groups at 9 months. IVUS results at 9 months demonstrated complete stent apposition (no cases of stent malapposition) in both arms and a significantly lower neointimal hyperplasia area for Orsiro compared with the Xience

Prime™ (0.16 ± 0.33 mm^2 vs. 0.43 ± 0.56 mm^2, respectively; *P* = 0.0428). The pre-specified secondary OCT endpoints at 9 months showed a significant difference in tissue coverage between the Orsiro and the Xience Prime™ groups (98.3 vs. 97.5%, respectively; odds ratio 1.51; 95% confidence interval [CI] 1.02, 2.45; *P* = 0.042). At 9 months, the Orsiro stent was associated with thinner neointima thickness (0.094 vs. 0.119 mm, *P* < 0.001). No significant differences in incomplete strut apposition (ISA) were found between the treatment groups at 9 months.

BIOFLOW-III

The BIOFLOW-III study is an open-label prospective, non-randomized, multicenter, international, observational all-comers registry that enrolled a total of 1,356 subjects at 43 centers in 14 countries across Europe and Chile (clinicaltrials.gov identifier NCT01553526). The purpose of the registry was to evaluate safety and performance of the Orsiro Sirolimus Eluting Stent (SES) in a large series of subjects under real-world conditions.

The primary endpoint was the 12-month rate of TLF, defined as cardiac death, target vessel Q-wave or non–Q-wave MI, emergent CABG or clinically driven TLR. The first subject was enrolled in August 2011 and enrollment was completed in March 2012. The subjects are currently in the follow-up phase of the trial.

The BIOFLOW-III registry enrolled an unselected subject population, including a high proportion of high-risk subjects presenting with diabetes (29.6%), small vessels (42.4%), acute MI (32.6%), and chronic total occlusions (4.3%). The rate of TLF was 5.1% at 12 months. The rate of ARC-defined definite or probable stent thrombosis at 12 months was 0.4%.

While BIOFLOW-I and II had mandatory angiographic follow-up and BIOFLOW-III did not, rates of 12-month TLR were 6.7%, 3.5%, and 3.3% for BIOFLOW-I, II and III, respectively.

Among subgroups, 12-month TLF rates were 7.7% in subjects with diabetes compared with 4.0% in non-diabetics, and 7.2% in subjects with acute myocardial infarction (AMI) compared with 4.0% in subjects without AMI.

BIOFLOW-IV

BIOFLOW-IV is a prospective, international, multicenter, randomized controlled trial designed to assess the Orsiro stent in the treatment of subjects with up to two de novo coronary artery lesions (clinicaltrials.gov identifier NCT01939249). Approximately 575–585 subjects at up to 50 sites in Japan and Europe will be enrolled in the trial to evaluate the safety and effectiveness of the Orsiro stent. The BIOFLOW-IV clinical trial consists of the following:

1. Randomized controlled trial (RCT) at up to 50 sites in Japan and Europe, which will enroll 555 subjects with up to two *de novo* lesions ≤ 26 mm in length in native coronary arteries 2.5–3.75 mm in diameter. Subjects will be randomized in a 2:1 fashion to receive the Orsiro stent or the Xience Prime™/Xpedition™ stent.

2. Concurrent, non-randomized pharmacokinetic (PK) sub-trial at 3–5 sites in Japan, which will enroll 20–30 subjects with up to two *de novo* lesions ≤ 26 mm in length in native coronary arteries 2.5–3.75 mm in diameter.

The primary endpoint for the main RCT is the 12-month TVF rate, defined as any clinically-driven TVR, target vessel Q-wave or non–Q-wave MI, emergent CABG or cardiac death. There is no primary endpoint for the PK sub-trial.

BIOFLOW-IV enrolled the first subject in September 2013. Enrollment was completed on January 25, 2015.

BIOSCIENCE

The BIOSCIENCE study is a prospective, multicenter, randomized controlled trial that enrolled 2,119 subjects at 13 clinical sites in Switzerland (clinicaltrials.gov identifier NCT01443104). The purpose of this study was to directly compare the Orsiro stent with the Xience Prime™ stent in a large series of 'all-comer' subjects. Subjects were randomized in a 1:1 fashion to receive the Orsiro stent or the Xience Prime™/ Xpedition™ stent. The primary endpoint was 12-month TLF rate, defined as cardiac death, target vessel Q-wave or non–Q-wave MI, emergent CABG or clinically driven TLR. The first subject was enrolled in February 2012, enrollment was completed in May 2013 and the primary endpoint results were reported on September 1, 2014 by Pilgrim et al in the Lancet.[48].

Of the 2119 subjects (3139 lesions) included in the study, 407 (19%) patients presented with ST-segment elevation myocardial infarction. A total of 1063 subjects (1594 lesions) were randomized to receive the Orsiro stent and 1056 patients (1545 lesions), were randomized to receive the Xience stent. At 12 months, the TLF rate for the Orsiro stent (69 subjects, 6.5%) was non-inferior to the Xience stent (70, 6.6%) at 12 months (absolute risk difference −0.14%, upper limit of one-sided 95% CI 1.97%, p for non-inferiority <0.0004). No significant differences were noted in rates of clinical events, including stent thrombosis.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

The objective of this study is to assess the safety and efficacy of the Orsiro Sirolimus Eluting Coronary Stent System in the treatment of subjects with up to three native de *novo* or restenotic (standard PTCA only) coronary artery lesions compared with the Xience coronary stent system.

4.2. Primary Endpoint

The primary endpoint is target lesion failure (TLF) rate at 12 months post–index procedure. Target lesion failure is defined as all cardiac death, target vessel Q-wave or non–Q-wave MI, or clinically driven target lesion revascularization.

4.3. Secondary Endpoints

Secondary endpoints include the following measures:

1. Device success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only.

   Note: Post-dilatation is allowed to achieve device success.

2. Lesion success, defined as attainment of < 30% residual stenosis of target lesion using any percutaneous method.
3. Procedure success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study stent only without occurrence of in-hospital MACE.

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

4. Death.
5. Myocardial infarction.
6. Cardiac death or MI.
7. MACE and individual MACE components (MACE: composite of all-cause death, Q-wave or non–Q-wave MI, and any clinically-driven TLR).
8. TLF and individual TLF components (TLF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and any clinically-driven TLR).
9. TVF and individual TVF components (TVF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and any clinically-driven TVR).
10. Stent thrombosis (all, definite, definite/probable, probable, possible) according to Academic Research Consortium (ARC) criteria for acute, subacute, late, very late and cumulative stent thrombosis.

5. STUDY DESIGN

The BIOTRONIK BIOFLOW-V clinical trial is a prospective, multicenter, randomized, controlled trial combining data on the randomized subjects with data from two historical studies by employing a Bayesian approach.

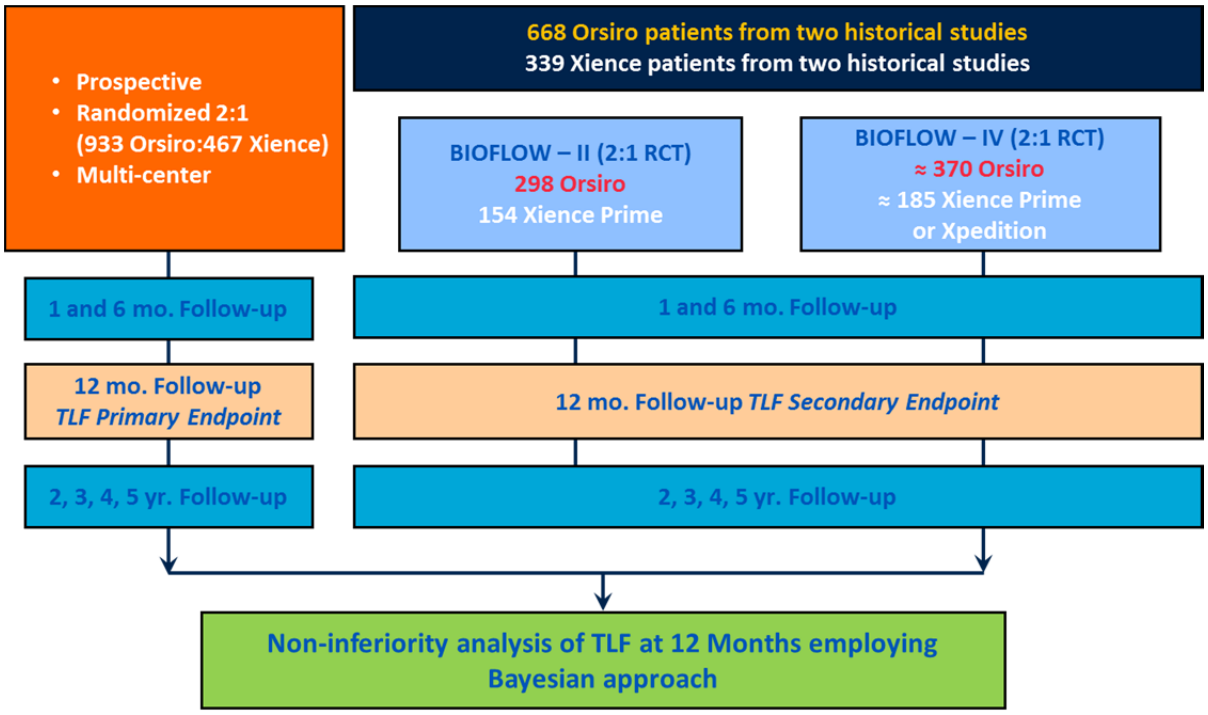
Subjects with CAD that qualify for PCI with stenting will be screened per the protocol inclusion and exclusion criteria to achieve a total of up to 1,400 randomized subjects. Eligible subjects will be randomized in a 2:1 ratio, stratified by study center, to undergo percutaneous coronary revascularization with either the Orsiro Sirolimus Eluting Stent System (treatment group) or the Xience Everolimus Eluting Stent System (control group).

Subjects may receive treatment of up to three target lesions, one or two target lesions per target vessel, for a maximum of two target vessels. The target lesion(s) must be *de novo* or restenotic lesion(s) of ≤ 36 mm in length in native coronary artery(ies), with a reference vessel diameter of 2.25–4.0 mm. Treatment of restenotic lesions is allowed provided that the target lesion was previously treated with PTCA only. All treatment with study stents is to be performed during a single index procedure. *Note: Concurrent treatment of non-target lesions during the index procedure is not allowed*.

Randomized subjects will have clinical follow-up at 1 month, 6 months, 12 months and at 2, 3, 4 and 5 years following the index procedure.

To assess the non-inferiority of the Orsiro stent compared to the Xience stent, BIOFLOW-V randomized subjects will be combined with historical subjects from the BIOFLOW-II and BIOFLOW-IV randomized trials employing a Bayesian approach. Only subjects who meet all clinical and angiographic eligibility criteria of the BIOFLOW-V trial will be included in the analysis. The trial design is shown in Figure 5-1.

Figure 5-1. Trial Design of the BIOFLOW-V Trial



5.1. Clinical Sites

The trial will be conducted at up to 100 sites in the United States and 50 sites outside of the United States.

5.2. Number of Subjects

Sufficient number of subjects will be provisionally enrolled to achieve a total of 1,334 randomized subjects. It is expected that approximately 50% will be enrolled in the United States. A maximum of 250 subjects may be enrolled at a single investigational site.

5.3. Study Participation Status

5.3.1. Status Definitions

Provisionally enrolled - Subject who is fully informed about the specifics of the study by authorized site personnel and provides informed consent by properly signing an informed consent form after confirmation of the initial enrollment criteria.

Subjects for whom consent was not obtained prior to participation in the study will not be considered provisionally enrolled. No data collected from these “subjects” will be included in any analysis. Failure to obtain consent will be reported as a protocol violation as outlined in Section 12.6.1.

Screen failure – Provisionally enrolled subject who withdraws consent prior to randomization or is unsuitable for randomization following laboratory assessments, pre-procedure electrocardiogram (ECG), diagnostic angiogram at the index procedure or unsuccessful crossing of the first target lesion with a guide wire. These subjects will be exited from the study once screen failure is confirmed. Subject informed consent forms will be kept in the site's administrative files.

Enrolled (Randomized) – Provisionally enrolled subject who meets all clinical and angiographic eligibility criteria, and has been randomized. These subjects will be followed in accordance with the protocol requirements.

Study exit - early termination of study participation applicable to subjects that have signed an informed consent form.

Study completion - subject who completes all protocol-required study procedures.

5.3.2. Subject Study Exit

Investigators should make every effort to ensure subjects complete all protocol-required procedures, including study follow-up visits. However, subjects may be required to exit the study, despite an investigator's best efforts. Good Clinical Practice (GCP) guidelines describe the need for clear subject exit procedures, to include when and how to exit subjects from the study, as well as to outline the type and timing of the follow-up and data collection for these subjects.

Subjects may be exited from this study in the following limited situations:

- Subject death
- Subject withdrawal of informed consent
- Investigator believes it is in the best medical interest of the subject to discontinue study participation due to safety reasons
- Subject is considered a screen failure

In the event of major protocol non-compliance, each case will be evaluated individually to determine the appropriate course of action regarding subject study participation. In any of the situations noted above, data collected up to and including the exit of the subject will be used in data analysis. No data will be collected after the exit of the subject from the study. Study exits are expected and will be taken into consideration during data analysis as described in Section 8. Additionally, subject attrition has been calculated into the study sample size; therefore, all subjects exited from the study will be counted toward the randomization goal and will not be replaced. Investigators must document, in subject medical records, the reasons and circumstances for all subject exits.

Generally, subjects should not be removed from the study due to late identification of eligibility criteria violations, unless increased subject risk is indicated. In cases where further participation in the study poses potential risk to the subject, study exit should be considered. In addition to subject safety, consideration should be given to the scientific

validity of the primary endpoints when making decisions concerning subject exit. Study follow-up options and requirements for subjects exited from the study should be determined and applied to all subjects exited for similar reasons. Deviations in subject eligibility, as defined in the protocol, should be considered protocol violations and reported to the Institutional Review Board (IRB) or Ethics Committee (EC) immediately upon discovery, in accordance with local regulations. Subjects that are randomized, but do not receive a study stent during the index procedure post-randomization (e.g. unable to cross the lesion with the predilatation balloon or stent, randomization error, or lack of sufficient disease, etc.) may be exited from the study after completion of the primary endpoint visit assessments (12-month follow-up).

If a subject cannot continue to participate in the study but the investigator is able to maintain contact with the subject and they have not withdrawn consent to collect further data, then contact should be maintained per the original follow-up schedule and vital status data will be confirmed by the investigator and reported. For example, a subject may change geographic location or move into a nursing home, but may still remain in contact with the investigator. Identification of vital status will be handled at the investigational site level. Subjects have the right to discontinue from the study at any time or be discontinued at the investigator's discretion.

5.3.2.1. Subject Lost to Follow-up

Subjects may be unable to adhere to the regularly scheduled study visits. Study sites should attempt to contact these subjects in order to maintain study visit compliance and all contact attempts should be documented. At a minimum, the site should make two attempts to contact the subject by phone and one by certified mail.

If the subject is able to be contacted, all efforts should be made to perform the required study visit and complete the relevant case report forms. However, if a subject is contacted and a study visit cannot be performed, the study site should complete the relevant case report forms with any relevant data obtained from the subject contact. Any missed visits prior to and after contact with the subject will be counted as protocol compliance issues. If a subject is unable to be contacted at any of the remaining study visits, either a missed visit will be entered for each visit or the subject may be exited as lost to follow-up, using the date of last actual contact as the study exit date. Subjects are not eligible to be exited as lost to follow-up until after the 12-month follow-up visit. After the 12-month follow-up visit, if a minimum of two consecutive study visits have been missed, after making two attempts by phone and one by certified mail at each time point, lost to follow-up may be an acceptable reason for exit.

Likewise, due to unforeseen circumstances, subjects may change providers (e.g. changes in insurance coverage) or relocate during the course of the study and may no longer be able to return for study follow-up visits. Attempts to collect data from these subjects should be made by the investigator in collaboration with the subject's new provider. All data that is obtained may be utilized in data analysis, but should be documented that it was collected by an unapproved investigator. If any data cannot be collected from the subject's new provider, the subject should be considered lost to follow-up and the site should follow the above procedures for continuing subject contact.

The investigative site should make an attempt to verify the vital status of subjects that are lost-to-follow-up through means including, but not limited to, the National Death Index/ Social Security Death Index, as applicable. BIOTRONIK and/or its designee may provide assistance to investigative sites to obtain vital status information, as permitted, for lost-to-follow-up subjects.

6. SUBJECT SELECTION

During the study enrollment phase, patients from the general interventional cardiology population will be screened according to protocol inclusion and exclusion criteria. Subjects should be consented and sign the informed consent prior to initiating any study-specific procedures that are not considered routine standard of care clinical assessments. Subjects who have met all clinical inclusion and exclusion criteria and signed the IRB/EC–approved consent form will then be screened for angiographic criteria during an index procedure.

6.1. Eligibility Criteria

6.1.1. Clinical Inclusion Criteria

Subjects must meet all of the following criteria to participate in the trial:

1. Subject is ≥18 years or the minimum age required for legal adult consent in the country of enrollment.
2. Subject is an acceptable candidate for PCI.
3. Subject is an acceptable candidate for CABG.
4. Subject has clinical evidence of ischemic heart disease, stable or unstable angina pectoris or documented silent ischemia.
5. Subject is eligible for dual anti-platelet therapy treatment with aspirin plus either, clopidogrel, prasugrel, ticagrelor or ticlopidine.
6. Subject has provided written informed consent.
7. Subject is willing to comply with study follow-up requirements.

6.1.2. Angiographic Inclusion Criteria

Each target lesion/vessel must meet all of the following angiographic criteria for the subject to be eligible for the trial:

1. Subject has up to three target lesions in up to two separate target vessels (twotarget lesions in one vessel and one target lesion in a separate vessel).
2. Target lesion must be *de novo* or restenotic lesion in native coronary artery; restenotic lesion must have been treated with a standard PTCA only.
3. Target lesion must be in major coronary artery or branch (target vessel).
4. 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, SPECT, or stress echo), cardiac computed tomography (CT), electrocardiography, fractional flow reserve, or post infarct angina.
5. Target vessel must have a Thrombolysis In Myocardial Infarction (TIMI) flow > 1.

6. Target lesion must be ≤ 36 mm in length by operator visual estimate.
7. Target vessel must have a reference vessel diameter of 2.25–4.0 mm by operator visual estimate.
8. Target lesion must be amenable to treatment with a maximum of two overlapping stents.

6.1.3. Clinical Exclusion Criteria

Subjects will be excluded from the trial if any of the following criteria are met:

1. Subject has clinical symptoms and/or ECG changes consistent with acute ST elevation MI (STEMI) within 72 hours prior to the index procedure.

   Note: Hemodynamically stable non-STEMI (NSTEMI) subjects are eligible for study enrollment.
2. Subject is hemodynamically unstable.
3. Subject is pregnant and/or breastfeeding or intends to become pregnant during the duration of the study.
4. 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.
5. 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.
6. Planned treatment of a lesion not meeting angiographic inclusion and exclusion criteria during the index procedure or after the index procedure.
7. Planned surgery within 6 months of index procedure unless dual antiplatelet therapy can be maintained throughout the peri-surgical period.
8. History of a stroke or transient ischemic attack (TIA) within 6 months prior to the index procedure.
9. Subjects with active bleeding disorders, active coagulopathy, or any other reason, who are ineligible for DAPT.
10. Subject will refuse blood transfusions.
11. 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.
12. Subject is dialysis-dependent.
13. 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).

14. 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).
15. 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).
16. Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent).
17. Subject has life expectancy of < 1 year.
18. 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.
19. In the investigator's opinion, subject will not be able to comply with the follow-up requirements.

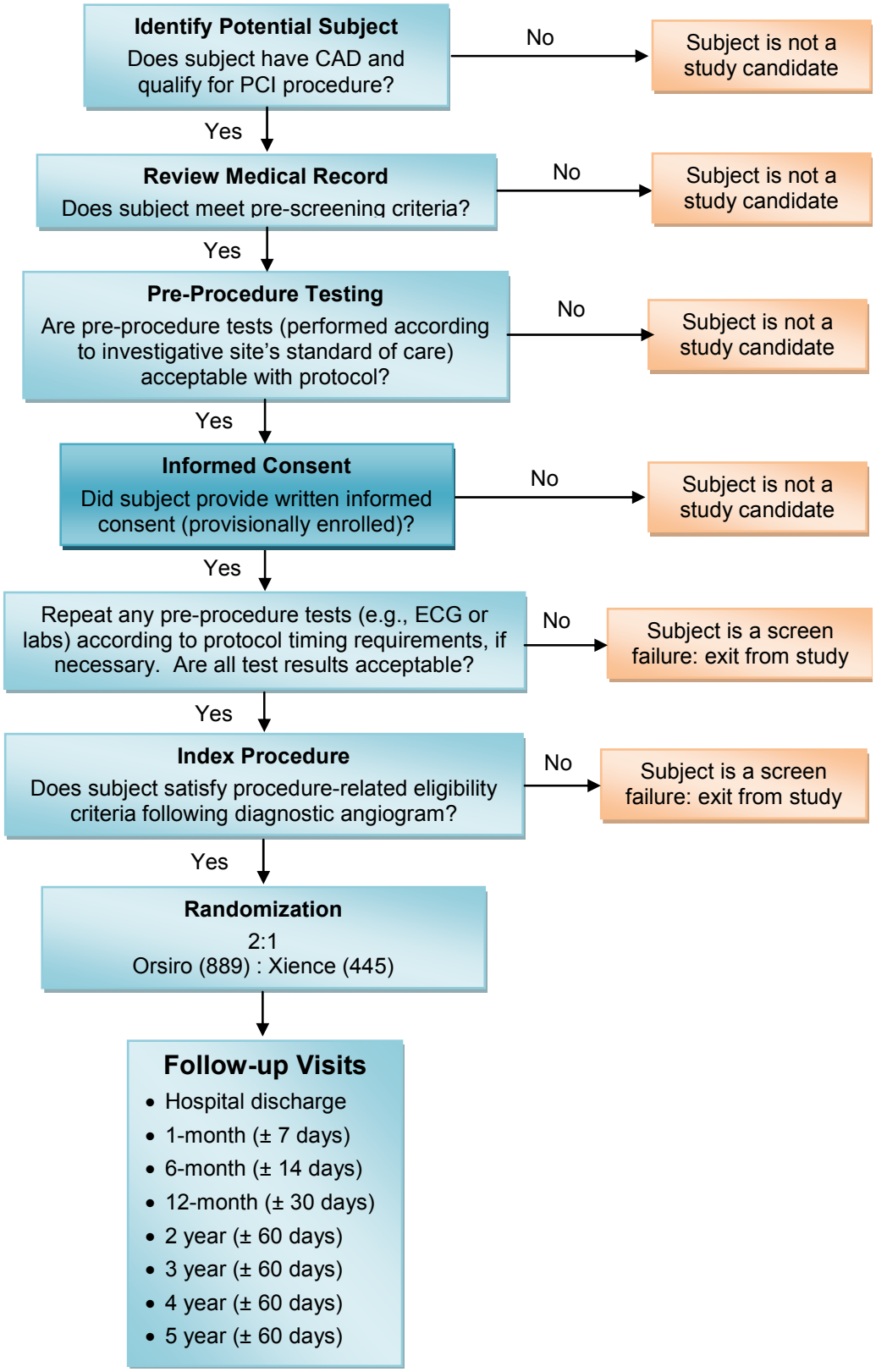
6.1.4. Angiographic Exclusion Criteria

Subjects will be excluded from the trial if any of the target lesions/vessels meets any of the following angiographic criteria:

1. Target lesion is located within a saphenous vein graft or arterial graft.
2. Target lesion is a restenotic lesion that was previously treated with a bare metal or drug eluting stent (in-stent restenosis).
3. Target lesion has any of the following characteristics:
    a. 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).
    b. Involves a side branch of > 2.0 mm in diameter.

    Note: Lesions within 3 mm of the origin of the right coronary artery may be treated.
4. 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.
5. Target vessel has angiographic evidence of thrombus.
6. Target lesion is totally occluded (100% stenosis).
7. Target vessel was treated with brachytherapy any time prior to the index procedure.

Figure 6-1. Clinical Study Design Flowchart



7. TRIAL PROCEDURES AND ASSESSMENTS

7.1. Schedule of Events

Table 7-1. Schedule of Events

	Screening/Baseline				**1 Month** ± 7 Days	**6 Months** ± 14 Days	**12 Months** ± 30 Days	**2, 3, 4, 5 Years** ±60 Days	**Unsch. Visit**
	Within 7 Days Prior to Procedure	**Within 24 Hours Prior to Procedure**	**Index Procedure**	**Post-Procedure[2]/ Discharge**	Telephone Contact or Office Visit	Telephone Contact or Office Visit	Office Visit	Telephone Contact or Office Visit	
Informed consent form[1]	X[1]								
Demographics, medical and cardiac history	X								
Physical examination	X								
Angina status	X			X	X	X	X	X	X
CBC with differential	X								
Creatinine blood test	X								
Pregnancy test[3]	X								
12-lead ECG		X		X (within 24 hours)	X[4]	X[4]	X		
CK and/ or CKMB[5] (CKMB required)		X[5]		X[5]					
Troponin[5] (only if CKMB not available)		X[5]		X[5]					
ACT measurements (heparin only)[6]			X	X (immediately post-procedure)					
Angiography to assess pre- and post- procedure lesion characteristics			X	X					X[7]
Randomization[8]			X						
AE/SAE monitoring[9]			X	X	X	X	X	X	X
Medication regimen	X	X	X	X	X	X	X	X	X

CBC: complete blood count; ECG: electrocardiogram; CKMB: creatine kinase myocardial band isoenzyme MB; ACT: activated clotting time; AE: adverse event; SAE: serious adverse event; URL: upper range limit; MACE: major adverse cardiac event.

[1] Informed consent may be obtained within 30 days prior to the index procedure.

[2] End of procedure defined as removal of guide catheter.

[3] For women of childbearing potential only per standard of care.
[4] 12-leads ECG at 1- and 6-month visits is only if there are office visits at these time points.
[5] CKMB testing is required (or Troponin if CKMB is not available). Baseline pre-procedure sample may be obtained from the sheath during the index procedure prior to randomization. CKMB (or Troponin if CKMB is not available) will be measured at 6–24 hours post index procedure. If CKMB is > 3x URL or Troponin > 3x URL, a series of CKMB (or Troponin) must be evaluated every 4-12 hours until values have returned to < 3x URL or until discharge, from when the first elevation is noted.
[6] ACT measurements are recommended but not required if the test is not performed as standard of care at the investigational institution. If ACT is not performed, sufficient anticoagulation should be confirmed based on standard of care procedures and applicable clinical guidelines.
[7] Any repeat or unscheduled diagnostic or interventional coronary angiography performed should include a diagnostic assessment of the target lesion(s) and investigational stent(s). Angiographic data collected during any repeat procedure on the target vessel(s) must be made available to the Clinical Events Committee (CEC) and angiographic core laboratory.
[8] Randomization only for subjects meeting all eligibility criteria and successful crossing of the first lesion by a guide wire.
[9] All AEs (serious and non-serious) will be reported for the entire study period to the extent required by national and/or local requirements. For US sites only: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable, and only serious adverse events, including MACE and clinical study endpoints, will be recorded.

7.2. Screening and Baseline Procedures

Individuals with CAD who qualify for a PCI procedure will be pre-screened by authorized site personnel by reviewing the medical record. Potential subjects will undergo CAD screening according to each investigative site's standard of care. Prior to possible entry into the trial, site personnel will review and compare the subject's medical history with the clinical inclusion and exclusion criteria to determine if they are an eligible candidate for the study.

Pre-screening logs will be kept at each investigational site of all subjects identified through pre-screening who meet the clinical eligibility criteria. For subjects who are not subsequently enrolled (consented), the reason for non-enrollment will be recorded.

Potential study subjects will proceed with the following standard of care procedures to further assess eligibility.

Pre-Procedure/Baseline Evaluations:

- Physical assessment within 7 days prior to the index procedure, including weight, height and blood pressure.
- Demographics within 7 day prior to the index procedure.
- Medical history within 7 days prior to the index procedure:
    - General medical, cardiac, neurologic and renal history.
    - Cardiovascular history (e.g., prior MI, prior PCI, history of congestive heart failure).
    - Risk factors (e.g., dyslipidemia, hypertension, diabetes mellitus, tobacco use).
    - History of peripheral vascular disease, stroke, TIA.
- Ischemic/anginal status assessment (according to Canadian Cardiovascular Society Classification [CCSC] or Braunwald).
- Current cardiovascular and diabetic medications, including anti-platelet/anti-coagulant medications within 7 days prior to the index procedure.
- 12-lead ECG according to each site's standard of care to ensure suitability to undergo a PCI procedure, within 24 hours prior to the index procedure.
- Routine laboratory assessments:
    - All subjects must have cardiac enzymes including CK and/or CKMB (CKMB is required [or troponin if CKMB is not available]), evaluated within 24 hours prior to the index procedure. Baseline cardiac enzyme sample may be obtained from the sheath during the index procedure, prior to randomization.
    - All subjects must have a creatinine blood level assessed within 7 days prior to the index procedure.

- Women of childbearing potential must have a negative pregnancy (serum and/or urine) test within 7 days prior to index procedure in accordance with the institutional standard of care. Female subjects who are surgically sterile or post-menopausal are exempt from having a pregnancy test.
- Complete blood count (CBC) with differential within 7 days prior to the index procedure. If white blood cell count is within normal limits, differential is not required.

If any of the Pre-procedure/ Baseline tests specified above are not routine standard of care or are required to be repeated in order to demonstrate protocol eligibility criteria leading up to the index procedure, written informed consent will be obtained before these tests are performed or repeated. Subjects are considered provisionally enrolled with the signature on the written informed consent form, however a subject will only proceed to the baseline evaluations and index procedure if all initial and applicable procedure-related eligibility criteria are met.

Written informed consent may be obtained on the day of the index procedure or within 30 days prior to the index procedure. The consenting process, including discussion of the study, with its possible benefits and risks, will be documented in the subject's medical record. A copy of the completed informed consent document must be given to the subject; the original must be placed in the medical record. Failure to obtain a signed and hand-dated informed consent prior to the procedure constitutes a protocol violation, which must be reported in accordance with all applicable regulations.

7.3. Concomitant Medications

Unless clinically contraindicated, all subjects should receive the recommended medication regimen listed in Table 7-2 at the investigator's discretion in accordance with clinical guidelines. The use of glycoprotein IIb/IIIa inhibitors is allowed and not mandatory.

Pre-and post-procedure activated clotting time (ACT) measurements for subjects receiving heparin are strongly recommended but not required if the test is not performed as standard of care at the investigational institution. If ACT is not performed, anticoagulation should be in accordance with standard of care procedures and applicable guidelines.

All cardiovascular and diabetic medications administered should be recorded in the medical record and reported in the electronic case report form (eCRF) from 24 hours pre-procedure through the 12-month follow-up assessment. Use of antiplatelet/anti-coagulant therapy will be recorded throughout the 5-year follow-up period.

Dual antiplatelet therapy (DAPT) administration post index procedure is recommended for a minimum of 6 months and highly recommended for 12 months for subjects who are not at a high risk of bleeding.

Table 7-2. Concomitant Medication Regimen Recommendations

Timing	Medication	Regimen
Prior to Procedure	Acetylsalicylic acid	A minimum of 150 mg (within 24 hours prior to procedure).
	Clopidogrel **or** Prasugrel/Ticagrelor	Loading dose of 600 mg clopidogrel within 24 hours prior to index procedure or immediately post-procedure (within 30 minutes). Alternatively, loading dose of 60 mg prasugrel or 180 mg ticagrelor. No loading dose is required for subjects on chronic thienopyridine therapy.
During Procedure	Heparin **or** Bivalirudin	Per routine hospital practice. For heparin, a bolus of 50-80 units/kg is recommended. If heparin is administered, it is recommended to maintain ACT of ≥ 250 seconds (or ≥ 200 seconds if a glycoprotein IIb/IIIa receptor blocker is administered) throughout the interventional portion of the procedure.
	Glycoprotein IIb/IIIa inhibitor	Per investigator's discretion.
	Intracoronary nitroglycerin **or** Intracoronary isosorbide or dinitrate	To eliminate coronary artery spasm that would interfere with accurate measurement of lumen obstruction due to plaque alone, 100–200 µg nitroglycerin or 1–3 mg of isosorbide or dinitrate must be administered prior to baseline and post-intervention angiograms.
Post-Procedure DAPT	Acetylsalicylic acid	A minimum of 75 mg daily indefinitely.
	Clopidogrel **or** Prasugrel/ticagrelor/ticlopidine	Post-procedure treatment with the same thienopyridine agent for a minimum of 6 months, highly recommended for 12 months for subjects not at high risk for bleeding, as follows: **Clopidogrel:** 75 mg daily: **Prasugrel:** 10 mg daily; a lower dose of 5 mg daily is allowed for subjects < 60 kg. **Ticagrelor:** 90 mg twice daily. **Ticlopidine:** 250 mg twice daily.
OUS investigators may follow medication administration recommendations in accordance with ESC guidelines, national guidelines and/or hospital standard of care.		

7.4. Index Procedure

7.4.1. Subject Preparation and Baseline Angiography

Subject preparation and percutaneous access should be performed according to standard hospital policy for care of interventional cardiology patients unless otherwise specified in this investigational plan. Both femoral and radial access techniques are acceptable. The procedure begins once percutaneous access has been established, defined as the time of sheath insertion.

Following intracoronary injection of nitroglycerin, isosorbide or dinitrate (see Table 7-2) baseline angiography of the vessels(s) will be performed in at least two orthogonal views to characterize the target lesion(s) and to confirm angiographic eligibility criteria. Assessment of angiographic eligibility criteria is based on visual assessment of the pre-procedure angiogram.

7.4.1. Randomization

Subjects who have satisfied all general and angiographic inclusion and exclusion criteria, after successful crossing of the first target lesion with a guide wire, will then be randomized in a 2:1 ratio to receive either the Orsiro stent (treatment group) or the Xience stent (control group). Each subject will receive one unique randomization number associated with a randomization assignment allocated via the BIOFLOW-V study EDC electronic Case Report Form (eCRF) website hosted by MedNet Solutions. Randomization will be stratified by study center and to prevent bias, the blocks and randomization schedules will be pre-defined prior to the first study enrollment and will be generated by HCRI.

Once randomization is completed and a treatment is assigned, crossover is not permitted. Once randomized the subject is considered enrolled in the trial and included in the intent-to-treat (ITT) population. This includes subjects that are randomized, but do not receive the study stent or receive a stent not in accordance with the randomization assignment.

7.4.2. Target Lesion(s) Pre-Dilatation

The target lesion(s) must be pre-dilated with standard percutaneous transluminal balloon angioplasty. The recommended sizes of pre-dilatation balloons are as follows:

- 2.0 mm for a 2.25-mm vessel.
- 2.0 mm for a 2.5-mm vessel.
- 2.5 mm for a 3.0-mm vessel.
- 3.0 mm for a 3.5-mm vessel.
- 3.5 mm for a 4.0-mm vessel.

The selected pre-dilatation balloon should be a minimum of 2 mm shorter than the length of the stent that is planned to be implanted.

The use of rotational atherectomy devices or cutting balloons is allowed. If rotational atherectomy is performed, it should be followed by successful balloon inflation prior to stenting.

7.4.3. Stenting

All target lesions should be treated with the assigned study stent per randomization. The stenting procedure will be performed according to the randomized stent IFU provided with each stent.

The delivery system should be advanced over the guide wire, through the introducer, and to the target lesion site. The stent should be positioned across the lesion and placement confirmed using the radiopaque marker bands on the delivery catheter and fluoroscopic angiographic test injections. In all cases, the stent should extend into surrounding healthy tissue by a minimum of 2 mm proximally and distally.

The stent should be deployed with a single inflation of the delivery system balloon according to the compliance table. It is recommended that inflation be maintained for approximately 15–30 seconds. The delivery system balloon must not be inflated beyond the labeled-rated burst pressure.

A maximum of two study stents are to be used per target lesion. If more than one stent is needed to cover the target lesion completely, the stents must overlap by at least 2 mm. However, Investigators are discouraged from treating two separate lesions with overlapping contiguous stents and should anticipate a minimum of 10 mm between stents when treating two lesions in the same target vessel.

After stent placement, the investigator should ensure that the stent is in full contact with the arterial wall. To achieve full contact, post-dilatation may be performed at the discretion of the investigator using the stent delivery system balloon or a shorter non-compliance balloon catheter. Optimal stent deployment is a visually (or by online quantitative coronary angiography [QCA]) estimated residual stenosis of < 30%.

Persistent dissections should be treated conservatively, with low-pressure prolonged balloon inflation, or with an additional study stent implantation (in accordance with the original randomization treatment assignment) per standard practice. Haziness, lucency or filling defects within or adjacent to the stent, and angiographic complications such as distal thromboemboli or no reflow, should be treated per standard practice. All angiographic complications that occur must be documented by angiography, reported on the appropriate eCRF, and submitted to the angiographic core laboratory for analysis.

7.4.4. End of Procedure

In all subjects, final angiography of the vessel(s) must be performed following intracoronary injection of nitroglycerin, isosorbide or dinitrate (see Table 7-2) and in the same views that were taken at baseline.

The end of the procedure is defined as the time the guide catheter is removed from the subject. If the subject is returned to the procedure room and a guiding catheter is

reinserted, a dilatation is performed, and an interventional device is inserted into the catheter, this should be considered a repeat intervention.

7.4.5. Bailout Procedures

In the event of a major dissection or an occlusive complication manifested as decreased target vessel flow, chest pain or ischemic ECG changes after index procedure that do not respond to repeat balloon inflations or intracoronary vasodilators (nitroglycerin, verapamil, diltiazem, nitroprusside), other bailout procedures may be performed, which may include additional stenting. Should an additional stent be used, it must be the assigned study stent unless clinically contraindicated. Multiple stenting with the Orsiro or Xience stents requires a 2-mm overlap. Such procedures must be documented in the eCRF.

All bailout procedures are considered adverse events (AEs) in this study. Bailouts procedures that result in any of the consequences characteristic of a serious adverse event (SAE) (e.g. death, prolonged hospitalization, etc. see Section 9.1.3) are considered SAEs.

7.4.6. Bailout-Staged Procedure

Planned staged procedures are not allowed in this clinical investigation. If during the intervention it becomes clinically necessary to postpone treatment of the second and/or third lesion to a later time point, this is regarded as a staged procedure and must be documented as such. For staged procedures, the use of an investigational stent is not allowed. Subjects requiring staged procedure should be treated according to the investigator's discretion and standard of care. These subjects should receive an approved, commercially available treatment and not a study stent.

All bailout procedures are considered adverse events (AEs) in this study.

7.5. Post-Procedure to Hospital Discharge

7.5.1. Immediately Post-Procedure

Immediately following the procedure:

- Heparin or bivalirudin should be discontinued.
- ACT should be monitored in accordance with hospital protocol.
- Vascular sheaths should be removed according to standard hospital practice.
- Approved vascular closure devices may be used at the discretion of the investigator in accordance with the manufacturer's instructions.

7.5.2. Clinical and Laboratory Assessments

The following clinical assessments and laboratory tests should be performed after the index procedure and before hospital discharge:

- Cardiac biomarkers CK and/ or CKMB (CKMB is required, or troponin if CKMB is not available) will be measured once within 6–24 hours post index procedure. CKMB or troponin is required.

  Note: Every effort must be made to obtain cardiac biomarker values within the specified time ranges. Results of all cardiac biomarker measurements, even measurements performed outside the time range, will be documented in the medical record and reported on the eCRF.

  If CKMB elevation (or troponin in the absence of CKMB) > 3x URL is noted post-procedure, CKMB (or troponin in the absence of CKMB) measurements should be performed every 4-12 hours and documented in the medical record and reported on the eCRF until values have returned to < 3x URL or until discharge, starting from when the first elevation is noted.

- A 12-lead ECG must be completed within 24 hours after the index procedure.
- Ischemic/angina assessment according to CCSC or Braunwald classification just prior to discharge.
- AE and SAE assessment.
- Anti-platelet/anti-coagulant medical therapy post procedure.
- Other cardiovascular and diabetic medications post procedure.

Prior to discharge, review of the study follow-up requirements with the subject is recommended to help ensure compliance with the follow-up schedule. In addition, confirmation of subject contact telephone numbers, including numbers for home, work numbers and primary physician, as applicable, should be completed.

7.6. Antiplatelet/Anticoagulation Regimen

Subjects will receive a minimum of 75 mg aspirin daily indefinitely, and 75 mg clopidogrel daily for a minimum of 6 months, 12 months are recommended for subjects who are not at high risk for bleeding.

Clopidogrel may be substituted with 5 mg or 10 mg prasugrel daily or 90 mg ticagrelor twice daily or 250 mg ticlopidine twice daily.

OUS investigators may follow medication administration recommendations in accordance with ESC guidelines, national guidelines and/or hospital standard of care.

7.7. Follow-Up Assessments

All randomized subjects will be followed through 5 years of follow-up, with assessments performed at 1 month, 6 months, 12 months and annually thereafter.

Subjects who are randomized, but do not receive a study stent (i.e., subjects who don ot receive an Orsiro or Xience stent) will be followed for 12-months only.

An office visit is required for the 12-month follow-up visit. All other visits may be performed by telephone interview with the subject if the subject is unable to return for an office visit within the applicable follow-up window.

For each follow-up visit, all clinical assessments should be performed on the same date. Requirements of each follow-up evaluation are described below.

7.7.1. One (1) Month Clinical Follow-Up (30 ± 7 Days)

Subjects will be evaluated at 1 month post-procedure (± 7 days) by a telephone interview and/or an office visit. The following assessments must be completed:

- Ischemic/anginal status (according to CCSC or Braunwald).
- AEs and SAEs since discharge.
- Anti-platelet/anti-coagulant medical therapy since discharge.
- Other cardiovascular and diabetic medications since discharge.
- Any coronary intervention (e.g., repeat revascularization) that occurred since the post-procedure discharge.
- 12-lead ECG (if an office visit is performed).

7.7.2. Six (6) Month Clinical Follow-Up (180 ± 14 Days)

Subjects will be evaluated at 6 months post-procedure (180 ± 14 days) by a telephone interview or an office visit. The following assessments must be completed:

- Ischemic/anginal status (according to CCSC or Braunwald).
- AEs and SAEs since the previous contact.
- Anti-platelet/anti-coagulant medical therapy since the previous contact.
- Other cardiovascular and diabetic medications since the previous contact.
- Any coronary intervention (e.g., repeat revascularization) that occurred since the previous contact.
- 12-lead ECG (if an office visit is performed).

7.7.3. Twelve (12) Month Clinic Visit (360 ± 30 Days)

Subjects will be evaluated at 12 months post-procedure (360 ± 30 days). The 12-month follow-up is required to be an office visit with the subject. During the 12-month follow-up visit, the following assessments must be completed:

- Ischemic/anginal status (according to CCSC or Braunwald).
- AEs and SAEs since the previous contact.
- Anti-platelet/anti-coagulant medical therapy since the previous contact.
- Other cardiovascular and diabetic medications since the previous contact
- Any coronary intervention (e.g., repeat revascularization) that occurred since the previous contact.
- 12-lead ECG.

7.7.4. Long-Term Clinical Follow-Up at 2, 3, 4 and 5 Years Post-Procedure (Annually ± 60 Days)

Subjects will be evaluated at 2, 3, 4 and 5 years post-procedure (± 60 days) by a telephone interview and/or an office visit. The following assessments must be completed:

- Ischemic/anginal status (according to CCSC or Braunwald).
- AEs and SAEs since the previous contact.

  Note: All AEs (serious and non-serious) will be reported for the entire study period to the extent required by national and/or local requirements. For US sites only: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable and only serious adverse events, including MACE and clinical study endpoints, will be recorded.
- Anti-platelet/anti-coagulant medical therapy since the previous contact.
- Other cardiovascular and diabetic medications since the previous contact.
- Any coronary intervention (e.g., repeat revascularization) that occurred since the previous contact.

7.8. Unscheduled Study Visit

Subjects may present to the clinic outside of the scheduled follow-up windows. Such unscheduled study visits will be reported if the subject has experienced an AE. For an unscheduled study visit, concomitant cardiac medications and data regarding adverse events will be collected.

Subjects assessed at an unscheduled study visit may require diagnostic testing (e.g. ECG, angiogram, CK/CKMB levels) and/or a revascularization procedure to further evaluate and treat ischemic symptoms. Any repeat procedure must be reported on the relevant case report forms, including any unscheduled visits prior to the repeat procedure and/or adverse events associated with the procedure. Only commercially available stents are allowed during repeat procedures. Use of investigational stents is not permitted.

Any repeat or unscheduled diagnostic or interventional coronary revascularization procedure performed should include a diagnostic assessment of the target lesion(s) and investigational stent(s). Angiographic data collected during any repeat procedure on the target vessel(s) must be made available to the CEC for an independent review and assessment. Likewise, the angiographic images should be submitted to the core laboratory for an independent review and assessment of the target lesion and investigational stent.

7.9. Angiographic Core Laboratory

The angiographic core laboratory will provide sites with a written procedural manual describing the acquisition and submission procedures for the baseline and subsequent

repeat angiograms. Sites will be requested to obtain and submit a minimum of two orthogonal views at baseline and post-procedure in accordance with the manual.

Baseline and procedural angiograms for all subjects will be sent to the independent angiographic core laboratory for evaluation. In addition, any coronary angiograms performed during the trial follow-up period due to suspicion of restenosis of the target lesion(s) will be forwarded to the angiographic core laboratory for analysis.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The BIOFLOW-V clinical trial is a prospective, multicenter, randomized, controlled study. A total of up to 1,400 subjects will be randomized, stratified by study center, in a 2:1 ratio with 933 subjects randomized to receive the Orsiro stent and 467 subjects randomized to receive the Xience stent.

The trial is designed to assess the non-inferiority of the Orsiro stent compared to the Xience stent with respect to the primary endpoint of 12-month TLF, defined as cardiac death, target vessel Q-wave or non–Q-wave MI, or any clinically-driven TLR.

For this purpose, data from BIOFLOW-V randomized subjects will be combined with data from historical subjects from the BIOFLOW-II and BIOFLOW-IV randomized trials employing a Bayesian approach. Only subjects who meet all clinical and angiographic eligibility criteria of the BIOFLOW-V trial will be included in the analysis.

8.1. Prior Data

The Orsiro clinical trial program includes BIOFLOW-II, BIOFLOW-IV and BIOSCIENCE, three randomized controlled trials in which subjects were randomized to the Orsiro stent against the Xience Prime™ or Xience Xpedition™ stents. A brief description of these trials is provided in Section 3.5. The inclusion and exclusion criteria for BIOFLOW-II and BIOFLOW-IV are nearly identical to those proposed for BIOFLOW-V, whereas the inclusion and exclusion criteria in BIOSCIENCE were more liberal to allow enrollment of a broadly inclusive real world population. We propose to use data from the BIOFLOW-II and BIOFLOW-IV trials prospectively using a Bayesian approach in the final non-inferiority analysis of the BIOFLOW-V study. A summary of the comparison of the study design of BIOFLOW-II and –IV trials along with the proposed BIOFLOW-V study can be found in Table 8-1. The current status of the studies is as follows:

- BIOFLOW-II – Enrollment into the trial was completed and 12-month results are available. A total of 298 subjects were randomized to receive the Orsiro stent and 154 were randomized to receive the Xience Prime™ stent. Of them, 287 Orsiro subjects and 148 Xience subjects completed their 12-month follow-up.
- BIOFLOW-IV - Enrollment into the trial is still ongoing and it is anticipated that 370 Orsiro subjects and 185 Xience Prime™/Xpedition™ subjects will be contributed from this trial.

To ensure the validity of data from subjects across trials, the following measures will be taken:

- Only subjects that meet all BIOFLOW-V clinical and angiographic eligibility criteria will be included.
- Evaluation of the 12-month TLF rate (a primary endpoint in the BIOFLOW-V trial and a secondary endpoint in the BIOFLOW-II and BIOFLOW-IV trials) will be performed in a uniform fashion, using a consistent set of definitions and similar follow-up schedule:
    - The measurement schedule of cardiac enzymes is similar in all trials: cardiac enzymes are collected once within 6-24 hours post index procedure. While all trials mandated collection of CK and CKMB, the BIOFLOW-II also mandated measurement of troponin. The BIOFLOW-IV and BIOFLOW-V trials allow measurement of troponin if CK and CKMB are not used. To address the differences in the collection of cardiac enzymes between the three trials, a uniform definition of peri-procedural MI that is based on CK and CKMB levels (with troponin levels used only in the absence of CK and CKMB) will be utilized.
    - All trials have similar clinical follow-up schedule at 1 month (telephone contact/clinic visit), 6 months (telephone contact/clinic visit) and 12 months (telephone contact/clinic visit for BIOFLOW-II clinic visit for BIOFLOW-IV and BIOFLOW-V).
    - The BIOFLOW-II and BIOFLOW-IV trials used the same independent angiographic core laboratory. To ensure consistency, angiograms from the BIOFLOW-II, BIOFLOW-IV and BIOFLOW-V trials will be analyzed or validated by the same angiographic core laboratory.
    - All clinical endpoints (potential TLR, MI and death events) will be re-adjudicated by the same independent CEC as will be employed for the BIOFLOW-V data, using uniform definitions.
- Data quality will be confirmed in accordance with the monitoring plan of each trial.

Table 8-1. Subjects' Poolability

	BIOFLOW-II	BIOFLOW-IV	BIOFLOW-V
Eligibility Criteria	All subjects will match BIOFLOW-V clinical and angiographic inclusion/exclusion criteria		
Primary or Secondary Endpoint Definition	**TLF:** cardiac death, target vessel Q-wave or non-Q wave MI, CABG, clinically driven TLR		
Follow-up schedule	1mo, 6mo, 9mo angio, **12mo**, 2yr, 3yr, 4yr, 5yr	1mo, 6mo, **12mo**, 2yr, 3yr, 4yr, 5yr	1mo, **12mo**, 2yr, 3yr, 4yr, 5yr
Enzyme measurements	CK, CKMB (optional) and Troponin: • Baseline • Within 6-24 hours after the index procedure or at discharge, whichever comes first	CK, CKMB (optional) or Troponin (if CK and CK-MB are not used): • Baseline • Within 6-24 hours after the index procedure or at discharge, whichever comes first	CK, CK-MB, Troponin (if CKMB is not available): • Baseline • Within 6-24 hours after the index procedure
Clinical Monitoring	• 100% source verification • Independent core labs for angiography, IVUS & OCT • On-site monitoring • Independent CEC adjudication	• 100% source verification • Independent angiographic core lab • On-site monitoring • Independent CEC adjudication	• 100% source verification • Independent angiographic core lab • On-site monitoring • Independent CEC adjudication

8.2. Bayesian Analysis

To assess the non-inferiority of the Orsiro stent compared to the Xience stent in the BIOFLOW-V study, a Bayesian approach using hierarchical models to formally incorporate data from the BIOFLOW-II and BIOFLOW-IV trials will be employed. The approach proposes using Binomial analysis for the presence of a TLF event and a Bayesian model that allows for a 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 parameters defining the bias are selected so that the proposed method is robust to misspecifications of the initial assumptions. Further details are presented in Section 8.7.

8.3. Software

Simulations were run in R statistical package (R citation) and OpenBUGS software,[49] version 3.2.2. For each scenario, 10,000 datasets were generated in R. OpenBUGS was then used to obtain samples from the posterior distribution of each parameter and to calculate the probability of success. For each analysis, 50,000 samples were obtained from the posterior distributions after 1,000 samples were discarded.

8.4. Criteria for Success

The criterion for success is based on the posterior probability of the alternative hypothesis (i.e., of non-inferiority being met). The Orsiro group will be declared non-inferior to the Xience group if the posterior probability of the alternative hypothesis $\mathrm{H_A}$ is large, that is

$$P(H_A|Data) = P(\pi_X^V - \pi_O^V > -\delta|Data) > \pi^*$$

where π_X^V and π_O^V are the 1-year TLF for the Xience and Orsiro groups of the BIOFLOW-V study, respectively, δ is the non-inferiority margin and $\mathrm{H_A}: \pi_X^V - \pi_O^V > -\delta$ is the alternative hypothesis indicating that non-inferiority is met and π^* is the level of evidence we require to declare the alternative hypothesis true.

8.5. Sample Size Determination

The BIOFLOW-V trial will assess non-inferiority of the 12-month TLF rate for the Orsiro stent vs. TLF rate in subjects treated with the Xience stent.

The null hypothesis is that the Orsiro stent will have a primary endpoint (TLF) rate equal to or exceeding that of the Xience group by the non-inferiority margin or more.

The alternative hypothesis is that the Orsiro stent will have TLF rate less than the Xience group rate plus the non-inferiority margin. Specifically:

$$\mathrm{H_0}: \pi_X^V - \pi_O^V \leq -\delta$$

$$\mathrm{H_A}: \pi_X^V - \pi_O^V > -\delta$$

Where π_O^V is the true 12-month TLF rate for the Orsiro stent, π_X^V is the true 12-month TLF rate for the Xience arm, and δ is the non-inferiority margin.

The assumptions for this analysis are:

- True 12-month TLF rate is 7.0% in both treatment groups ($\pi_X^V = \pi_O^V$).
- Power is 89%.
- 3.85% is the absolute non-inferiority margin (55% relative non-inferiority margin).
- Discount the results of the BIOFLOW-IV data by 20% and 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 is 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 is 0.3.
- Non-inferiority assessment will be assessed using the posterior probability of the alternative hypothesis as specified above, where $\pi^* = 0.975$

Rejection of the null hypothesis will signify that the Orsiro stent is not inferior to the Xience stent with regards to 12-month TLF. A total of 1,200 subjects (800 in the Orsiro

group and 400 in the Xience group) will have 89.6% power to reject the above null hypothesis in favor of the alternative under the stated assumptions. To account for loss to follow-up (expected to be approximately 10%), a total of 1,334 subjects will need to be randomized. The one-sided type I error estimates are 4.0%, 3.3%, and 4.2% if the actual ODDS for the 12-month TLF rate of event in the Xience group of the BIOFLOW-IV study are the same, 10% lower and 10% higher when compared with the ODDS for the 12-month TLF rate of event in the Xience group of the BIOFLOW-V study.

True Rate

The current assumption of the 12-month TLF rate of 7.0% is based on expected inclusion criteria for BIOFLOW studies and results from recent everolimus eluting stent trials.

The BIOFLOW-IV trial remains in follow-up for its primary endpoint results. An interim analysis of the observed TLF rate for Orsiro and Xience combined for the two historical trials will not be performed due to the timing of data availability. To mediate the effect on power of possible discrepancies between the assumed rate in BIOFLOW-V and BIOFLOW-IV, the sample size may be increased by up to 60 additional subjects (40 in the Orsiro and 20 in the Xience arm). The resultant group sizes, 840 Orsiro and 420 Xience, for a total of 1260 subjects, will result in 89% power or higher. Taking into consideration loss for follow-up, the up to 1400 subjects may be enrolled.

Non-Inferiority Margin

The non-inferiority margin was calculated based on a meta-analysis rate of the difference in treatment effect between DES and BMS. Randomized clinical trials comparing treatment with DES and treatment with BMS with 9 months or longer clinical follow-up data were included in the meta-analysis. Nine-month rates were used whenever 12-month rates were not available, as shown in Table 8-2. Depending on study definitions, TVF or MACE rates were used to match as closely as possible the TLF definition in this study.

The meta-analytic rate of the difference in treatment effect between DES and BMS was 10.0% with a lower bound of the 2-sided 95% CI of 8.2%. A common practice is to take 50% of this lower bound of the DES-BMS difference as the non-inferiority margin, therefore an absolute non-inferiority margin of 3.85%, which is approximately 46% of the lower bound, is supported.

Table 8-2. TVF/MACE Rates at 9 or 12 Months, DES vs. BMS

Trial	Target Vessel Failure Rate				Major Adverse Cardiac Event Rate			
	9 Months		12 Months		9 Months		12 Months	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS
RAVEL[1] (MACE: death, MI, CABG, target lesion percutaneous revascularization)	–	–	–	–	–	–	5.8% (7/120)	28.8% (34/118)
SIRIUS[2] (TVF: cardiac death, MI, target vessel repeated percutaneous or surgical revascularization)	–	–	9.8% (52/533)	24.8% (130/525)	–	–	–	–
E-SIRIUS[3] (MACE: death, MI, CABG, TLR)	–	–	–	–	8.0% (14/175)	22.6% (40/177)	–	–
C-SIRIUS[4] (MACE: death, MI, emergent CABG, clinically-driven TLR)	–	–	–	–	4.0% (2/50)	18.0% (9/50)	–	–
TAXUS-I[5] (MACE: death, Q-wave MI, TVR, stent thrombosis)	–	–	–	–	–	–	3.3% (1/30)	10.0% (3/30)
TAXUS-II[6] (MACE: death, MI, TVR) TAXUS-SR arm	–	–	–	–	–	–	10.9% (14/129)	22.0% (29/132)
TAXUS-MR arm	–	–	–	–	–	–	9.9% (13/131)	21.4% (28/131)
TAXUS-IV[7] (TVF: death, MI, ischemia-driven TVR; MACE: cardiac death, MI, ischemia-driven TVR)	–	–	–	–	–	–	10.8% (69/639)	20.0% (126/633)
TAXUS-V[8] (TVF: death, MI, ischemia-driven TVR; MACE: cardiac death, MI, ischemia-driven TVR)	–	–	–	–	15.0% (84/560)	21.2% (120/567)	–	–
TAXUS-VI[9] (MACE: death, MI, TLR and TVR)	–	–	–	–	16.4% (36/219)	22.5% (51/227)	–	–
ENDEAVOR II[10] (TVF: TVR, recurrent MI, cardiac death not clearly attributed to non-target vessel; MACE: death, MI, emergent CABG, TLR)	7.9% (47/592)	15.1% (89/591)	–	–	–	–	–	–

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[2] Weisz G, Leon MB, Holmes Jr DR *et al*. Two-year outcomes after sirolimus-eluting stent implantation results from the Sirolimus-Eluting Stent in *de Novo* Native Coronary Lesions (SIRIUS) Trial. *J Am Coll Cardiol* 2006;47:1350–1355.

[3] Schofer J, Schlüter M, Gershlick AH *et al*. for the E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;362:1093–1099.

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[7] Stone GW, Ellis SG, Cox DA *et al*. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: The TAXUS-IV trial. *Circulation* 2004;109:1942–1947.
[8] Stone GW, Ellis SG, Cannon L *et al*. for the TAXUS V investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. *J Am Med Assoc* 2005;294:1215–1223.
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[10] Fajadet J, Wijns W, Laarman G-J *et al*. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: Clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006;114:798–806.

8.6. Statistical Analysis Sets

8.6.1. Intent-to-Treat Analysis Population

The Intent-to-Treat (ITT) population is defined as all randomized subjects. Subjects are analyzed according to the stent to which they were randomized (regardless of the actual stent that they received). This is the primary analysis population.

8.6.2. Per-Protocol Population

The Per-Protocol (PP) population is defined as all randomized subjects who received at least one assigned study stent, have sufficient follow-up data (at least 11 months of follow-up or experienced the primary endpoint) and no major protocol eligibility violations (i.e. inclusion/exclusion criteria violations that could impact the primary endpoint).

8.6.3. Modified Intent-to-Treat Analysis Population

The Modified ITT population is defined as all randomized subjects who received at least one study stent according to their treatment assignment.

8.7. Endpoint Analyses and Reporting of Results

Descriptive statistics will be used to summarize clinically relevant demographic and background characteristics, and safety and effectiveness data collected in this study. The statistics for continuous variables will include sample sizes, means, medians, standard deviations, inter-quartile ranges, minimum and maximum values. Categorical variables will be described with counts and percentages. Proportions will be calculated using known non-missing values. Unless otherwise indicated, all statistical tests and/or confidence intervals will be performed at $\alpha = 0.05$ (2-sided).

All descriptive statistical analyses will be performed using Statistical Analysis Software (SAS) for Windows (version 9.1 or higher).

8.8. Analysis of Primary Endpoint

Bayesian analyses will be performed using OpenBUGS[49] version 3.2.2 or higher. This study will assess non-inferiority of the 12-month TLF rate for the Orsiro stent vs. the Xience stent. The analysis will be carried out on the ITT set (primary) and PP analysis sets.

The null hypothesis is that the Orsiro stent will have a primary endpoint (12-month TLF) rate equal to or exceeding that of the Xience group by the non-inferiority margin or more.

The alternative hypothesis is that the Orsiro stent will have a 12-month TLF rate less than the Xience group rate plus the non-inferiority margin.

$$\mathrm{H}_0: \pi_X^V - \pi_O^V \leq -\delta$$

$$\mathrm{H}_\mathrm{A}: \pi_X^V - \pi_O^V > -\delta$$

where π_O^V is the true 12-month TLF rate for the Orsiro stent, π_X^V is the true 12-month TLF rate for the Xience arm, and δ is the non-inferiority margin chosen to be 0.0385 (or 3.85%).

Due to the randomized nature of the study, we do not expect the two treatment groups to differ on clinically important baseline characteristics, therefore no adjustment is proposed in the primary analysis.

The proposed model is a Bayesian hierarchical model that assumes a bias between the 12-month TLF rates in BIOFLOW-II and BIOFLOW-V as well as BIOFLOW-IV and BIOFLOW-V studies. Full details will be provided in the SAP.

Center heterogeneity

To assess consistency of treatment effect size across study centers, Bayesian models will be employed for the subject level data. Any study center with less than 5 subjects per treatment group will be pooled with other study centers by geographic region prior to carrying out this assessment.

Individual data, for treatment i, study j and individual k will be assumed to follow a Bernoulli distribution:

$$Y[i,j,k] \sim dbern(p[i,j,center[k]])$$

where center is an index variable that indicates the center that the individual k was recruited in.

The assumptions are based on a similar model to the model proposed in Legrand et al. 2005.[50] The event rate is assumed to have an additive effect for center that varies with study:

$$logit\big(p\big[i,j,center[k]\big]\big) = \delta\big[center[k]\big] + \big(beta[j] + \gamma\big[center[k]\big]\big) * (TRT_k = i)$$

The two random effects can be interpreted as the influence of the center on the overall TLF rate and on the overall treatment effect, respectively. The center effects, $\delta\big[center[k]\big]$ and $\gamma\big[center[k]\big]$, are assumed to be exchangeable and a priory to follow a normal distribution with mean mu_delta and mu_gamma and standard deviation $sigma\_delta$ and $sigma\_gamma$, respectively. As recommended by Geltman et al. 1995[51] uniform prior on (0.1, 100) will be assumed on the two variances. The standard deviation of the random effects can be viewed as a measure of heterogeneity across centers and treatment effect. As indicated in Spiegelhalter 2004 (Spielgelhalter, D.J., Abrams, K.R. and Myles, J.P. (2004). Bayesian Approaches to Clinical Trials and Health-Care Evaluation, John Wiley and Sons, page 169) a value of 1 for standard deviation of random effects '…corresponds to substantial heterogeneity.', therefore, if the posterior probability that $sigma\_delta > 1$ or $sigma\_gamma > 1$ exceeds 0.85 *and* the credible intervals discussed above indicate the interaction is qualitative in nature, then this may preclude all sites from being pooled for the primary analysis, in which case the primary analysis may be re-run excluding study centers causing the interaction. Additional details will be provided in the full SAP.

Region (US/OUS) heterogeneity

To assess consistency of treatment effect size across regions (United States [US] vs. Outside United States [OUS]) region and an interaction of region and treatment will be included in the model. For the interaction coefficient, we will calculate p_int as the 2-sided posterior probability of observing an interaction value that is more extreme than 0. This value is similar to a traditional p-value. If p_int<0.15 we will conclude that heterogeneity across region is significant and the treatment effect will be calculated and tested within region.

8.9. Handling of Missing Data in the Analysis of Primary Endpoint

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. The following analysis strategies will be adopted to handle missing data with results compared for consistency prior to carrying out the above analysis:

1. Only subjects who experienced the primary endpoint (TLF at 12 months) or who had appropriate follow-up (at least 330 days post baseline, given the 30-day visit window allowed around the 12-month visit) will be included in the analysis.
2. All subjects will be included in the analysis set including data for subjects missing primary endpoint status due to not experiencing the event and not reaching at least 330 days of follow-up. Data for these subjects will be included as 'NA'. A model will be used for the event probabilities:

$$Y[i,j,k] \sim dbern(p[i,j,center[k]]$$

with

$$logit\left(p\left[i,j,center[k]\right]\right) = beta * X[k] + logit(p[i,j])$$

where $X[k]$ are predictors values for subject k. A noninformative prior will be assumed on the slope parameters $beta$ and similarly to the analysis of the primary endpoint, bias will be assumed between TLF rates in different studies.

The following variables will be included in the model as covariates:

- Age
- Gender
- Diabetes
- Lesion length
- Others (the complete set will be detailed in the full SAP)

3. Time to event analysis using a Bayesian Cox regression analysis. For each study, a separate hazard ratio comparing Xience to Orsiro stent will be included. Similar to the method proposed as a primary method, a bias will be assumed between the hazard ratio of BIOFLOW-II or BIOFLOW-IV and the hazard ratio of the BIOFLOW-V. Further details will be provided in the full SAP.

4. A tipping point analysis will be carried out. Here, it is assumed that for all Xience patients with missing primary endpoint (12-month TLF) status, TLF did not occur. For Orsiro patients with missing data, it will be first assumed that the primary endpoint of TLF occurred for exactly one such patient; then the primary analyses will be re-run to assess if non-inferiority is met under this assumption. Then it will be assumed the primary endpoint occurred for exactly two Orsiro patients with missing data, and the primary non-inferiority analysis will be rerun. The process will continue sequentially in this manner until all Orsiro patients with missing data are considered to have met the primary endpoint of TLF. Of interest is the "tipping point", or i.e., the number of imputed Orsiro TLFs where non-inferiority is not met in this analysis.

8.10. Analysis of Secondary Endpoints

Analyses of secondary endpoints will be carried out on the ITT, Modified ITT and PP analysis sets using the same method proposed for the primary endpoint. Secondary Endpoints include the following measures:

1. Device success
2. Lesion success
3. Procedure success

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

4. Death
5. MI
6. Cardiac death or MI
7. MACE and individual MACE components
8. TLF and individual TLF components
9. TVF and individual TVF components
10. Stent thrombosis according to ARC criteria

Included in the analysis, will be subjects experiencing the event or who have adequate follow-up (e.g., at least 23 days for 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).

As an additional analysis, for time-to-event endpoints, Bayesian Cox regression will be used. For each study, a separate hazard ratio comparing Xience to Orsiro stent will be included. Similarly to the method proposed as a primary method, a bias will be assumed between the hazard ratio of BIOFLOW-II or BIOFLOW-IV and the hazard ratio of the BIOFLOW-V. All subjects will be included, where subjects not experiencing the event will be censored at last known follow-up or at the end of the relevant follow-up time, whichever is earlier.

8.11. Analysis of Baseline Demographics and Procedural Characteristics

Although we do not expect differences between the two treatment groups due to randomization, a comparison of the demographic and baseline characteristics in between the two treatment groups will be performed. Demographic, medical history and other clinically relevant baseline variables will be summarized by treatment using descriptive statistics (i.e. number of observations available, mean, standard deviation, minimum, and maximum for continuous variables and counts and percentages for qualitative variables). Treatment difference on dichotomous variables will be evaluated using Fisher's exact tests. Categorical variables will be compared between treatments using the Cochran-Mantel-Haenszel (CMH) Modified Ridit Scores, i.e. CMH of general association for nominal variables and CMH of row mean score for ordinal variables). Continuous variables will be compared between treatments using a two-sample t-test.

8.12. Subgroup Analysis

Subgroups for secondary analysis of clinical endpoints include:

- Reference vessel diameter ≤ 2.75 mm/ > 2.75 mm.

  Note: Subjects with at least one target lesion ≤ 2.75 mm will be classified with the small vessel subgroup.
- Subjects > 75 years of age/subjects ≤ 75 years of age.
- Women/men.
- Subjects with diabetes/subjects without diabetes.
- Lesion length > 26 mm and ≤ 26 mm in length
- Single stents versus overlapping stents for lesion lengths > 26 mm

Treatment group difference (Orsiro minus Xience) in the primary endpoint rate and the two-sided 95% credible interval of the difference will be presented within each subgroup. A test of interaction on the primary endpoint will be performed to formally assess heterogeneity of treatment effect on the primary endpoint across subgroups in the same manner that will be used the assessment of region heterogeneity discussed above. The purpose of this analysis is 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 will be included in this analysis.

8.13. Adverse Event Analysis

Only AEs whose frequency exceeds 10 will be compared between the two groups. For those AEs, if p_O and p_X are the probability of the AE with the Orsiro and Xience stents, we will report the posterior distribution that $p_O > p_X$, that is, the posterior probability that the probability of the AE is larger with the Orsiro stent than with Xience stent. Non-informative independent priors Beta (0.1,0.1) will be assumed on p_O and p_X, respectively.

9. ADVERSE EVENTS

In this study, subjects should be encouraged to report adverse events (AEs) spontaneously or in response to general, non-directed questioning (e.g., “How has your health been since the last visit?”). Any time during the study, the subject may volunteer information that resembles an adverse event. If it is determined that an AE has occurred, the investigator should obtain all information required to complete the AE eCRF.

9.1. Definitions

9.1.1. Adverse Events

An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in clinical trial subjects, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: Abnormal laboratory findings will be considered AEs, only if determined by the investigator to be clinically significant**.**

Any current condition that is recorded as a pre-existing condition either in the medical history of physical examination section, unless there is a change in nature, severity, or degree of incidence, is not an AE.

Adverse events shall be assessed and documented throughout the course of the trial beginning after the subject has been enrolled. All adverse events should be recorded on the appropriate subject eCRF and followed through to their resolution regardless of time window.

9.1.2. Adverse Device Effect

An adverse device effect (ADE) is a device-related adverse event, i.e., any adverse event for which a causal relationship between the device and the event is at least a reasonable possibility (the relationship cannot be excluded). Note that this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device, as well as any event resulting from user error or from intentional misuse of the investigational medical device.

Device Failure: A device has failed if it is used in accordance with the IFU, but does not perform according to IFU and negatively impacts treatment.

Device Malfunction (ISO 14155:2011): Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or Clinical Investigation Protocol (CIP).

Device Deficiency (ISO 14155:2011): Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, user errors and inadequate labeling.

Near Incident: Malfunction or deterioration in characteristics and/or performance of the device, which might have led to death or serious deterioration in health; incident occurred and is such that if it occurred again, it might lead to death or serious deterioration in health.

User Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. User error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not in itself constitute a user error.

9.1.3. Serious Adverse Event

Due to the international conduct of the study, the ISO 14155 definition of serious adverse events and device effects will be utilized.

A serious adverse event (SAE) is an adverse event that leads to:

- Death.
- Serious deterioration in the health of the subject that either results in life-threatening illness or injury; permanent impairment of a body structure or a body function; hospitalization or prolonged hospitalization; or medical or surgical intervention to prevent life-threatening illness, injury or permanent impairment to a body structure or a body function.
- Fetal distress, fetal death, congenital abnormality or birth defect

Note that planned hospitalization for pre-existing condition (scheduled prior to the subject signing the informed consent for the study), or a procedure required by the clinical study plan, without a serious deterioration in health, is not considered to be an SAE.

Also note that in the European Union and OUS countries, SAEs also include device deficiencies that might have led to an SAE if suitable action had not been taken, intervention had not been made, or if circumstances had been less fortunate. These are handled under the SAE reporting system.

9.1.4. Serious Adverse Device Effect

A serious adverse device effect is an adverse device effect that results in any of the consequences characteristic of a serious adverse event.

9.1.5. Anticipated Adverse Event

An anticipated adverse event is any undesirable experience (sign, symptom, illness, abnormal laboratory value or other medical event) occurring to a subject, whether or not considered related to the investigational product(s) or drug regimen prescribed as part

of the clinical protocol, pre-defined in the clinical protocol and/or IFU, that is identified or worsens during a clinical study.

For anticipated AEs that have been identified as possible complications of the Orsiro stent, please see Section 13.1.

9.1.6. Unanticipated Adverse Device Effect or Unanticipated Serious Adverse Device Effect

An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of a subject.

In the European Union and other OUS countries, the term unanticipated serious adverse device effect (USADE) as defined in ISO14155:2011, is any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

9.1.7. Device Failures, Malfunctions and Misuse

Investigators are instructed to report all possible device failures, malfunctions or misuse observed during the course of the trial. These incidents will be documented in the electronic case report form provided as follows:

Device Failure: A device failure has occurred when the device is used in compliance with the IFU, but does not perform as described in the IFU and also negatively impacts treatment of the study subject.

Device Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or CIP.

Device Misuse: Any use of the investigational device by an investigator that is contradictory to the application described in the IFU will be categorized as device misuse and is to be reported as a significant protocol deviation.

9.2. Documentation

Adverse events must be listed on the appropriate eCRF. All adverse events will be characterized by the following criteria:

- Relatedness to the study device and procedure
- Outcome
- Treatment or action taken

All adverse events (serious and non-serious) will be reported for the entire study period in accordance with national laws.

For US sites only: All adverse events will be reported for the first 12 months of the subject's study participation until the primary endpoint is determined. After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable and only serious adverse events, including MACE and clinical study endpoints, are required to be reported.

9.3. Relatedness

The Principal Investigator (PI) will evaluate if the AE or SAE is related to the investigational device or study procedure. Relatedness is defined in the following manner:

Not related: The PI has determined that the complication is not related to the study device.

Possible: The PI has determined that the event has a possible relationship to the use of the investigational device.

Definite: The PI has determined that the complication is related to the investigational device.

Both possible and definite relationship designations will be considered device-related for reporting purposes.

9.4. Reporting of Serious Adverse Events

All participating study sites should report SAEs to BIOTRONIK or its designee as soon as possible, preferably by completing an Adverse Event eCRF.

OUS centers should report SAEs immediately upon awareness of the event and completes the AE eCRF Serious Adverse Event section, which will then trigger an initial SAE notification to a pre-defined recipient list.

The investigator should notify BIOTRONIK or its designee as soon as possible concerning any subject death during the study in EDC. The death should be reported on the Study Exit eCRF. In addition, the precipitating cause of death should be recorded on an Adverse Event eCRF, reflecting an outcome of death, once determined. Documentation of the death event should be sent to BIOTRONIK as soon as it is available, and should include the appropriate completed CRFs, a death certificate and a copy of the notification of the death sent to the IRB/EC, as required. If a death certificate is not available, a detailed statement (death report) signed by the investigator should be provided.

The death report should include all of the following, if available:

- Date, time and place of death
- Immediate cause of death
- Circumstances surrounding the death
- Relationship to the investigational stent and/or any study-related procedures

It is the responsibility of each investigator to report all SAEs to the reviewing IRB/EC, according to national regulations and IRB/EC requirements. A copy of the IRB/EC report should be forwarded to the sponsor or its authorized representative.

Additionally, at OUS sites, SAEs will be reported to the competent authorities in accordance with applicable regional/national regulations. BIOTRONIK or its authorized representative, and/or the investigator will report SAEs to the applicable regulatory agencies in accordance with national regulations.

OUS Sites Primary contact for Serious Adverse Events:

BIOFLOW–V Safety Team
Harvard Clinical Research Institute
930-W Commonwealth Ave.
Boston, MA 02215-1212

Tel: +1 617 307–5200
Fax: +1 617 307–5656
HCRIBIOFLOW-VSAFETY@hcri.harvard.edu

9.5. Reporting of Adverse Events

Study sites are required to adhere to applicable US FDA regulations, as well as ISO requirements for EU sites, as well as local IRB/EC adverse event reporting. In specific OUS regions, there may also be requirements for OUS investigators to report specific adverse events directly to their competent authority or national regulatory body.

Table 9-1. Adverse Events Reporting

Adverse Event	Report in EDC	Report to IRB/EC	Report to CA – OUS sites only
Event resulting in death*	Required	Required	CA-dependent
Unanticipated adverse device effect	Required	Required	CA-dependent
Procedure and/or stent related adverse event	Required	IRB/EC-dependent	CA-dependent
Serious adverse event (not stent or procedure related)	Required	IRB/EC-dependent	CA-dependent
Other adverse events – not related**	Required	IRB/EC-dependent	CA-dependent

CA: Competent Authority; EC: Ethics Committee; IRB: Institutional Review Board; OUS: Outside of United States
* The cause of death to the extent available should be reported as an adverse event, with the outcome reflected as death. Reporting to EC in accordance with local requirements.
** US sites only: reporting required through the 12-month follow-up visit or longer if required by the IRB/EC.

9.5.1. Reporting Adverse Device Effects

All participating study sites should report adverse device effects (ADE) and serious adverse device effects (SADE) to BIOTRONIK or its designee as soon as possible, preferably upon awareness of the event (OUS sites), by completing an Adverse Event eCRF.

At sites in the OUS or other participating countries where the Orsiro stent is market-released, these events must also be reported in addition to the product complaint management department of BIOTRONIK. The retrievable part of the devices should be returned to BIOTRONIK for analysis. If there is also a suspected relation to accessory material (guide wire, etc.) the accessory material in question should also be sent to BIOTRONIK for analysis.

Complaint Management Department
BIOTRONIK AG
Ackerstrasse 6
8180 Bülach
Switzerland
cnf.vi@biotronik.com
Fax: +41 44 864 5181

Investigational stents that are returned to the US will be sent to BIOTRONIK AG, Bülach, Switzerland, for analysis. Those analyses will be trended (as appropriate) and reported to FDA as soon as they are available.

9.5.2. Reporting of Unanticipated Adverse Device Effects or Unanticipated Serious Adverse Device Effects

If an adverse event occurs that the investigator believes may be a potential UADE/USADE, the site should immediately contact the sponsor or its authorized representative to determine reporting requirements. In addition, when there is a reason to believe a device may have malfunctioned, causing potential harm to a subject, the site should immediately notify the sponsor.

The investigator shall submit to BIOTRONIK and the reviewing IRB/EC a report of any potential UADE occurring during the study as soon as possible, but in no event later than 10 calendar days after the investigator first learns of the effect in accordance with FDA regulations. In the EU or other OUS countries, any potential USADE shall be reported according to national regulations. All UADEs/USADEs must be documented by the investigator, including date of onset, complete description of event, possible reason(s) for event, severity, duration, actions taken and outcome. Copies of all supporting documents should be submitted concurrently with the AE eCRF documenting the UADE/ USADE.

Subsequently, BIOTRONIK or its designee will submit a report to FDA (and any other applicable competent authorities) and to all reviewing IRBs/ECs and participating investigators within 10 calendar days after the Sponsor first receives notice of the effect. The Sponsor or its designee will submit other reports as required by the FDA and other

applicable regulatory agencies. The final determination of an event being classified as an unanticipated event will be initially determined by HCRI, and confirmed by BIOTRONIK.

9.6. Reporting of Study Endpoint Adverse Events

Whenever a clinical event related to a study endpoint is suspected or identified, all supporting source documents (i.e. progress notes, discharge summaries, catheterization lab reports, ECGs, lab results, etc.) should be submitted according to CEC source documentation collection procedures as soon as they are available. The source documentation required for each reported event is listed in the CEC charter.

9.7. Reporting Responsibilities

Table 9-2. Investigator Reporting Responsibilities

Type of Report	Investigator Reporting Responsibilities	
	Report Prepared For	**Reporting Timeframe**
FDA-Defined Reports		
Unanticipated adverse device effect	Sponsor IRB/EC*	As soon as possible, upon awareness of the effect. **Written:** within 10 calendar** days after the investigator first learns of the effect.
Subject's death	Sponsor and IRB/EC*	**Written:** as soon as possible and as required by reviewing IRB/EC, but not to exceed 10 days from date of site notification of subject death.
Withdrawal of IRB/EC approval or other action on part of the IRB/EC that affects the study	Sponsor	**Written**: within 5 working days of IRB/EC decision.
Progress reports	IRB/EC*	At regular intervals, but in no event less than yearly.
Significant deviations from investigational plan	Sponsor and IRB/EC*	**Emergency**: ASAP but in no event later than 5 working days after deviation occurs to protect the life or physical well-being of a subject in an emergency. **Non-emergency**: prior approval by Sponsor and, if deviation may affect scientific soundness of the trial or the rights, safety or welfare of subject, also by the IRB/EC and FDA as an IDE supplement.
Informed consent not obtained	Sponsor and IRB/EC*	Within 5 working days of use of the investigational device.
Final report	Sponsor and IRB/EC*	Within 3 months after termination or completion of study or termination of site's participation.
Other Reports		
Adverse Events	Sponsor and IRB/EC*	In accordance with the protocol, applicable local regulations, and IRB/ EC requirements.

ASAP: as soon as possible; EC: Ethics Committee; FDA: Food and Drug Administration; IDE: investigational device exemption; IRB: Institutional Review Board.
* Reporting to IRB/EC only where required by local legal requirements.
** FDA requires 10 working days.

Table 9-3. Sponsor Reporting Responsibilities

Type of Report	Sponsor Reporting Responsibilities	
	Report Prepared For	**Reporting Timeframe**
FDA-Defined Reports		
Unanticipated adverse device effects/unanticipated serious adverse device effects	FDA, all reviewing IRBs/ECs*, participating investigators and appropriate CAs*	**Written**: within 10 calendar** days from the time the sponsor first learns of the effect.
Withdrawal of IRB/EC approval	FDA, all reviewing IRBs/ECs*, participating investigators and appropriate CAs*	**Written**: within 5 working days.
Withdrawal of FDA approval	Reviewing IRBs/ECs*, participating investigators and appropriate CAs*	**Written**: within 5 working days.
Device recall	FDA, all reviewing IRBs/ECs*, participating investigators and appropriate CAs*	**Written**: within 30 working days.
Progress reports	FDA, all reviewing IRBs/ECs*, participating investigators and appropriate CAs*	At regular intervals, but in no event less than yearly.
Current Investigator List	FDA	Names and addresses of participating investigators at 6-month intervals (starting at 6 months after FDA approval).
Informed consent not obtained	FDA and appropriate CAs*	Within 5 working days of notification.
Study closure	FDA, all reviewing IRBs/ECs*, participating investigators and appropriate CAs*	Within 30 working days of completion or decision to terminate the study.
Final report	FDA, all reviewing IRBs/ECs*, participating investigators and appropriate CAs*	Within 6 months of study closure.
Other Reports		
Periodic SAE / ADE summaries	Reviewing EC* and appropriate CAs*	In accordance with EU regulations or other OUS national regulations, and/or local legal requirements, or upon request.

CA: Competent Authority; EC: Ethics Committee; FDA: Food and Drug Administration;
IRB: Institutional Review Board
*EC and CA reporting to the extent required by national, local laws and EC-specific requirements.

**FDA requires 10 working days.

10. DATA HANDLING AND RECORD KEEPING

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation.

10.1. Electronic Data Capture

MedNet Solutions Incorporated is a privately-held company that specializes in web-based clinical database and data management technology. MedNet will partner with BIOTRONIK in the development, implementation, and on-going support of a system for EDC of clinical trial data for the study. MedNet may host the database utilized for the EDC system. This system will be 21 CFR Part 11 compliant and will be the conduit for the electronic case report form (eCRF) data entry, data validation, and access to real-time configured functions, tools, and reports for BIOTRONIK, specified study sites and any other parties authorized by BIOTRONIK.

10.2. Electronic Case Report Form Completion

An electronic data capture (EDC) system will be built for the study. The EDC system will include electronic case report forms (eCRFs) designed to capture study information, which are completed by trained site staff.

eCRFs documenting SAEs, U(S)ADEs, device failures and device malfunctions, should be submitted via the EDC system as soon as possible, preferably within 24 hours after the investigator becomes aware of the event.

All other eCRFs should be completed in a timely manner, preferably within 5-10 days of the subject's enrollment or follow-up visit.

All angiographic media should be prepared and sent to the angiographic core laboratory preferably within 7 working days of data collection.

All collected study data will be made available (and sent in the appropriate format) to the sponsor, if requested, after the study has reached its primary endpoint at 12 months post-procedure.

10.3. Investigator Records

Investigators are required to maintain on file the following accurate, complete and current records relating to this study:

- All correspondence relating to the study with another investigator, an IRB/EC, BIOTRONIK, a monitor, the FDA (e.g., a letter sent from the investigator to the IRB/EC), or any other regulatory agency.
- All clinical forms and documentation, including:
    - A copy of the signed subject consent form
    - Date and time of exposure to investigational stent

- All procedure and follow-up report forms, including supporting documents
- Records of any adverse event, including supporting documentation
- Records pertaining to subject deaths during the study
- Documentation and rationale for any deviations from the clinical protocol
- Any other records required by BIOTRONIK

10.4. Sponsor Records

BIOTRONIK will maintain the following records:

- All correspondence pertaining to study with the investigator(s), IRB/EC and FDA (or any other competent authority)
- Investigational stent shipment and inventory reconciliation reports (US sites only)
- Investigator agreements, financial disclosures and current curriculum vitae
- Name and address of each investigator and each IRB/EC involved with the study
- Adverse events and complaints
- Adverse device effects (whether anticipated or unanticipated)
- Completed eCRFs
- Confirmation of completed subject informed consent forms
- Clinical Investigational Plan and report of prior studies
- Screening visit reports
- Monitoring reports
- Clinical progress reports
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.
- Records pertaining to DMC and CEC activities.
- Statement of the extent to which the good manufacturing practice regulation Part 21 CFR 820 will be followed in manufacturing the stent

11. STUDY COMMITTEES

11.1. Steering Committee

The steering committee is composed of the US and OUS study principal investigators, the steering committee chairman and experts representing the field of cardiology, interventional radiology and statistics. The steering committee participates in sponsor-requested meetings to review study progress and conduct, and to provide feedback to the sponsor on an ad hoc basis. Steering committee membership will be decided by the sponsor.

11.2. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will have responsibility for monitoring safety and efficacy aspects of the study. Its conduct will be governed by a written charter describing its rules of operation and responsibilities. It will be composed of at least four members with experience in clinical trial research: three physicians from the fields of cardiology and interventional cardiology and one biostatistician who are not directly involved in the conduct of the trial.

The DMC will review aggregate and individual subject data related to safety, data integrity, and overall conduct of the trial on a periodic basis, to be defined at their first meeting prior to enrollment of the first subject in the study. The DMC will be unblinded to BIOFLOW-V treatment group assignment.

The primary responsibility of the DMC will be to provide oversight on safety aspects of the study. The DMC may make three primary types of recommendations to the steering committee and study Sponsor as a result of its monitoring activities:

- Continuing the study without changes;
- Stopping the study for safety reasons; or,
- Continuing the study with changes to its protocol or conduct.

There is no planned formal interim efficacy analysis for the DMC to inspect. The study will not be stopped for accumulating evidence of benefit or futility.

Any material changes to the study protocol or conduct recommended by the DMC that affect the collection or evaluation of scientific evidence, or terms and conditions of the IDE approval, and which the sponsor desires to implement, will be subject to prior review and approval by the FDA.

11.3. Clinical Events Committee

The clinical events committee (CEC) for this study will consist of the standing members of the CEC who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the trial.

Explicit rules outlining the minimum amount of data required, and the algorithm followed to classify study endpoint–related clinical events will be established and provided in a separate CEC charter and adjudication manual. The CEC will then meet regularly to review and adjudicate study endpoint–related clinical events in which the required minimum data are available. The committee will also review and rule on all deaths that occur throughout the trial. All members of the CEC will be blinded to the randomized treatment group of the subject and to the primary results of the trial.

To ensure consistency and poolability of subjects across trials, the BIOFLOW-V CEC will perform re-adjudication to validate the potential study endpoint–related clinical events (TLR, MI and cardiac deaths) occurring in the BIOFLOW-II and BIOFLOW-IV studies using the same criteria established for the BIOFLOW-V.

12. ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki and all local GCP requirements.

12.1. Role of the Study Sponsor

BIOTRONIK as the study sponsor, has the overall responsibility for the conduct of the study, including ensuring that the study meets and is conducted within the regulatory requirements specified by each reviewing regulatory authority. In this study, the sponsor will have certain direct responsibilities and may delegate other responsibilities to Harvard Clinical Research Institute (HCRI) and/or other designees. The sponsor, HCRI and/or other designees will ensure adherence to the sponsor general duties, selection of investigators, monitoring, supplemental applications, maintaining records and submitting reports.

12.2. General Duties

BIOTRONIK's general duties include submitting the application to appropriate regulatory authorities and obtaining overall regulatory approval.

BIOTRONIK is responsible to obtain the approval from the competent authority, if applicable, prior to any site initiation. BIOTRONIK will report to the competent authorities any new information that may affect the safety of the subjects or the conduct of the clinical investigation, as applicable.

The sponsor or its designees are responsible for ensuring informed consent is obtained, proper clinical site monitoring is performed, providing quality data that satisfy regulations, and informing study investigators of UADE/USADE and deviations from the protocol, as appropriate.

As the designated data coordinating center, BIOTRONIK or its designee will prepare written reports and a final report as directed, and will coordinate data collection and transfer with the angiography core laboratory and other vendors.

12.3. Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code (ID number and subject name code) will be used that allows identification of all data reported for each subject.

Data relating to the study might be made available to third parties (e.g., in case of an audit performed by regulatory authorities) provided the data are treated as confidential and that the subject's privacy is guaranteed.

"Protected health information" will be treated and maintained in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 privacy rule, the directive 95/46/EC (European Directive for data protection law) and applicable local laws on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

The duration of storage time of personal data at the investigational sites will be in accordance with national regulations.

12.4. Informed Consent and Institutional Review Board or Ethics Committee

Prior to the subject's participation in the study, written informed consent is required from all subjects in accordance with their IRB/EC. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50), ISO 14155, ICH/GCP Guidelines, the Declaration of Helsinki and any other national or local requirements. The investigator is required to inform BIOTRONIK and the reviewing IRB/EC within five days if any subject has not appropriately consented to participate in the study. BIOTRONIK is then required to report any failure to obtain subject consent to the FDA within five working days of learning of such an event. In order to assist with the consent process, BIOTRONIK will provide a subject consent template form to study sites as a basis for adaptation to local requirements and submission to their IRB/ EC for approval.

IRB/EC approval is required from each institution prior to participation in this clinical study. Subject enrollment may not begin until the IRB/EC and BIOTRONIK have granted approval for the study site. IRB/EC approval is also required throughout the duration of this clinical study. If IRB/EC approval is withdrawn, BIOTRONIK must be notified within 5 working days.

12.5. Monitoring

Qualified monitors representing the sponsor will conduct on-site monitoring visits to ensure that all investigators conduct the study in compliance with the protocol and investigators' agreements. The site will receive notification prior to each monitoring visit during the course of the study. It is expected that the investigator and/or sub-investigator, research coordinator assigned to the study, and other appropriately trained study staff will be available on the day of the visit.

The progress of the study will be monitored by:

- Ensuring completed eCRFs match source documents, and resolution of any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data.
- Periodic on-site visits and, if necessary, remote monitoring of data.
- Frequent telephone or email communications between the investigator and assigned study site monitors.

12.5.1. Visits

Periodic monitoring visits will be made in accordance with the approved monitoring plan throughout the clinical study to ensure that the investigator's obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made

to the sponsor and the IRB/EC, device and device inventory are controlled, and the investigator is executing all agreed-upon activities.

The sponsor or its designees retain the right to remove either the investigator or the investigational site from the study for issues of non-compliance with the protocol or regulatory requirements. BIOTRONIK or its designee will perform the monitoring responsibilities according to its standard operating procedures.

On one or more occasions, the study site may be inspected or audited by the sponsor, its designee, or applicable regulatory authorities. The investigator will be informed in advance of this audit and is expected to allow access to the original medical records and provide all requested information.

A representative or designee of the sponsor may accompany the study site monitor to the site.

12.6. Protocol Compliance

The investigator is required to conduct the study in accordance with the signed investigator agreement and clinical protocol. The investigator shall notify BIOTRONIK and the reviewing IRB/EC in writing, no later than 5 working days after any significant deviation from the study plan, to protect the life or physical well-being of a subject in an emergency. Except in such emergency, prior approval by BIOTRONIK is required for significant deviations from the study plan.

BIOTRONIK categorizes instances of protocol non-compliance as either violations or deviations.

12.6.1. Protocol Violations

Protocol violations are defined as instances where the protocol requirements and/or regulatory guidelines were not followed and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the study and/or the rights, safety or welfare of subjects.

Protocol violations include, but are not limited to:

- Failure to obtain informed consent
- An unapproved (BIOTRONIK and IRB/EC) investigator implanting an investigational stent for study purposes
- Subject inclusion/exclusion violations and protocol requirement violations that affect the primary endpoints of the study design

In some instances, compliance issues with the consent process may occur. The investigator should seek guidance from the site's IRB/EC to ensure the subject received appropriate information to consider their participation in the study. The investigator is obligated to take any action the IRB/EC feels is necessary, including subject removal from the study.

Deviations in the consent process for subjects that the IRB/EC allows to continue in the study will be considered protocol violations in the analysis of study data.

All violations will be reported to FDA in accordance with applicable regulatory timelines. The study site should report the protocol violation to the reviewing IRB/EC and provide a copy of the notification to BIOTRONIK. The site should also report the protocol violation to BIOTRONIK on the applicable CRF.

12.6.2. Protocol Deviations

Protocol deviations are defined as instances where protocol requirements are not followed in such a manner whereby data is unusable or unavailable. Protocol deviations are less serious in nature and do not require IRB/EC notification, as long as they do not have an effect on the rights, safety or welfare of the study subject.

Protocol deviations include, but are not limited to:

- Procedure not performed within the allowed follow-up window
- Required data not obtained
- Follow-up procedure performed at an unapproved location

The study site should report the protocol deviation on the applicable CRF. Both protocol deviations and violations will be reported to FDA in progress reports.

12.7. Device Accountability and Storage

Tracking of the investigational product used in this study will be consistent with 21 CFR Part 821 and ISO 14155:2011, and in accordance with location-specific requirements.

If an Orsiro stent is opened, but not implanted, it must be returned to the sponsor in accordance with the sponsor's packaging and shipping instructions.

Subject to availability, the sponsor will provide the site with replacement consignment inventory of the Orsiro stent. Additionally, the PI or designee will ensure that an adequate supply of Orsiro stents is on hand to support uninterrupted enrollment of subjects in the study. Orders for additional devices must originate from the PI or designated study personnel. Orders for additional devices will be fulfilled by delivery directly to the PI or to study personnel designated by the PI.

Note: in the EU or other participating countries where the Orsiro stent is market-released, specific investigational handling restrictions may not apply.

12.7.1. Labeling

The Orsiro stent and its associated components will have a label that will be visible on the pertinent shipping cartons and storage containers. The required labels or manuals will bear the following information:

- Name, model and lot number of the stent
- Name and addresses of the manufacturer and distributor

- Labeling statement: “CAUTION - Investigational Device. Limited by United States Law to Investigational Use.” - applicable for US sites only
- Quantity of contents
- All relevant contraindications, hazards, adverse device effects, interfering substances or devices, warnings and precautions
- Expiration date

12.8. Supplemental Applications

If required, the sponsor will submit changes in the investigational plan to the appropriate regulatory authorities for approval and investigators to obtain IRB/EC approval to implement the changes.

12.9. Other Institutions and Physicians

The study is not transferable to other institutions attended by the investigator unless prior approval is obtained from BIOTRONIK, the governing competent authority (if applicable) and the appropriate IRB/EC. Additional sites may be included in this study, but may not exceed the limits set by the FDA. Only approved investigators are authorized to participate in the study; however, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject with an investigational stent (e.g. when a subject goes to the emergency room for medical treatment). In any such situations, the IRB/EC and the investigator must continue to provide oversight for that subject’s medical care and rights as a research subject. BIOTRONIK will ensure that the necessary support is available to any physician providing immediate care for a subject in order to answer questions about the investigational stent and provide guidance in collecting the necessary documentation required for the clinical study. Documentation obtained will then be forwarded to the approved investigator for review and signature before this data may be used to support the endpoints of the study.

12.10. Subject Insurance

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements.

BIOTRONIK has issued clinical trial liability insurance with appropriate coverage for the continuation of the entire study.

13. RISK ANALYSIS

13.1. Potential Risks

Risks associated with the use of the Orsiro stent include those seen with currently marketed drug eluting stents. Possible adverse events associated with PTCA and Orsiro stent placement include but are not limited to:

- Cardiac events: Myocardial infarction or ischemia, abrupt closure of coronary artery, restenosis of treated artery (greater than 50% obstruction), cardiogenic shock, angina, tamponade, perforation or dissection of coronary artery or aorta, cardiac perforation, emergency cardiac surgery, pericardial effusion, aneurysm formation
- Arrhythmic events: Ventricular tachycardia, ventricular fibrillation, atrial fibrillation, bradycardia
- Stent system events: Failure to deliver stent to intended site, stent dislodgement from the delivery system, stent misplacement, stent deformation, stent embolization, stent thrombosis or occlusion, stent fracture, stent migration, inadequate apposition or compression of stent/s, inflation difficulties, rupture or pinhole of the delivery system balloon, deflation difficulties, withdrawal difficulties, embolization of catheter material
- Respiratory events: Acute pulmonary edema, congestive heart failure, respiratory insufficiency or failure
- Vascular events: Access site hematoma, hypotension/ hypertension, pseudoaneurysm, arteriovenous fistula formation, retroperitoneal hematoma, vessel dissection or perforation, restenosis, thrombosis or occlusion, vasospasm, peripheral ischemia, dissection, distal embolization (air, tissue debris, thrombus)
- Neurologic events: Permanent (stroke) or reversible (TIA) neurologic event, femoral nerve injury, peripheral nerve injury
- Bleeding events: Access site bleeding or hemorrhage, hemorrhage requiring transfusion or other treatment
- Allergic reactions to contrast media, antiplatelets, anticoagulants, amorphous silicon carbide, L-605 cobalt chromium alloy (including the major elements cobalt, chromium, tungsten and nickel), PLLA polymer matrix, Sirolimus or Sirolimus derivatives.
- Infection and sepsis
- Death

Potential adverse events related to Sirolimus (following oral administration) 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
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia
- Renal events: renal insufficiency/renal failure

The potential risks related to the Xience stent and Everolimus may be found in the current product Instructions for Use..

13.2. Potential Benefits

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the Orsiro stent may reduce the potential for late and very late stent thrombosis, a complication associated with the occurrence of MI and death.

Moreover, in this clinical investigation all subjects will have a more intense medical follow-up compared with standard practice, which can be beneficial to the long-term clinical outcome of study participants.

Additionally, information gained from the conduct of this study may be of benefit to others with the same medical condition. Efficacy and safety data collected on the Orsiro stent will contribute to expand the knowledge of use of drug eluting stents in interventional cardiology.

13.3. Risk Mitigation

All subjects will receive chronic daily antiplatelet therapy for a minimum of 6 months and for the recommended 12 months post-procedure (per American Heart Association Scientific Advisory guidelines) to reduce risk of stent thrombosis and provide extended protection for potentially delayed endothelialization. Subjects will also receive a minimum of 75 mg aspirin daily, to be taken indefinitely.

To minimize potential risks associated with study procedures, all efforts will be made to select investigators who are experienced and skilled in using interventional devices. Additionally, at study initiation all investigators will be trained regarding the IFU and

protocol. All enrolling investigators will be instructed on appropriate subject selection in an effort to minimize the risk of recruiting ineligible subjects to the study.

Subjects will be monitored closely throughout the trial duration and will be evaluated at pre-specified time points to assess their clinical status.

An independent data monitoring committee will monitor safety of study participants throughout the trial (see Section 0).

For participating OUS subjects, the Orsiro stent is CE-marked and routinely being used in Europe. The safety and efficacy profile is known. Moreover, OUS subjects in participating countries with market approval, may be treated with this device regardless of their participation in the study or not, if the physician determines the device to be the best treatment option for that subject.

13.4. Sex and Gender in Coronary Heart Disease

Coronary heart disease (CHD) is recognized as the single leading cause of death among both American men and women.[52,53] Although CHD has historically been perceived as affecting more men, heart disease killed 26% of both the men and women who died in 2006 (http://www.cdc.gov/nchs). This impact of CHD on women highlights the need to analyze both disease trends and treatment patterns in women to further understand if sex-specific outcomes exist in clinical evaluations of investigational devices.

Prevalence

The total prevalence of CHD among U.S adult men is 8.3% and is 6.1% for US adult women. Among women, CHD prevalence is highest among non-Hispanic blacks at 7.6%. More specifically, the overall prevalence of MI among US adult men is 4.3% and is 2.2% for US adult women, with the highest prevalence among women in non-Hispanic blacks.[53]

Diagnosis and Treatment Patterns

The increasing impact of CHD in women is compounded by the diagnosis and treatment patterns of women with heart disease. According to the American Heart Association, 64% of women who die suddenly of CHD have no previous symptoms, which greatly impacts the evaluation and appropriate management of CHD, leading to potential sex-based clinical outcomes. Likewise, the American Heart Association reports that following a first MI in subjects over 45 years of age, a greater proportion of women are likely to die, develop recurrent MI, fatal CHD, heart failure or stroke. Because of the increased association of asymptomatic, fatal CHD, along with the increased risk for further, fatal CHD associated with a first MI, women have a lower likelihood of receiving treatment for their heart disease. A recent Mayo Clinic study found that women were 55% less likely than men to participate in cardiac rehabilitation following an MI.[54] Likewise, a study at Massachusetts General Hospital in 2005 found that women with both diabetes and CHD were significantly less likely to be prescribed aspirin than men or when treated for hypertension or hyperlipidemia, were significantly less likely to have blood pressure levels < 130/80 mmHg or LDL cholesterol levels < 100 mg/dl.[55]

Proportions and Clinical Outcome Differences for Women in Past Studies

A total of five PMA approvals for coronary, bare-metal stents were found in the past 10 years.[56,57,58,59,60] Each of the IDE clinical studies conducted to support the PMA application had a similar subject population as that proposed for this study. The approximate average proportion of women enrolled in the five clinical studies was 30%. A gender analysis was provided in four of the safety summaries, with each noting no difference in clinical outcomes for the investigational device based on gender.

Clinical Study Enrollment Plan for Women

Historically, women have been under-represented or excluded from enrollment in clinical studies, which has led to a lack of information regarding the risks and benefits of many medical treatments. For the purposes of this study, an enrollment goal of 30% women will be targeted to match the proportion of women in past coronary clinical studies. In order to enhance enrollment of women into this IDE study, the following will occur:

- Investigational sites in more densely populated, urban areas will be targeted to where recruitment of women can be more easily facilitated
- Women physicians will be targeted as enrolling investigators
- Screening logs will be periodically reviewed for screen failures to identify reasons for non-enrollment into the study"

14. USE OF INFORMATION AND PUBLICATION

BIOTRONIK intends to publish the results of this clinical investigation. BIOTRONIK reserves the right to include the report of this clinical investigation in any regulatory documentation or submission or in any informational materials prepared for the medical profession. The ownership of the data shall at all times be held by BIOTRONIK.

BIOTRONIK and the Steering Committee reserve the right for the first publication of the clinical investigation results. BIOTRONIK agrees that investigators shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the clinical investigation after the first publication. Any prior publication in any way or form is not permitted, without approval by BIOTRONIK.

Institution and Investigator reserve the right to publish the results of data obtained solely at their investigational site for the study. Before publishing, however, the institution and Principal Investigator shall submit copies of any manuscript proposed for publication to BIOTRONIK for review at least 30 days in advance of submission for publication or presentation to a publisher or other third party. The Study National Principal Investigators and/or Study Steering Committee reserve the right to review and approve all manuscripts prior to publication. The Sponsor reserves the right to delete any confidential information or other proprietary information (including trade secrets and patent protected materials) that is being utilized and inappropriately released, and to provide input from other investigators in the study regarding the content and conclusions of the publication or presentation. In addition, the Sponsor may extend

such review period for another 90 days, if deemed necessary, but will not unreasonably delay review and comment.

15. PREMATURE TERMINATION OF THE STUDY

No formal statistical rule for early termination of the trial due to insufficient effectiveness or safety issues has been defined. However the DMC may define rules by which an early termination may be recommended.

BIOTRONIK reserves the right to discontinue the clinical trial at any stage, with suitable written notice to the investigator. Possible reason(s) may include but are not limited to:

- An unanticipated adverse device effect occurs and it presents an unreasonable risk to subjects.
- The Data Monitoring Committee or Steering Committee makes a recommendation for the early termination of the trial.
- Further product development is cancelled.

Should discontinuation of the trial occur, the investigator shall return all clinical trial materials (including devices) to the sponsor, and provide a written statement to the IRB/EC explaining reasons for premature termination. In the event of a premature termination of the clinical investigation enrolled subjects will be followed up as per the institution's standard of care.

16. APPENDIX A: ABBREVIATIONS AND ACRONYMS

Abbreviation/Acronym	Complete Term
ACT	activated clotting time
ADE	adverse device effect
AE	adverse event
AMI	acute myocardial infarction
ARC	Academic Research Consortium
atm	atmosphere
BMS	bare metal stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
CBC	complete blood count
CCSC	Canadian Cardiovascular Society Classification
CEC	clinical events committee
CIP	clinical investigational plan
CK	creatine kinase
CKMB	creatine kinase myoglobin band
cm	centimeter
Co-Cr	cobalt-chromium
CT	computed tomography
CRO	clinical research organization
DAPT	dual antiplatelet therapy
DES	drug eluting stent
dl	deciliter
DMC	data monitoring committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EES	everolimus eluting stent
EU	European Union

Abbreviation/Acronym	Complete Term
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPIIb/IIIa	glycoprotein IIb/IIIa
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
h	hour
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
IDE	investigational device exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISA	incomplete strut apposition
ITT	intent-to-treat
IVUS	intravascular ultrasound
L	liter
LAD	left anterior descending
LBBB	left bundle branch block
LCX	left circumflex
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events
µg	microgram
mg	milligram
MI	myocardial infarction
mm	millimeter
mmol	millimole
MOP	manual of operating procedures
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
OCT	optical coherence tomography
OpenBUGS	OpenBUGS software for Bayesian analyses

Abbreviation/Acronym	Complete Term
OUS	Outside the United States
PCI	percutaneous coronary artery intervention
PI	principal investigator
PK	pharmacokinetic
PLLA	poly-L-lactic acid
PP	per-protocol
PTCA	percutaneous transluminal coronary angioplasty
QCA	quantitative coronary angiography
RCT	randomized controlled trial
RVD	reference vessel diameter
SAE	serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SES	sirolimus eluting stent
SESS	sirolimus eluting stent system
STEMI	ST elevation myocardial infarction
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
TLF	target lesion failure
TLR	target lesion revascularization
TVF	target vessel failure
TVR	target vessel revascularization
UADE	unanticipated adverse device effect
URL	upper range limit
USADE	unanticipated serious adverse device effect
WH	workhorse

17. APPENDIX B: DEFINITIONS

ACUTE CLOSURE

Occurrence of new (during the procedure) severely reduced flow (TIMI grade 0–1) within the target vessel that persists and requires rescue by stenting or other treatment, or results in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not mean “no reflow” (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not mean transient closure with reduced flow in which the index treatment application does reverse the closure.

Subacute Closure: Abrupt closure that occurs after procedure is completed (and subject left the catheterization laboratory) and before the 1-month follow-up evaluation.

Threatened Acute Closure: Grade-B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.

ACUTE GAIN

Immediate dimensional change in minimal luminal diameter (mm) that occurred after the final post-dilatation as compared with the minimal luminal diameter at baseline and measured by quantitative coronary angiography from the average of two orthogonal views.

ADVERSE DEVICE EFFECT (ADE)

An adverse device effect (ADE) is a device-related adverse event, i.e., any adverse event for which a causal relationship between the device and the event is at least a reasonable possibility (the relationship cannot be excluded). Note that this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device, as well as any event resulting from user error or from intentional misuse of the investigational medical device.

ADVERSE EVENT

An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory finding) in clinical trial subjects, whether or not related to the investigational medical device.

> **NOTE 1:** This definition includes events related to the investigational medical device or the comparator.
>
> **NOTE 2:** This definition includes events related to the procedures involved.
>
> **NOTE 3:** abnormal laboratory findings will be considered AEs, only if determined by the investigator to be clinically significant**.**

ANTICIPATED ADVERSE EVENT

Any undesirable experience (sign, symptom, illness, abnormal laboratory value or other medical event) occurring to a subject, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the clinical protocol, pre-defined in the clinical protocol and/or Instructions for Use, that is identified or worsens during a clinical study.

BLEEDING COMPLICATION

According to the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) classification of severe, moderate and mild bleeding events:

Severe or Life-Threatening: Intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

Mild: Bleeding that does not meet criteria for either moderate or severe bleeding.

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA

Severity

Class 1: New onset of severe or accelerated angina. Patients with new onset (< two months in duration) exertional angina pectoris that is severe or frequent (> three episodes/day) or patients with chronic stable angina who develop accelerated angina (i.e., angina distinctly more frequent, severe, longer in duration or precipated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding months.

Class 2: Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

Class 3: Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Clinical Circumstances in Which Unstable Angina Occurs

Class A: Secondary unstable angina. Patients in whom unstable angina develops secondary to a clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia. Such conditions reduce myocardial oxygen supply or increase myocardial oxygen demand and include anemia, fever, infection, hypotension, uncontrolled hypertension, tachyarrhythmia, unusual emotional stress, thyrotoxicosis and hypoxemia secondary to respiratory failure.

Class B: Primary unstable angina. Patients who develop unstable angina pectoris in the absence of an extra-cardiac condition that has intensified ischemia, as in Class A.

Class C: Post-infarction unstable angina. Patient who develop unstable angina within the first two weeks after a documented acute myocardial infarction.

CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION (CCSC) OF ANGINA[1,2]

Class I: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Class II: Slight limitation of ordinary activity. Angina upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold or wind, or under emotional stress, or only during the first hours after awakening. Angina if walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III: Marked limitations of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

Class IV: Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest.

CEREBROVASCULAR ACCIDENT or STROKE

Cerebrovascular accident is defined as the occurrence of cerebral infarction (ischemic stroke) or intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke). Stroke is defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis or rupturing aneurysm that either:

1. Persists > 24 hours or results in death in < 24 hours, or
2. Persists < 24 hours duration if the following treatments were used:
    a. Pharmacologic, i.e. thrombolytic drug administration, or
    b. Non-pharmacologic, i.e. neurointerventional procedure (e.g. intracranial angioplasty)
3. Persists < 24 hours but has neuro-radiological (MRI or CT) diagnostic changes suggestive of acute tissue injury.

CLINICALLY DRIVEN TARGET LESION REVASCULARIZATION (TLR)

Revascularization at the target lesion associated with positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis ≥50% by QCA, or revascularization of a target lesion with diameter stenosis ≥70% by QCA without either angina or a positive functional study.

[1] Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol* 2002;18:371–379.

[2] Campeau L. Letter: Grading of angina pectoris. *Circulation* 1976;54: 522–523.

CLINICALLY-DRIVEN TARGET VESSEL REVASCULARIZATION (TVR)

Revascularization in the target vessel associated with positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis ≥50% by QCA, or revascularization of a target vessel with diameter stenosis ≥70% by QCA without either angina or a positive functional study.

***DE NOVO* LESION**

A native coronary artery lesion not previously treated.

DEATHS

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

Cardiac Death: Death due to immediate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure-related deaths, including those related to concomitant treatment.

Vascular Death: Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other vascular cause.

Non-Cardiovascular Death: Death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

DEVICE SUCCESS

Attainment of < 30% residual stenosis of the target lesion using the assigned study stent only.

Note: Post-dilatation is allowed to achieve device success.

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute) CLASSIFICATION[3]

Grade A: Small radiolucent area within vessel lumen disappearing with passage of contrast material.

Grade B: Appearance of contrast medium parallel to vessel lumen disappearing within a few cardiac cycles.

Grade C: Dissection protruding outside vessel lumen persisting after passage of contrast material.

Grade D: Spiral-shaped filling defect with or without delayed run-off of contrast material in antegrade flow.

[3] Detre K, Holubkov R, Kelsey S *et al*. One-year follow-up results of the 1985–1986 National Heart, Lung, and Blood Institute's percutaneous transluminal coronary angioplasty registry. *Circulation* 1989;80:421–428.

Grade E: Persistent luminal filling defect with delayed run-off of contrast material in distal lumen.

Grade F: Filling defect accompanied by total coronary occlusion.

DISTAL EMBOLIZATION

New abrupt cut-off or filling defect distal to the treated lesion.

EMERGENT BYPASS SURGERY

Coronary bypass surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

IN-SEGMENT MEASUREMENT

Measurements either within stented segment or within 5 mm proximal and distal to stent edges.

IN-STENT MEASUREMENT

Measurements within boundaries of the stent.

INTRACORONARY THROMBUS

Presence of a filling defect within lumen, surrounded by contrast material seen in multiple projections in absence of calcium within the filling defect, or persistence of contrast material within lumen, or a visible embolization of intraluminal material downstream.

LATE LOSS INDEX

Ratio of late loss to acute gain.

LATE LUMEN/LUMINAL LOSS

Difference between post-procedure minimal lumen diameter and follow-up angiography minimal lumen diameter.

LESION CLASS (American College of Cardiology/American Heart Association Class)[4]

Type A: Minimally complex, discrete (length < 10 mm), concentric, readily accessible, non-angulated segment (< 45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, absence of thrombus.

Type B: Moderately complex, tubular (length 10–20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (> 45°, < 90°), irregular contour, moderate or heavy calcification, total occlusions < 3 months old, ostial in location, bifurcation lesions requiring double guide wires, some thrombus present.

Type B1: one adverse characteristic.

Type B2: two or more adverse characteristics.

Type C: Severely complex, diffuse (length > 20 mm), excessive tortuosity of proximal segment, extremely angulated segments > 90°, total occlusions > 3 months old and/or bridging collaterals, inability to protect major side branches, degenerated vein grafts with friable lesions.

LESION SUCCESS

Attainment of < 30% residual stenosis of target lesion using any percutaneous method.

MAJOR ADVERSE CARDIAC EVENTS (MACE)

All-cause death, myocardial infarction (Q-wave or non–Q-wave), any clinically-driven target lesion revascularization.

MINIMAL LUMINAL DIAMETER

Average of two orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent or in segment. Visually estimated during angiography by the investigator and measured during QCA by the angiographic core laboratory.

[4] Smith SC Jr, Dove JT, Jacobs AK *et al*. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines) –Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 2001;37:2215–2239.

MYOCARDIAL INFARCTION – PROTOCOL DEFINITION[5]

I. PCI (PERCUTANEOUS CORONARY INTERVENTION)

Ia. Baseline Biomarkers of Myocardial Damage

Periprocedural < 48 hours post PCI
A. Baseline CKMB and Troponin < 1*URL Appropriate cardiac enzyme data: **a1.** Confirmed by : - CKMB > 3*URL or - in the absence of CKMB, Troponin > 3*URL or - in the absence of CKMB and Troponin: CEC decision upon clinical scenario
B. Baseline CKMB or Troponin > 1*URL Appropriate cardiac enzyme data: **b1.** Confirmed by : - A rise in CKMB ≥ 50% above the previous level and > 3* URL or - In absence of CKMB, a rise in Troponin ≥ 50% above the previous level and > 3*URL. - in the absence of CKMB and Troponin: CEC decision upon clinical scenario **AND** **b2.** Evidence that cardiac biomarker values were decreasing (e.g., two samples at least 4 hours apart) prior to the suspected MI.
C. New pathologic q waves in 2 contiguous ECG leads

URL = upper range limit, defined as 99th percentile of normal reference range

Ib. If Baseline Biomarkers of Myocardial Damage: CK and/or CKMB > 1*URL or acute MI in progress

Myocardial infarction, re-infarction (extension) < 48 hours post PCI
A. If CK (or CKMB) from index MI has not yet reached its maximum level: - Recurrent thoracic chest pain or ischemia equivalent > 20 minutes (or new ECG changes consistent with MI)

[5] Adapted from Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: Balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention* 2010;5:871–874.

AND

- Appropriate cardiac enzyme data:
  - A rise in CK within 24 hours of the index event > 2*URL (confirmed by either CKMB or Troponin > 1*URL) and ≥ 50% above the previous level or
  - In absence of CK: a (post PCI) rise in CKMB within 24 hours of the index event > 3*URL and ≥ 50% above the previous level

  or

  - In absence of CK and CKMB: a (post PCI) rise of Troponin within 24 hours of the index event > 3*URL and ≥ 50% above the previous level.

B. If elevated CK (or CKMB) following the index MI has peaked AND CK level has returned < URL then any new rise in:

- CK > 2*URL(confirmed by either CKMB > URL or Troponin > URL) or
- in the absence of CK: CKMB > 3*URL or
- in the absence of CK and CKMB, Troponin > 3*URL

C. If CK (or CKMB) following the index MI has peaked AND CK level has NOT returned to < URL:

- A rise in CK ≥ 50% above the previous level and > 2 URL confirmed by either CKMB > URL or Troponin > URL or
- In absence of CK, when CKMB has NOT returned < URL, a rise in CKMB ≥ 50% above the previous level and > 3* URL or
- In absence of CK, when CKMB and Troponin has not returned < URL a rise in Troponin ≥ 50% above the previous level and > 3*URL

Spontaneous MI > 48 hours(PCI)
A. Recurrent thoracic chest pain or ischemic equivalent **AND** New pathologic q waves in ≥ 2 contiguous ECG leads **AND** - any CKMB > 1*URL or - in the absence of CKMB: Troponin > 1*URL or - in the absence of CKMB and Troponin: CK > 1*URL or - in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario
B. Appropriate cardiac enzyme data (respecting top-down hierarchy): **b1.** CK ≥ 2* URL Confirmed by: - CKMB > 1*URL or - in the absence of CKMB: Troponin > 1*URL or - in the absence of CKMB and Troponin: CEC decision upon clinical scenario **OR** **b2.** In the absence of CK: CKMB > 3*URL
OR **b3.** In the absence of CK and CKMB: Troponin > 3*URL
OR **b4.** In the absence of CK, CKMB and Troponin, clinical decision based upon clinical scenario.

II. CABG (CORONARY ARTERY BYPASS GRAFTING)

IIa. Baseline Biomarkers of Myocardial Damage (CK and CKMB and Trop < 1*URL) and not acute MI in progress.

Periprocedural < 72 hours post CABG
A. New pathologic q waves in ≥ 2 contiguous ECG leads or recurrent signs or symptoms consistent with myocardial ischemia AND - CKMB > 5x URL or - in the absence of CKMB: Troponin > 5*URL or - in the absence of CKMB and Troponin: CK > 5 URL or - in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario
B. Appropriate cardiac enzyme data - CKMB ≥ 10* URL or - In the absence of CKMB: Trop > 10*URL. or - - In the absence of CKMB and Troponin: CK > 10*URL

IIb. If Baseline Biomarkers of Myocardial Damage: CK and/or CKMB > 1*URL or acute MI in progress

Myocardial infarction, re-infarction (extension) < 72 hours post CABG
A. If Peak CK (or CKMB) from index MI has not yet reached its maximum level: - Clinical signs or symptoms consistent with recurrent myocardial ischemia AND - Appropriate cardiac enzyme data: - A rise in CKMB within 24 hours of the index event > 10*URL and ≥ 50% above the previous level. - In absence of CKMB: a rise in Troponin within 24 hours of the index event > 10*URL and ≥ 50% above the previous level. - In absence of CKMB and Troponin: a rise in CK within 24 hours of the index event > 10*URL and ≥ 50% above the previous level. B. If elevated CK (or CKMB) following the index MI has peaked AND CKMB level has returned < URL, any new rise in: - CKMB > 10*URL or - in the absence of CKMB: Troponin > 10*URL or - in the absence of CKMB and Troponin: CK > 10*URL **C.** If elevated CK (or CKMB) following the index MI has peaked AND CKMB level has NOT

returned < URL:

- A rise in CKMB ≥ 50% above the previous level and > 10 URL or
- In absence of CKMB: a rise in Troponin ≥ 50% above the previous level and > 10* URL or
- In absence of CKMB and Troponin: a rise in CK ≥ 50% above the previous level and > 10*URL

MYOCARDIAL INFARCTION (MI) – ACADEMIC RESEARCH CONSORTIUM (ARC) DEFINITION[6]

Classification	Biomarker Criteria*	Additional Criteria
Peri-procedural PCI (within 48 h after PCI)† or	Troponin > 3 times URL or CKMB > 3 times URL	Baseline value < URL
Peri-Procedural CABG (within 72 h after CABG)	Troponin > 5 times URL or CKMB > 5 times URL	Baseline value < URL and any of the following: new pathologic‡ Q waves or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium
Spontaneous (> 48 h following PCI, > 72 h following CABG)	Troponin > URL or CKMB > URL	Baseline value < URL and any of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new LBBB), development of pathological Q waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Silent	No biomarker data available	New pathologic‡ Q waves or LBBB
Sudden Death	Death before biomarkers obtained or before expected to be elevated	Symptoms suggestive of ischemia and any of the following: new ST elevation or LBBB, documented thrombus by angiography or autopsy
Reinfarction, spontaneous and peri-procedural (base definition; infarction extension)	Stable or decreasing values on 2 samples > 6 h apart and 20% increase 3–6 h after second sample	If biomarkers not stable (increasing or peak not reached), then insufficient data to diagnose recurrent myocardial infarction

Adapted from Global Task Force Universal Definition of Myocardial Infarction, Thygesen *et al*.

PCI: percutaneous coronary intervention; h: hour; URL: upper range limit (99th percentile of normal reference range); CKMB: creatinine kinase myocardial band isoenzyme MB; CABG: coronary artery bypass graft; LBBB: left bundle branch block; ECG: electrocardiogram.

*Baseline biomarker value required before study procedure and presumes a typical rise and fall.
†Assessment of CKMB is preferred over assessment of troponin for diagnosis of peri-procedural MI, if possible.
‡Pathologic Q waves may be defined according to the Global Task Force, Minnesota code or Novacode.

NO REFLOW

Sustained or transient reduction in antegrade flow not associated with an obstructive lesion at treatment site.

[6] Cutlip DE, Windecker S, Mehran R *et al*. for the Academic Research Consortium. Clinical endpoints in coronary stent trials: A case for standardized definition. *Circulation* 2007;115:2344–2351.

PERCENT DIAMETER STENOSIS

The value calculated as 100 x (RVD – MLD)/RVD using the mean values from two orthogonal views (when possible) by quantitative coronary angiography. (RVD: reference vessel diameter; MLD: minimal lumen diameter.)

PERFORATION

Perforations will be classified as follows:

Angiographic Perforation: Perforation detected by clinical site or core laboratory at any point during procedure.

Clinical Perforation: Perforation requiring additional treatment (including efforts to seal perforation or pericardial drainage), or resulting in significant pericardial effusion, acute closure, myocardial infarction or death.

Pericardial Hemorrhage/Tamponade: Perforation resulting in cardiac tamponade.

PERCUTANEOUS CORONARY INTERVENTION (PCI)

All interventional cardiology methods for treatment of coronary artery disease.

PERSISTING INCOMPLETE APPOSITION

Incomplete apposition at follow-up that was present post-procedure. See also *Incomplete Apposition*.

PROCEDURE SUCCESS

Attainment of < 30% residual stenosis of the target lesion using the assigned study stent only without occurrence of in-hospital major adverse cardiac events (MACE).

RESTENOTIC LESION

Lesion in a vessel segment that has undergone prior percutaneous treatment with or without a stent placement.

REFERENCE VESSEL DIAMETER (RVD)

Average of normal segments within 10 mm proximal and distal to target lesion from two orthogonal views using quantitative coronary angiography.

SERIOUS ADVERSE DEVICE EFFECT

Adverse device effect that results in any of the consequences characteristic of a serious adverse event.

SERIOUS ADVERSE EVENT

Adverse event that leads to:

- Death.
- Serious deterioration in the health of the subject that either results in life-threatening illness or injury; permanent impairment of a body structure or a body function; hospitalization or prolonged hospitalization; or medical or surgical intervention to prevent life-threatening illness, injury or permanent impairment to a body structure or a body function.
- Fetal distress, fetal death, congenital abnormality or birth defect.

STENT THROMBOSIS – ACADEMIC RESEARCH CONSORTIUM (ARC) DEFINITION

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the catheterization lab.

Timing

Acute stent thrombosis*	0–24 hours post–stent implantation
Subacute stent thrombosis*	> 24 hours–30 days post–stent implantation
Late stent thrombosis†	30 days–1 year post–stent implantation
Very late stent thrombosis†	> 1 year post–stent implantation

*Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0–30 days) is a definition currently used in the community.
†Including primary as well as secondary late stent thrombosis. Secondary late stent thrombosis is a stent thrombosis after a target segment revascularization.

Categories (Definite, Probable and Possible)

Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

*Angiographic Confirmation of Stent Thrombosis**

Presence of an intracoronary that originates in the stent or in the segment 5 mm proximal or distal to the stent, and presence of at least one of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest.
- New ischemic ECG changes that suggest acute ischemia.
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI).

Non-occlusive: Intracoronary thrombus is defined as a spheric, ovoid or irregular non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive Thrombus: TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from side branch).

Pathological Confirmation of Stent Thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

*The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

Probable Stent Thrombosis

Probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within first 30 days.†
- Regardless of time after index procedure, any MI related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
  †For studies with ST-elevation MI population, exclusion of unexplained death within 30 days may be considered evidence of probable stent thrombosis.

Possible Stent Thrombosis

Possible stent thrombosis is considered to have occurred with any unexplained death from
30 days after intracoronary stenting until end of trial follow-up.

STROKE

See *Cerebrovascular Accident or Stroke*.

STUDY DEVIATION

Incident in which the investigator or site personnel did not conduct the study according to the clinical protocol or investigator agreement.

Major Deviation: Any deviation from subject inclusion and exclusion criteria or subject informed consent procedures.

Minor Deviation: Deviation from a clinical protocol requirement such as incomplete/inadequate subject testing procedures, non-compliance with study thienopyridine medication regimens, follow-ups performed outside specified time windows, etc.

TARGET LESION FAILURE (TLF)

Cardiac death, target vessel myocardial infarction (Q-wave or non–Q-wave), or clinically-driven target lesion revascularization.

TARGET LESION REVASCULARIZATION (TLR) – ACADEMIC RESEARCH CONSORTIUM (ARC) DEFINITION

Repeat percutaneous intervention of target lesion or bypass surgery of target vessel performed for restenosis or other complication of target lesion.

Target lesion is defined as the treated segment starting 5 mm proximal to the stent and ending 5 mm distal to the stent.

See also *Clinically Driven Target Lesion Revascularization*.

TARGET VESSEL FAILURE (TVF)

Composite endpoint comprised of cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization.

Target vessel failure will be reported when any of the following events occur:

- Recurrent MI occurs in territory not clearly attributed to a vessel other than target vessel.
- Cardiac death not clearly due to a non-target vessel endpoint.
- Target vessel revascularization is determined.

TARGET VESSEL MYOCARDIAL INFARCTION (MI)

Myocardial infarction that occurs in a territory that cannot be clearly attributed to a vessel other than the target vessel.

TARGET VESSEL REVASCULARIZATION (TVR) – ACADEMIC RESEARCH CONSORTIUM (ARC) DEFINITION

Repeat percutaneous intervention or surgical bypass of any segment of the target vessel.

Target vessel is defined as the entire major coronary vessel proximal and distal to target lesion, including upstream and downstream branches and the target lesion itself.

See also *Clinically Driven Target Vessel Revascularization*.

THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI) CLASSIFICATION[7]

TIMI 0: No perfusion.

TIMI 1: Penetration with minimal perfusion. Contrast fails to opacify entire bed distal to stenosis for duration of cine run.

[7] TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985;312: 932–936.

TIMI 2: Partial perfusion. Contrast opacifies entire coronary bed distal to stenosis. However, rate of entry and/or clearance is slower in coronary bed distal to obstruction than in comparable areas not perfused by dilated vessel.

TIMI 3: Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

TOTAL OCCLUSION

Lesion with no flow (TIMI 0). Total occlusions are usually classified as persisting less than or more than 3 months (chronic total occlusion).

TRANSIENT ISCHEMIC ATTACK (TIA)

Focal neurological abnormality of sudden onset and brief duration (lasting less than 24 hours) that reflects dysfunction in the distribution of the affected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax, defined as a transient episode of monocular blindness, or partial blindness, lasting 10 minutes or less) and transient hemispheric attacks.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE) or UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of a subject.

In the OUS countries, the term unanticipated serious adverse device effect (USADE) is used for serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

UNSTABLE ANGINA

Per the American College of Cardiology/American Heart Association 2002 Guideline Update for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction, there are 3 principal presentations of unstable angina[8]:

1. *Rest Angina*: Angina occurring at rest, and prolonged, usually > 20 minutes.
2. *New-Onset Angina*: New-onset angina of at least CCS class III severity.
3. *Increasing Angina*: Previously diagnosed angina that has become distinctly more frequent, longer in duration or lower in threshold (i.e., increased by greater than or equal to one CCS class to at least CCS class III severity).

[8] Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – Summary article: A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2002;40:1366–1374.

VASCULAR COMPLICATIONS

Vascular complications may include the following:

1. Pseudoaneurysm.
2. Arteriovenous fistula.
3. Peripheral ischemia/nerve injury.
4. Vascular event requiring transfusion or surgical repair.

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