Clinical Protocol for the BIOFLOW-VII Study

BIOTRONIK - A Prospective Multicenter Study to Confirm 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 - **VII**

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BIOFLOW-VII

Protocol Signature Page

The signature below constitutes the receipt and review of the BIOFLOW-VII protocol 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 U.S. federal regulations, ICH and GCP guidelines.

Principal Investigator:

_____
Name (please print)

_____ _____
Signature Date

Primary Contacts

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Study Principal Investigator	[redacted]

Protocol Summary

Title	**BIO**TRONIK - A Prospective Multicenter Study to Confirm 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 – **VII**
Purpose	The purpose of this post-approval study is to confirm that the clinical performance of the Orsiro stent in a real-world setting is similar to the clinical performance observed for Orsiro in the BIOFLOW-V Investigational Device Exemption pivotal trial, as a condition of the US Food and Drug Administration (FDA) approval (P170030).
Design	Prospective, multi-center, single-arm study
Study Device	Orsiro® Sirolimus Eluting Coronary Stent System
Subject Population	Subjects with coronary artery disease (CAD), including those with diabetes mellitus, with symptomatic heart disease, stable angina, unstable angina, non-ST elevation myocardial infarction or documented silent ischemia due to atherosclerotic lesions in the native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm and a lesion length of ≤ 36 mm.
Enrollment	556 subjects to achieve 500 evaluable subjects
Clinical Sites	Up to 50 clinical sites in the United States
Visit Schedule and Follow-up Duration	Subjects will be followed 5-years post-index procedure. Post-procedure follow-up intervals: 1 month and 1, 2, 3, 4 and 5 years post-index procedure.
Primary Endpoint	Target lesion failure (TLF) at 1 year post-index procedure. TLF is defined as a composite of cardiac death, target vessel myocardial infarction (MI), or clinically-driven target lesion revascularization (TLR).

Secondary Endpoints	The following secondary endpoints will be evaluated prior to discharge, at 1 month, 1 year, and annually thereafter through 5 years follow-up. 1. All-cause death. 2. MI. 3. Cardiac death or MI. 4. Major Adverse Cardiovascular Events (MACE) and individual MACE components (MACE: composite of all-cause death, Q-wave or non–Q-wave MI, and any clinically-driven TLR). 5. TLF (evaluated at 2, 3, 4, and 5 years) and individual TLF components (TLF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and clinically-driven TLR). 6. 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 target vessel revascularization (TVR)]. 7. Stent thrombosis (definite, definite/probable, probable) according to Academic Research Consortium (ARC)-2[1] criteria for acute, subacute, late, very late and cumulative stent thrombosis. 8. Device success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using the Orsiro study stent only. Note: Post-dilatation is allowed to achieve device success. 9. Lesion success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using any percutaneous method. 10. Procedure success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using the Orsiro study stent only without occurrence of in-hospital MACE.

Clinical Inclusion Criteria	Subjects must meet all of the following criteria to be eligible for the trial: 1. Subject is ≥ 18 years of age. 2. Subject was an acceptable candidate for treatment with a drug eluting stent at the qualifying index procedure, in accordance with the applicable guidelines on percutaneous coronary interventions and manufacturer's Instructions for Use. 3. Subject received at least one Orsiro stent during an index procedure occurring within 24 hours prior to informed consent, as assessed by the end time of procedure. If more than one stent was implanted during the index procedure, all stents were Orsiro stents. 4. Subject is eligible for dual antiplatelet therapy (DAPT) treatment with aspirin plus either clopidogrel, prasugrel, ticagrelor or ticlopidine. 5. Subject is willing to comply with study follow-up requirements. 6. Subject has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site. Legally authorized representatives are not allowed to consent on a subject's behalf.
Clinical Exclusion Criteria	Subjects will be excluded from the trial if any of the following criteria are met: 1. Subject had clinical symptoms and/or electrocardiogram (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 pregnant and/or breastfeeding or intends to become pregnant during the duration of the study. 3. 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), silicon carbide, Poly-L-Lactic Acid (PLLA), sirolimus. 4. Revascularization of any target vessel within 9 months prior to the index procedure or previous percutaneous coronary intervention (PCI) of any non-target vessel within 30 days

Clinical Exclusion Criteria (continued)	prior to the index procedure or any PCI planned within the next 1 year. 5. Presence of an untreated clinically significant stenosis post-procedure whether treatment is planned or not. 6. Planned surgery within 6 months of index procedure unless DAPT can be maintained throughout the peri-surgical period. 7. History of a stroke or transient ischemic attack (TIA) within 6 months prior to the index procedure. 8. Subject has documented left ventricular ejection fraction (LVEF) < 30% prior to or during the index procedure. 9. Subject is dialysis-dependent. 10. Subject has impaired renal function (blood creatinine > 2.5 mg/dL or 221 µmol/L prior to the index procedure). 11. 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). 12. Any significant concurrent medical diagnosis that would potentially impact DAPT effectiveness or increase thrombotic risk. 13. Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent). 14. Subject has life expectancy of < 1 year. 15. Subject is participating in an 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 follow-up requirements of this study or does not involve a drug that may confound the interpretation of any relevant clinical events of interest (e.g. investigational DAPT therapy). 16. In the investigator's opinion, subject will not be able to comply with the follow-up requirements.

Angiographic Inclusion Criteria	Each target lesion/vessel must have met all of the following angiographic criteria from the index procedure 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 percutaneous transluminal coronary angioplasty (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. 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 have been treated with a maximum of two overlapping stents.

Angiographic Exclusion Criteria	Subjects will be excluded from the trial if any of the target lesions/vessels met any of the following angiographic criteria during the index procedure: 1. Target lesion was located within or treated through a saphenous vein graft or arterial graft. 2. Target lesion was a restenotic lesion that was previously treated with a bare metal or drug-eluting stent (in-stent restenosis). 3. Target lesion had 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 was 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 had angiographic evidence of thrombus. 6. Target lesion was totally occluded (100% stenosis). 7. Target vessel was treated with brachytherapy any time prior to the index procedure.
Study Principal Investigator	[redacted]
Clinical Events Committee	To Be Determined
Core Lab	To Be Determined
Electronic Data Capture Vendor	MedNet Solutions, Inc. [redacted]

Sponsor	BIOTRONIK, Inc. Clinical Studies Department 6024 SW Jean Road Lake Oswego, Oregon 97035 Referred to as "BIOTRONIK" for the remainder of this protocol. For technical assistance 24 hours a day, call: 800-547-0394

1 Introduction

1.1 Study Overview

The BIOFLOW-VII study is a prospective, multi-center, single-arm study to confirm that the clinical performance of the Orsiro® Sirolimus Eluting Coronary Stent (hereinafter referred to as Orsiro) in a real-world setting is similar to the clinical performance observed for Orsiro in the BIOFLOW-V Investigational Device Exemption (IDE) pivotal trial. The study will enroll 556 subjects at up to 50 sites in the United States (US). Clinical outcomes will be collected and reported through 5 years post-index procedure.

1.2 Background

The Orsiro stent has been studied extensively (refer to **Section 1.5**) and first received CE Mark on February 23, 2011. The safety and the effectiveness of the Orsiro stent was demonstrated by the pivotal BIOFLOW-V IDE study and Premarket Approval (PMA) application approval (P170030) was received on February 22, 2019. As part of the PMA approval, FDA has requested post-approval data collection for the performance of the Orsiro stent in a real-world setting.

1.3 Rationale for the Study Design

A prospective, single-arm study design has been proposed for this post-approval study as the study population and key endpoints are well-defined and patient-level data is available from multiple prior studies. The design includes comparison against a performance goal based on the BIOFLOW-V trial Orsiro target lesion failure (TLF) rate, taking into consideration TLF rates from other US market-released drug-eluting stents (DES).

1.4 Orsiro Stent System Description

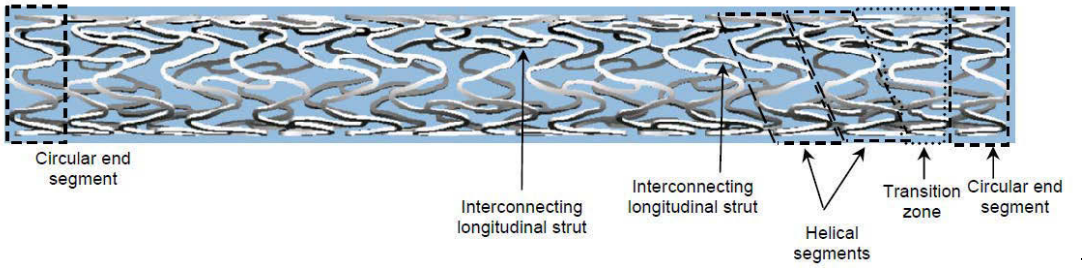
The Orsiro stent system is a drug-eluting balloon-expandable stent that is pre-mounted on a fast-exchange percutaneous transluminal coronary angioplasty (PTCA) catheter delivery system with a working length of 140 cm. There are two stent configurations - small (2.25 – 3.0 mm stent inner diameter) and medium (3.5 – 4.0 mm stent inner diameter).

The stent is made from a cobalt chromium alloy (L-605) and the stent geometry consists of circular end segments, a transition zone, and repeating helical segments which are connected by three interconnecting longitudinal struts.

The stent is intended as a permanent implant and is completely covered with a thin layer of amorphous silicon carbide (referred to as proBIO™ coating). The stent surface is circumferentially coated with BIOlute™, a bioabsorbable drug matrix consisting of the drug substance sirolimus and polymer poly-l-lactide (PLLA). The nominal drug content of the stent is 1.4 µg of sirolimus per mm². The stent is positioned between two radiopaque markers for fluoroscopic visualization.

A full description of the Orsiro stent system and the Indications and Contraindications for use are located in the Instructions for Use (IFU) / Technical Manual available online (https://manuals.biotronik.com). **Figure 1** shows an image of the Orsiro stent.

Figure 1. Image of Orsiro Stent



1.5 Orsiro Clinical Data Summary

The development of the Orsiro stent system has been supported by an extensive clinical trial program. 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; the BIOFLOW-V IDE international randomized study against the Xience™ stent; the BIOSCIENCE international, randomized all-comers study against the Xience Prime stent; and the BIO-RESORT randomized study against the Synergy™ and Resolute Integrity™ stents.*

BIOTRONIK and Investigator sponsored trials represent more than 48,500 subjects who have enrolled in an Orsiro clinical trial. Overall, more than 70,000 subjects are planned to enroll in greater than 70 Orsiro clinical trials that have started or are planned. These trials are designed to collect both short and long-term safety and performance measures. The vast majority of these study designs include a randomized comparison of Orsiro against comparator DES evaluating long-term safety and performance, often with follow-up durations up to five years.

Table 1 summarizes the key design elements of the major Orsiro clinical studies. A more detailed description of each study and its results is provided in **Section 15**.

*Xience, Xience Prime, and Xience Xpedition are trademarks of the Abbott Group of Companies. Synergy is a trademark of Boston Scientific. Resolute Integrity is a trademark of Medtronic.

Table 1: Prior Orsiro Clinical Studies

	BIOFLOW -I	BIOFLOW -II	BIOFLOW -III	BIOFLOW -IV	BIOFLOW -V	BIO SCIENCE	BIO-RESORT
Location	Romania	Europe	Europe, Chile	Europe, Japan, Israel, Australia	United States, Europe, Asia Pacific	Switzerland	The Netherlands
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 • Random-ized (2:1 vs Xience Prime/ Xpedition)	• Prospective • Multi-center • Randomized (2:1 vs Xience)	• Prospective • Multi-center • Randomized (1:1: vs Xience Prime/ Xpedition)	• Prospective • Multi-center • Randomized (1:1:1 vs Synergy and Resolute Integrity)
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	Target lesion failure at 12 months	Target vessel failure a 12 months
Number of Subjects	30	452 (Orsiro: 298, Xience Prime: 154)	1,356	575 (Orsiro 385, Xience Prime/ Xpedition: 190)	1,334 (Orsiro: 884, Xience: 450)	2,119 (Orsiro: 1063, Xience Prime/ Xpedition: 1056)	3,514 (Orsiro: 1169, Synergy: 1172, Resolute Integrity: 1173)
Lesion Criteria	• Single, de novo lesion • Native artery • ≥50 to <100%	• 1-2 de novo lesions • Native arteries • ≥50 to <100% • LL ≤ 26 mm • RVD 2.25 - 4.0 mm	• All-comers	• 1 or 2 de novo lesions • Native arteries • ≥50 to <100% • LL ≤ 26 mm • RVD 2.50 -3.75 mm	• ≤ 3 de novo/ PTCA restenotic lesions/ 2 TV • Native arteries • ≥50 to <100% • LL ≤ 36 mm • RVD 2.25 - 4.0 mm	• All-comers • >50% • RVD corresponding with stent diameter of 2.25 – 4.0 mm	• All-comers (de novo/ restenotic)
Follow-up	1, 4, 9mos, 1, 2, 3 yrs	1, 6, 9mos, 1, 2, 3, 4, 5yrs	6mos, 1, 3, 5yrs	1, 6mos, 1, 2, 3, 4, 5yrs	1, 6mos, 1, 2, 3, 4, 5yrs	1mo, 1, 2, 5yrs	1mo, 1, 2, 3, 4, 5yrs
Clinical Trials. gov Number	NCT 01214148	NCT 01356888	NCT 01553526	NCT 01939249	NCT 02389946	NCT 01443104	NCT 01674803

The BIOFLOW-VII study is a prospective, multi-center, single-arm study to confirm that the clinical performance of the Orsirostent in a real-world setting is similar to the clinical performance observed for Orsiro in the BIOFLOW-V IDE pivotal trial.

BIOFLOW-V is a prospective, multicenter, randomized, controlled trial designed to assess the safety and efficacy of the BIOTRONIK Orsiro Sirolimus Eluting Coronary Stent System compared with the Xience Everolimus Eluting Coronary Stent System

(Abbott Vascular, Santa Clara, CA) in subjects with up to three native de novo or restenotic (after standard PTCA only) coronary artery lesions[2] (ClinicalTrials.gov identifier NCT02389946). A total of 1,334 subjects were enrolled into the BIOFLOW-V trial. BIOTRONIK completed the BIOFLOW-V study as the pivotal US IDE trial for the Orsiro stent system.

The primary endpoint was TLF at 1 year, defined as the composite of cardiac death, target vessel myocardial infarction (MI) or clinically-driven target lesion revascularization (TLR). For the analysis of the primary endpoint, the trial combined data on the randomized subjects with data from two prior studies (BIOFLOW-II and BIOFLOW-IV) by employing a Bayesian approach.

The 1-year Orsiro TLF rate in the BIOFLOW-V study was 6.2%[3] utilizing the protocol-definition for peri-procedural MI and 2.6% utilizing the Society for Cardiovascular Angiography and Interventions (SCAI) definition[4] for peri-procedural MI.

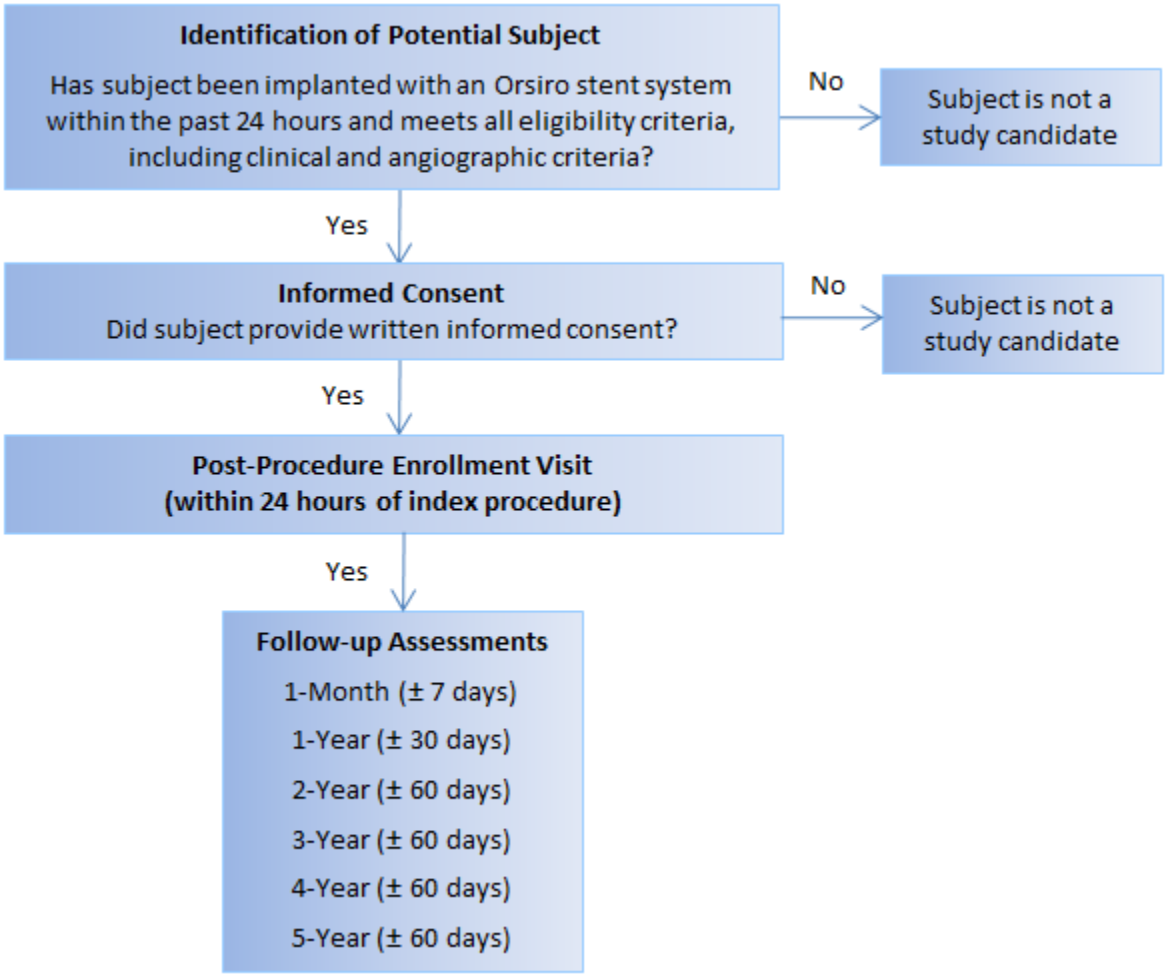
2 Study Design

The BIOFLOW-VII study is a prospective, multi-center, single-arm study to confirm that the clinical performance of the Orsiro stent in a real-world setting is similar to the clinical performance observed for Orsiro in the BIOFLOW-V IDE pivotal trial. Subjects who undergo an on-label percutaneous coronary intervention (PCI) with a placed Orsiro stent within the prior 24 hours will be screened per the protocol inclusion and exclusion criteria to achieve the desired evaluable subject counts (N=500) for the primary endpoint. The study will enroll subjects at up to 50 sites in the US.

Subjects may have received treatment of 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). The target lesion(s) must have been *de novo* or restenotic (PTCA only) atherosclerotic lesion(s) of ≤ 36 mm in length in native coronary artery(ies), with a reference vessel diameter of 2.25–4.0 mm. All lesions treated during a single index procedure must meet target lesion criteria.

Enrolled subjects will have clinical follow-up at 1 month, 1 year and then annually at 2, 3, 4 and 5 years following the index procedure. The study design flow chart is shown in **Figure 2**.

Figure 2: Study Design Flow Chart



2.1 Study Endpoints

2.1.1 Primary Endpoint

The primary endpoint will evaluate the rate of TLF at 1 year post-index procedure. TLF is defined as a composite of cardiac death, target vessel myocardial infarction (MI) or clinically-driven target lesion revascularization (TLR).

The BIOFLOW-V trial utilized a primary protocol target vessel-MI definition adapted from Vranckx P et al[5]. The adjudication of peri-procedural MI to this definition requires compliance and availability of pre- and post-index procedure cardiac biomarkers, which is feasible in a well-controlled IDE clinical trial. However, measurement of cardiac biomarkers pre- and/or post-index procedure is not standard of care at all sites. Due to standard of care differences in cardiac biomarker collection, the BIOFLOW-VII protocol design has been adjusted to account for this potential difference in a real-world post-approval registry. To minimize the overall impact of potentially missing pre- and/or post-index procedure

cardiac biomarkers, the SCAI[4] peri-procedural MI definition will be used for the primary endpoint analysis. The BIOFLOW-V definition will be used for spontaneous MI.

The BIOFLOW-VII post-approval study will consent subjects within 24 hours post-index procedure. Pre- and post-procedural cardiac biomarker data will be collected, if testing is performed per standard of care. It is anticipated that cardiac biomarker testing per standard of care generally would include subjects with positive cardiac biomarkers prior to the procedure, patients with procedural complications and patients with signs or symptoms of possible coronary ischemia post procedure.

The Clinical Events Committee (CEC) adjudicated event classification will be utilized for calculation of the TLF rate.

2.1.2 Secondary Endpoints

The following secondary endpoints will be evaluated prior to discharge, at 1 month, 1 year, and annually thereafter through 5 years follow-up.

1. All-cause death.
2. MI.
3. Cardiac death or MI.
4. Major Adverse Cardiovascular Events (MACE) and individual MACE components (MACE: composite of all-cause death, Q-wave or non–Q-wave MI, and clinically-driven TLR).
5. TLF (evaluated at 2, 3, 4, and 5 years) and individual TLF components (TLF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and clinically-driven TLR).
6. Target vessel failure (TVF) and individual TVF components [TVF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and clinically-driven target vessel revascularization (TVR)].
7. Stent thrombosis (definite, definite/probable, probable) according to Academic Research Consortium (ARC)-2[1] criteria for acute, subacute, late, very late and cumulative stent thrombosis.
8. Device success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using the Orsiro study stent only.

   Note: Post-dilatation is allowed to achieve device success.
9. Lesion success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using any percutaneous method.
10. Procedure success, defined as attainment of < 30% residual stenosis of the target lesion (based on operator visual estimate) using the Orsiro study stent only without occurrence of in-hospital MACE.

2.2 Additional Data of Interest

Additional information will be collected to characterize the study population, implanted device(s), and progress of the study. Specifically, data of interest will include:

- Baseline demographics, including age, gender, race and ethnicity, weight, height, blood pressure, New York Heart Association (NYHA) classification, left ventricular ejection fraction (LVEF), ischemic/angina status.
- Medical history, cardiac history [including prior PCI or coronary artery bypass graft (CABG)], indication for PCI, co-morbidities, other risk factors (e.g. smoking, diabetes), and relevant laboratory values.
- Index procedure information including pre- and post-procedure lesion characteristics, lesion preparation including pre-dilatation, residual stenosis, and procedure and antiplatelet/anticoagulant medications.
- Implanted Orsiro device information, including lot number, model, variant (e.g. length, diameter), device identifier (lot number), and implant date.
- Antiplatelet medical therapy.
- Device- or procedure-related adverse events.
- MI event rates utilizing alternative MI definitions, including Third Universal[6] and the BIOFLOW-V protocol definition[5]. Alternative MI definitions will be specified in the CEC Charter.
- TLF event rates at 1 year utilizing alternative MI definitions, including Third Universal[6] and the BIOFLOW-V protocol definition[5].

2.3 Subject Status

The definitions in **Table 2** define subject statuses throughout the study. Screen failure criteria are defined to target enrollment of a 100% on-label population.

Table 2: Subject Status Definitions

Subject Status	Definition
Enrolled	Subject who successfully meets all inclusion/exclusion criteria and provides written informed consent.
Pre-Screen failure	Subject in whom an Orsiro stent is deployed (or in whom an Orsiro stent implantation is attempted) and informed consent is not obtained due to subject not meeting inclusion/exclusion criteria or subject is not willing to participate in the study.
Screen failure	Subject who provides written informed consent but does not meet key inclusion/exclusion criteria and will be exited from the study. A subject is considered a screen failure if: • Subject did not receive at least one Orsiro stent within 24 hours prior to informed consent. If more than one stent was implanted during the index procedure, not all stents were Orsiro stents (Clinical Inclusion criterion #3 is not met). • Subject is not eligible for dual antiplatelet therapy (Clinical Inclusion criterion #4 is not met or Clinical Exclusion criterion #6 is met). • Subject had a 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 or any PCI planned within the next 1 year (Clinical Exclusion criterion #4 is met). • Subject met any of the following Clinical Exclusion criteria: STEMI (#1), allergies to contrast and/or other specified medications or materials (#3), or significant renal disease (#9, #10). • Subject had greater than three target lesions in up to two separate target vessels (Angiographic Inclusion criterion #1 is not met). • Target lesion was >36 mm in length by operator visual estimate (Angiographic Inclusion criterion #6 is not met). • Target vessel has a reference vessel diameter outside of 2.25-4.0 mm by operator visual estimate (Angiographic Inclusion criterion #7 is not met). • Target lesion(s) met any of the following Angiographic Exclusion criteria: located within or treated through a graft (#1), was a restenotic lesion that was previously treated with a bare metal or drug-eluting stent (in-stent restenosis) (#2), location within the left main coronary artery, or within 3 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX) (#3a), involves a side branch of > 2.0mm (#3b), total occlusion (#6). • Target vessel/lesion was excessively tortuous/angulated or is severely calcified, that would prevent complete inflation of an angioplasty balloon. Assessment based on visual estimation (Angiographic Exclusion criterion #4 is met). • Target vessel(s) meet any of the following Angiographic Exclusion Criteria: angiographic evidence of thrombus (#5), was treated with brachytherapy any time prior to the index procedure (#7).
Premature study exit	Enrolled subject who exits prior to completion of the 5-year follow-up.

3 Protocol Requirements

3.1 Subject Population

The investigator is responsible for screening all potential subjects and selecting those who are appropriate for study inclusion. The subjects selected for participation should be from the investigator's general patient population according to the inclusion and exclusion criteria described in Sections 3.1.3 through 3.1.6.

3.1.1 Indications

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

3.1.2 Contraindications

Orsiro is contraindicated for use in patients with:

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

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

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

3.1.3 Clinical Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the trial:

1. Subject is ≥18 years of age.
2. Subject was an acceptable candidate for treatment with a drug eluting stent at the qualifying index procedure, in accordance with the applicable guidelines on percutaneous coronary interventions and manufacturer's Instructions for Use.
3. Subject received at least one Orsiro stent during an index procedure occurring within 24 hours prior to informed consent, as assessed by the end time of procedure. If more than one stent was implanted during the index procedure, all stents were Orsiro stents.
4. Subject is eligible for dual antiplatelet therapy (DAPT) treatment with aspirin plus either clopidogrel, prasugrel, ticagrelor or ticlopidine.

5. Subject is willing to comply with study follow-up requirements.
6. Subject has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site. Legally authorized representatives are not allowed to consent on a subject's behalf.

3.1.4 Clinical Exclusion Criteria

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

1. Subject had clinical symptoms and/or electrocardiogram (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 pregnant and/or breastfeeding or intends to become pregnant during the duration of the study.
3. 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), silicon carbide, PLLA, sirolimus.
4. 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 or any PCI planned within the next 1 year.
5. Presence of an untreated clinically significant stenosis post-procedure whether treatment is planned or not.
6. Planned surgery within 6 months of index procedure unless DAPT can be maintained throughout the peri-surgical period.
7. History of a stroke or transient ischemic attack (TIA) within 6 months prior to the index procedure.
8. Subject has documented LVEF < 30% prior to or during the index procedure.
9. Subject is dialysis-dependent.
10. Subject has impaired renal function (blood creatinine > 2.5 mg/dL or 221 µmol/L prior to the index procedure).
11. 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).
12. Any significant concurrent medical diagnosis that would potentially impact DAPT effectiveness or increase thrombotic risk.

13. Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent).
14. Subject has life expectancy of < 1 year.
15. Subject is participating in an 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 follow-up requirements of this study or does not involve a drug that may confound the interpretation of any relevant clinical events of interest (e.g. investigational DAPT therapy).
16. In the investigator's opinion, subject will not be able to comply with the follow-up requirements.

3.1.5 Angiographic Inclusion Criteria

Each target lesion/vessel must have met all of the following angiographic criteria from the index procedure 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.
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 have been treated with a maximum of two overlapping stents.

3.1.6 Angiographic Exclusion Criteria

Subjects will be excluded from the trial if any of the target lesions/vessels met any of the following angiographic criteria during the index procedure:

1. Target lesion was located within or treated through a saphenous vein graft or arterial graft.

2. Target lesion was a restenotic lesion that was previously treated with a bare metal or drug-eluting stent (in-stent restenosis).
3. Target lesion had 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 was 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 had angiographic evidence of thrombus.
6. Target lesion was totally occluded (100% stenosis).
7. Target vessel was treated with brachytherapy any time prior to the index procedure.

3.2 Study Procedures and Visits

Subjects will be followed for a period of 5 years post-index procedure.

Table 3 provides an overview of the study schedule including required visits and associated follow-up windows.

Table 3: Visit Assessment Schedule / Schedule of Events

	Index Procedure	Post-Procedure Enrollment Visit	1 Month ± 7 Days	1 Year ± 30 Days	2, 3, 4, 5 Years ±60 Days	Unsched. Visit
			Telephone Interview or Office Visit	Telephone Interview or Office Visit	Telephone Interview or Office Visit	
Informed consent form[1]		X[1]				
Demographics, clinical status, medical history, pre-procedure cardiac biomarkers (CK, CKMB or troponin), CBC, cardiovascular and antiplatelet/anticoagulant medications		X[2]				
Index procedure information		X[3]				
Post-procedure cardiac biomarkers (CK, CKMB or troponin)		X[4]				
Ischemic/angina status		X	X	X	X	
12-lead ECG		X	X[5]	X[5]	X[5]	
Angiography to assess lesion characteristics and final stent location	X[6]					X[6]
AEs and SAEs[7]		X	X	X	X	X
Antiplatelet medical therapy		X	X	X	X	X

AE = adverse event; CBC = complete blood count; CK = creatine kinase; CKMB = creatine kinase myocardial band; ECG = electrocardiogram; SAE = serious adverse event

[1] Informed consent must be obtained after the index procedure. The date of index procedure is considered day 0 and informed consent (enrollment) can occur as late as 24 hours post-index procedure.

[2] Retrospective collection of pre-procedure information. Laboratory results (including cardiac biomarkers and CBC) collected only if testing performed per standard of care.

[3] Retrospective collection of index procedure information.

[4] Cardiac biomarkers collected only if testing performed per standard of care. It is anticipated that cardiac biomarker testing per standard of care generally would include subjects with positive cardiac biomarkers prior to the procedure, subjects with procedural complications and subjects with signs or symptoms of possible coronary ischemia post procedure.

[5] ECG collected only if an office visit is performed and if ECG is performed per standard of care.

[6] Images from standard of care angiography during index procedure should be retained and may be requested for submission to Angiographic Core Lab if subject undergoes a repeat angiogram. 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 Lab.

[7] All SAEs, potential endpoint events, and AEs possibly related to the device and/or procedure will be reported for the entire study period.

3.2.1 Assessment Details

Cardiac Biomarkers
Cardiac biomarker testing [CK (creatine kinase), CKMB (creatine kinase myocardial band, or troponin)], should be performed according to standard of care. Any cardiac biomarker testing performed per standard of care throughout the study duration should be collected and reported in the Electronic Data Capture (EDC) system.

It is anticipated that cardiac biomarker testing per standard of care generally would include subjects with positive cardiac biomarkers prior to the procedure, subjects with procedural complications and subjects with signs or symptoms of possible coronary ischemia post procedure.

Antiplatelet Regimen
Subjects should receive dual antiplatelet (DAPT) therapy according to current guidelines.[7]

All antiplatelet medications administered should be recorded in the medical record and reported in EDC from 72 hours prior to the index procedure (retrospectively collected) through the 5-year assessment.

3.2.2 Pre-Screening

At each site, all patients in whom an Orsiro stent has been deployed should be screened for study eligibility and enrolled if they meet enrollment criteria and are willing to participate. Reasons for subject non-eligibility for study enrollment (e.g. inclusion/exclusion criteria not met) or eligible for enrollment but not enrolled (e.g. patient unwilling to sign consent or death prior to being approached for consent) should be recorded on the electronic pre-screening log provided by BIOTRONIK. Additionally, all patients or in whom an Orsiro stent implantation was attempted, should also be recorded on the pre-screening log. Pre-screening logs should be submitted to BIOTRONIK at monthly intervals during the enrollment phase.

3.2.3 Post-Procedure Enrollment Visit

All clinical, angiographic, and other procedural inclusion and exclusion criteria should be confirmed post-procedure. After the patient has been determined to be eligible for the study, written informed consent must be obtained within 24 hours after the index procedure (as assessed by the end time of procedure) and prior to discharge for the patient to be enrolled in the study. The end time of the procedure is defined as the time the guide catheter is removed from the subject. Timing of consenting should be conducted in accordance with IRB requirements.

After informed consent has been obtained, the following procedures/data are required at the Enrollment Visit:

1. Retrospective collection of pre-procedure information from the medical record, including:
    - Demographics (e.g., age, sex at birth, race, and ethnicity).

- Clinical status (e.g., weight, height, blood pressure, ischemic/angina status assessment according to Canadian Cardiovascular Society Classification [CCSC] or Braunwald [refer to **Section 17**]).
- Medical history:
    - General medical, cardiac, neurologic and renal history.
    - Cardiac 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.
- Cardiovascular and antiplatelet/anticoagulant medications from 72 hours prior to the index procedure through enrollment.
- Pre-procedure laboratory test results (if performed per standard of care):
    - CK, CKMB, and/or troponin prior to the procedure. If more than one draw was performed prior to the index procedure, the most recent value should be recorded.
    - Creatinine, Complete Blood Count, etc.

2. Retrospective collection of index procedure and post-procedure information from the medical record, including:
    - Procedure information (e.g., lesion characteristics, device information, dilatation details, vessel preparation, residual stenosis.)
    - Adverse events occurring during or after the index procedure through the Enrollment Visit (refer to **Section 5.3** for reporting requirements).
    - Collect post-procedure laboratory cardiac biomarker data (if testing performed per standard of care).
3. Performance and/or collection of 12-lead ECG and ischemic/angina assessment per CCSC/Braunwald classification prior to discharge.
4. Review of the study follow-up requirements with the subject, to help ensure compliance with the follow-up schedule and DAPT medication regimen. Confirmation of subject contact telephone numbers, including numbers for home, work, and primary physician, as applicable, should be completed.
5. Reminder to subjects to contact site research personnel if approached by other clinical personnel about enrollment into another study. Subjects should not be enrolled in any investigational drug or device clinical study during the BIOFLOW-VII study. Co-enrollment in post-market studies may be allowed as long as the post-market study device, drug or protocol does not interfere with the follow-up requirements of this study or does not involve a drug that may confound the interpretation of any relevant clinical events of interest. The co-enrollment

study's information should be reviewed with BIOTRONIK personnel and, if needed, the site's IRB.

Procedural angiograms from the index procedure should be archived for possible later evaluation by the Core Laboratory. Two copies of the angiograms are suggested (one for the site, one for the Core Laboratory).

3.3 Follow-up Assessments

All enrolled subjects will be followed through 5 years of follow-up, with assessments performed at 1 month, 1 year and annually thereafter. All visits should be performed by telephone interview with the subject, unless a standard of care routine office visit is planned 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.

Target windows for follow-up visits are provided on the subject's record page in the EDC system and are based on the date of index procedure. It is recommended to schedule subjects early in the visit window, to allow for potential re-scheduling within the visit window, if necessary. Visits completed outside of the target window will require completion of a Protocol Noncompliance electronic Case Report Form (eCRF).

3.3.1 One (1) Month Follow-up (30 ± 7 Days)

Subjects will be evaluated at 1 month post-procedure by a telephone interview or an office visit. The following assessments must be completed:

- Ischemic/angina status (according to CCSC or Braunwald).
- AEs and SAEs since the previous contact (refer to **Section 5.2**)
- Antiplatelet medical therapy since the previous contact.
- Any coronary intervention (e.g., repeat revascularization) that occurred since the Enrollment Visit.
- 12-lead ECG (collected only if an office visit is performed and if ECG is performed per standard of care).

3.3.2 One (1) Year Follow-up (360 ± 30 Days)

Subjects will be evaluated at 1-year post-procedure by a telephone interview or an office visit.

During the 1-Year follow-up visit, the following assessments must be completed:

- Ischemic/angina status (according to CCSC or Braunwald).
- AEs and SAEs since the previous contact.
- Antiplatelet medical therapy since the previous contact.
- Any coronary intervention (e.g., repeat revascularization) that occurred since the previous contact.

- 12-lead ECG (collected only if an office visit is performed and if ECG is performed per standard of care).

3.3.3 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 by a telephone interview or an office visit.

The following assessments must be completed:

- Ischemic/angina status (according to CCSC or Braunwald).
- AEs and SAEs since the previous contact.
- Antiplatelet medical therapy since the previous contact.
- Any coronary intervention (e.g., repeat revascularization) that occurred since the previous contact.
- 12-lead ECG (collected only if an office visit is performed and if ECG is performed per standard of care).

3.3.4 Reporting of Unscheduled Evaluations

Subjects may present to the clinic outside of the scheduled follow-up windows. Such unscheduled study evaluation will be reported if the subject has experienced an AE.

Subjects assessed at an unscheduled study evaluation may require diagnostic testing (e.g. ECG, angiogram, CKMB or troponin levels)and/or a revascularization procedure to further evaluate and treat ischemic symptoms. Any repeat procedure must be reported on the relevant eCRFs, including any unscheduled evaluations prior to the repeat procedure and/or adverse events associated with the procedure, including separate AEs for each revascularization site if multiple sites were treated.

Any repeat or unscheduled diagnostic or interventional coronary revascularization procedure performed should include a diagnostic assessment of the target lesion(s) and study 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 Angiographic Core Laboratory for an independent review and assessment of the target lesion and study stent.

3.4 Study Exits

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

In the event of major protocol noncompliance, 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. Study exits are expected and will be taken into consideration during data analysis as described in **Section 4**. Additionally, subject attrition has been calculated into the study sample size. Investigators must document, in subject study records, the reasons and circumstances for all subject exits.

3.4.1 Withdrawal of Consent

Subjects may withdraw their consent for study participation at any time without stating the reason and without any unfavorable consequences. A Study Termination eCRF will be completed and the reasons for withdrawal should be documented if willingly provided by the subject.

The date of study exit is the date of withdrawal of consent.

3.4.2 Vital Status

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 study site level. Subjects have the right to discontinue from the study at any time or be discontinued at the investigator's discretion.

3.4.3 Subject Death

In the event of subject death during study participation, personnel at the study site are requested to notify BIOTRONIK promptly by completing an Adverse Event eCRF and a Study Termination eCRF. All actions taken, which were initiated to gain further information must be documented in writing and provided to BIOTRONIK.

The date of study exit is the date of death.

The following information will be required for any subject death:

• Death certificate, death report signed by the investigator, or relevant medical records that include:

- Date of death
- Primary cause of death

- Any other circumstances surrounding the death
- Investigator's assessment of relatedness to device or procedure

3.4.4 Lost to Follow-up

Subjects lost to follow-up are those for whom contact is lost despite the investigator's best efforts to locate the subject. 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 attempt by certified mail and document the contact attempts.

In the event the subject cannot be contacted using the above methods, the subject is terminated from the clinical investigation by completing a Study Termination eCRF. Subjects are not eligible to be exited as lost to follow-up until after the 1-Year Follow-up. If the 1-Year Follow-up was not completed and subject could not be contacted, and the required contact attempts (at a minimum) have been documented, then lost to follow-up may be an acceptable reason for exit.

The date of exit in the Study Termination eCRF is the date that the site determines the subject to be lost to follow-up. The date of last documented contact with the subject will also be collected. Both dates should be clearly documented.

3.4.5 Study Completion

All subjects are expected to be followed for 5-years. After a subject completes their final routine study follow-up, the subject's study participation is complete and the subject should be exited from the study by completing a Study Termination eCRF.

The date of exit is the date of the final study visit.

3.4.6 Screen Failures

Subjects who provide informed consent and do not meet key inclusion and exclusion criteria as defined in **Table 2** will be considered screen failures for the study and exited. These patients will continue to receive the same standard of care treatment.

4 Statistical Design and Analysis Plan

4.1 Analysis of Study Endpoints

The BIOFLOW-VII study is a prospective, multicenter, single-arm study. A total of 556 subjects will be enrolled.

4.1.1 Primary Endpoint

The purpose of the primary endpoint is to evaluate the rate of TLF of the Orsiro stent at 1 year compared to a performance goal of 6.9%.

H_o: The TLF rate of the Orsiro stent at 1 year is greater than or equal to a performance goal of 6.9%

Rate ≥ 6.9%

H_a: The TLF rate of the Orsiro stent at 1 year is less than a performance goal of 6.9%

Rate < 6.9%

A rejection of the null hypothesis (H_o) would demonstrate that the primary endpoint is met.

TLF is defined as a composite of cardiac death, target vessel-MI or clinically-driven TLR. Target vessel MI will utilize the SCAI definition[4] for peri-procedural MI and the BIOFLOW-V protocol definition[5] for spontaneous MI.

4.1.2 Secondary Endpoints

There are no formal hypotheses for the secondary endpoints.

4.2 Sample-Size Analysis

The study is designed to limit the number of subjects involved while still exposing the device to a sufficiently large patient population in order to ensure a representative and statistically meaningful sample.

The estimated sample size for the study is based on TLF results from the BIOFLOW-V study and in consideration of recent published relevant clinical TLF rates of other comparable stents that utilized the SCAI definition[4] of peri-procedural MI. The BIONICS IDE study utilized the Third Universal definition[6] of spontaneous MI, which is deemed to be similar to the spontaneous definition of MI used in the BIOFLOW-V study[5].

Comparable stents were evaluated in these two IDE studies involving a total of over 2,000 subjects and had consistent TLF upper 95% confidence bounds in the range of 6.9% - 7.1% (**Table 4**). A performance goal was derived considering this potential TLF rate range and was adjusted to account for the potential differences in the prospectively enrolled BIOFLOW-VII population enrolled under real world post-approval conditions.

Differences in standard of care practices and patient population may impact the final TLF rate. Specifically, cardiac biomarkers are infrequently analyzed post-procedure in asymptomatic patients as standard of care. Analysis of troponins is more frequent in clinical practice, whereas CKMB was measured more frequently as part of the protocol in the BIOFLOW-V study. It is also anticipated that a post-approval real-world population may have different frequencies of factors (e.g. diabetes, prior MI, etc.) and patient and lesion characteristics than those enrolled in IDE trials. These factors could result in a higher observed TLF rate than in BIOFLOW-V or other prior trials.

Table 4: 1-Year TLF Rates for DES Utilizing SCAI Definition of Peri-Procedural MI

Study	TLF Rate at 1 Year	95% Confidence Interval
BIOFLOW-V: Orsiro	2.6% (22/833)	(1.7%, 4.0%)
BIOFLOW-V: Xience	4.5%(19/426)	(2.7%, 6.9%)
BIONICS[8,9,10] EluNIR	5.4% (50/926)	(4.0%, 7.1%)
BIONICS: Resolute	5.4% (50/930)	(4.0%, 7.0%)

4.2.1 Assumptions for Primary Endpoint of TLF* at 1 Year

The sample size required to evaluate the primary endpoint was estimated using the following design criteria:

- Performance goal: 6.9% (upper 95% CI acceptability for BIOFLOW-VII)
- Target Orsiro TLF rate: 4.0%
- Statistical power: 80%
- Significance level: one-sided 0.025

Table 5: Primary Endpoint Sample Size

	Primary Safety Endpoint 1
Sample Size of Evaluable Subjects	495 subjects
Sample Size Adjusted for Post-Approval Study Requirement	500 subjects
Total Adjusted for Attrition	556 subjects

*Peri-procedural MI based on SCAI definition[4]. Spontaneous MI based on BIOFLOW-V protocol definition[5].

In order to collect additional data on the performance of the Orsiro stent, the sample size will increased to a target minimum of 500 evaluable subjects at 1-year post-index procedure as recommended by the FDA. Assuming a 10% attrition rate through the first 1 year of subject follow-up, a total enrollment of 556 subjects has been estimated.

4.2.2 Maximum Number of Subjects per Site

Enrollment at a single site will be limited to no more than 20% of the projected total study enrollment (approximately 111 subjects). It is anticipated that a minimum of 20 sites will enroll subjects.

4.3 Data Analysis Plan

Descriptive statistics will be used to present and summarize the data collected in the clinical study. Frequency distributions and cross tabulations will be presented for discrete variables. Means, standard errors, and ranges will be presented for continuous variables.

Interim progress reports will be submitted to FDA every 6 months during the first 2 years of the study and annually thereafter, unless otherwise specified by FDA. Summary and descriptive analyses of all endpoints will be included in the progress reports and may be posted on the FDA Post-Approval Studies webpage. Follow-up compliance rates will also be included in the progress reports.

4.3.1 Patient Demographics and Target Lesion Characteristics

Patient demographics and target lesion characteristics will be compared with those of the BIOFLOW-V (IDE) study cohort at 25%, 50%, and 75% of the expected total enrollment to ensure that the enrolled patient population is comparable with the BIOFLOW-V (IDE) study population.

4.3.2 Analysis Population Definition(s)

Table 6 provides definitions of the study analysis populations.

Table 6: Study Analysis Populations

Analysis Population	Definition
Intent-to-Treat (ITT)	The ITT population is defined as all enrolled subjects who received at least one Orsiro stent and were not considered a screen failure.
Per-Protocol (PP)	The PP population is defined as all ITT subjects who have no major protocol eligibility violations that could impact the primary endpoint. Criteria defining the PP population will be pre-specified prior to any PP analyses being performed.

4.3.3 Analysis Methods

All clinical data will be analyzed based upon the pre-defined analysis populations. The following methods will be used to evaluate the study endpoints.

Primary Endpoint

The primary analysis of the primary endpoint of the TLF rate of the Orsiro stent at 1 year will be in the intent-to-treat (ITT) population. The primary endpoint will be tested against a performance goal of 6.9% using a one-sided, exact test for one proportion with a Type I error level of 0.025. A supporting analysis will be performed in the PP population. A Kaplan-Meier survival analysis (time-to-event) for the primary endpoint outcome will also be performed in the PP population.

For each analysis population, subjects who have sufficient follow-up data (at least 330 days of follow-up) or experienced the primary endpoint will be included in the primary endpoint analysis.

Secondary Endpoints

There are no formal hypotheses for the secondary endpoints. Secondary clinical endpoints 1 through 7 will be evaluated prior to discharge, at 1 month, 1 year, and annually thereafter through 5 years of follow-up. Analyses of these secondary endpoints will be carried out on the ITT and PP analysis populations:

1. All-cause death.
2. MI.
3. Cardiac death or MI.
4. MACE and individual MACE components (MACE: composite of all-cause death, Q-wave or non–Q-wave MI, and clinically-driven TLR).
5. TLF (evaluated at 2, 3, 4, and 5 years) and individual TLF components (TLF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and clinically-driven TLR).
6. TVF and individual TVF components (TVF: composite of cardiac death, target vessel Q-wave or non–Q-wave MI, and clinically-driven TVR).
7. Stent thrombosis (definite, definite/probable, probable) according to Academic Research Consortium (ARC)-2[1] criteria for acute, subacute, late, very late and cumulative stent thrombosis.

Analyses of the following additional secondary endpoints will be carried out on the ITT and PP analysis populations.

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

4.3.4 Handling of Missing Data

All reasonable methods will be taken to ensure a minimum of missing data, including site monitoring, training, and corrective actions, if required, ongoing review of collected data for accuracy and completeness, and repeated, documented attempts to contact subjects with missing study visits. Any reasons for missing data or withdrawal from the study will be documented when possible. The impact of missing data on conclusions about the primary study endpoint will be examined in sensitivity analyses, which may include multiple imputation methods, if warranted.

4.3.5 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.
- Stent diameter ≤ 3.0 mm or > 3.0 mm.
- Subjects with acute coronary syndrome versus non-acute coronary syndrome.

There is no formal hypothesis for this subgroup analysis. Subjects with an event and/or with appropriate follow-up will be included in this analysis.

4.3.6 Poolability Analysis

The poolability of study results between clinical sites in the US will be analyzed and reported but there are no pre-specified tests of the statistical significance for site differences.

4.3.7 Sex Analysis

Any differences between sexes in study results between clinical sites in the US will be analyzed and reported but there are no pre-specified tests of the statistical significance for sex differences.

5 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 Adverse Event eCRF.

5.1 General Definitions

Table 7: Adverse Event Definitions

Adverse Event (AE) *ISO 14155:2011(E)*	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, 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 – For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE) *ISO 14155:2011(E)*	Adverse event related to the use of an investigational medical device. Note 1 - 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. Note 2 – This definition includes any event resulting from user error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE) *ISO 14155:2011(E)*	Adverse event that: 1. led to death, 2. led to serious deterioration in the health of a subject, that either resulted in a. a life threatening illness or injury, or b. a permanent impairment of a body structure or a body function, or c. an in-patient or prolonged hospitalization, or d. medical or surgical intervention to prevent life-threatening illness or injury or a permanent impairment to a body structure or a body function, 3. led to fetal distress, fetal death or a congenital abnormality or birth defect. Note - Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *ISO 14155:2011(E)*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

5.2 Protocol Defined Reportable Adverse Events

The investigator shall report to the sponsor, by completing the appropriate eCRF, the following types of events experienced by the subject after enrollment (consent)*:

- All serious adverse events.
- All potential endpoint events, including death, MI, stent thrombosis, TLR, and TVR adverse events.
- All adverse events possibly related to the device and/or procedure.
- Abnormal laboratory findings will be considered AEs only if related to potential endpoint events (e.g., elevated cardiac biomarkers), or if determined by the investigator to be clinically significant.

***Note: Adverse events occurring since the beginning of the initial index procedure (prior to consent), will be collected retrospectively.**

Other than adverse events occurring since the beginning of the initial index procedure, pre-existing conditions (underlying conditions present prior to obtaining subject consent) that are clearly documented in the subject's medical record are not required to be reported as adverse events, unless there is an increase in severity or frequency or a change from the pre-enrollment baseline during the course of the study.

All complaints will be reported through the standard market release product reporting process.

5.3 Reporting Adverse Events

5.3.1 Site Reporting

The study site should report each reportable adverse event to BIOTRONIK via completion of an Adverse Event eCRF. Adverse events should be reported as soon as possible, even if this results in an incomplete eCRF.

The investigator will be required to assess and characterize each protocol defined adverse event's relatedness to the study device and procedure, seriousness, outcome, treatment or action taken. The investigator must ensure that all source documentation and relevant information is available. This also includes information from other parties such as family, other treatment facilities/hospitals, etc. Copies of all supporting documents, with identifying information redacted, should be submitted concurrently with the Adverse Event eCRF.

The investigator must characterize each event by a single primary diagnosis. The primary diagnosis may describe an event consisting of several clinically recognizable features, symptoms or secondary diagnoses. Note: The observed symptoms and secondary diagnoses must be properly documented in the Adverse Event eCRF.

Multiple events may occur simultaneously in one subject. For each medically independent event with a primary diagnosis an individual report must be provided.

The investigator must follow-up all ongoing reportable events either as long as the subject participates in the clinical study, the clinical study is terminated, or until the event has been resolved, whatever comes first.

Investigators are required to adhere to applicable regulations and reviewing IRB reporting requirements for adverse events. Refer to **Section 13.1** for further details on adverse event reporting timing requirements.

The adverse events that an IRB considers reportable are dependent on the particular IRB. To avoid underreporting, BIOTRONIK recommends that, at a minimum, the investigator reports all deaths and serious device related events to the IRB. If the IRB is notified, provide a copy of the IRB adverse event notification to BIOTRONIK.

Additionally, study sites may report adverse events through MedWatch FDA's adverse event reporting tool for market-released devices.

5.3.2 Sponsor Reporting

BIOTRONIK may determine that study adverse events meet the manufacturer's reporting requirements through MedWatch reports.

6 Additional Study Conditions

6.1 Regulatory Compliance

This study will be conducted according to local legal and regulatory requirements and applicable federal regulations. The study will be conducted in compliance with the international scientific and ethical quality standard for clinical trials known as Good Clinical Practice (GCP). This study will be publicly registered on https://clinicaltrials.gov/.

6.2 IRB Approval

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

6.2.1 Other Institutions and Physicians

This clinical study is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK and the appropriate IRB. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject enrolled in the clinical study (such as a subject emergency room visit for medical treatment). In these instances a protocol deviation will not be issued and all available data will be utilized. In any such situations, the IRB and the investigator must continue to provide oversight for that patient's medical care and rights as a research subject.

6.3 Informed Consent

All subjects must sign and date an IRB approved Informed Consent Form (ICF) prior to enrollment or any protocol related procedures. Legally authorized representatives are not allowed to consent on a subject's behalf. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50), ICH/GCP Guidelines, the Declaration of Helsinki and any other national or local requirements. The consent process, including discussion of the study, should be documented within the subject's medical record. A copy of the completed (signed) informed consent form should be given to the subject.

This study does not include vulnerable patient populations. The investigator is required to inform BIOTRONIK and the reviewing IRB within 5 days if any subject was not appropriately consented to participate in the study.

7 Data Collection

7.1 Electronic Data Capture (EDC)

MedNet Solutions, Inc. is a privately held company that specializes in web-based clinical data management technology. MedNet will host the EDC system and provide a secure environment that is accessible to authorized individuals through the internet. BIOTRONIK will implement a study specific configuration using this software to meet the data collection requirements of the protocol. The EDC system is 21 CFR Part 11 compliant and is the platform for eCRF data entry, clinical data discrepancy resolution, and access to reports for BIOTRONIK, specified study sites, and any other parties authorized by BIOTRONIK.

7.2 Electronic Case Report Forms (eCRFs)

Original data will be collected from each study site and recorded into the EDC system, audited and monitored by BIOTRONIK, via completion of eCRFs. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs.

The iMedNet EDC system incorporates the ability for sites to upload subjects' signed and dated ICFs for the purposes of remote review of signed ICFs by Centralized Monitors to help identify any potential ICF compliance concerns early in the study prior to an on-site monitoring visit. As BIOTRONIK utilizes risk-based monitoring, the ability to upload unredacted informed consent forms is one of the factors taken into account when determining the need for a monitoring visit. An unredacted version of the subject's signed and dated ICF allows the Centralized Monitor to verify that the ICF was signed and dated by the subject prior to study procedures being conducted and that the subject signature and date are legible, complete, and correlate with the subject initials entered into EDC.

iMedNet is compliant with 21 CFR Part 11 Electronic Records; Electronic signatures. MedNet systems utilize industry standard methods for maintaining confidentiality and integrity of client data, and include (but are not limited to) SSL encryption, digital signatures, and secure technology policies and procedures. If additional information is required, iMedNet's Traceability Matrix illustrating evidence of iMedNet's compliance with all 21 CFR Part 11 requirements can be provided upon request.

If a site is not allowed to upload unredacted subject ICFs to the EDC system based on institutional policies, the site must provide to BIOTRONIK either a copy of the IRB or institutional policy or if a formal policy does not exist, a Note to File documenting this policy signed and dated by the Principal Investigator.

7.3 Data Quality Control

BIOTRONIK will review study data. At any time, reports may be generated on data completion and missing data for each study site. The EDC system will be used to track received and expected follow-up data and eCRFs for each participant. This

system provides the capability to monitor the status, volume, and disposition of data. In addition, study data will undergo automatic edit and plausibility checks which provide information to the study sites to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies.

To ensure protocol compliance at all participating study sites, BIOTRONIK monitors will conduct monitoring visits and/or centralized monitoring throughout the course of the study (refer to **Section 11**).

7.4 Subject Data Confidentiality

All information and data collected for the BIOFLOW-VII study concerning subjects or their participation in this investigation will be considered confidential by personnel at BIOTRONIK, BIOTRONIK's parent company, its subsidiaries and affiliates, as well as contracted designees, such as the CEC, Core Laboratory, EDC vendor and any other authorized third parties. Only authorized BIOTRONIK personnel or an authorized BIOTRONIK representative will have access to these confidential files. All data will be handled in accordance with applicable international, national and local laws, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996. In order to verify the study data and ensure study integrity, monitors from BIOTRONIK, the FDA, other national regulatory and/or public health authorities and the reviewing IRB, if applicable, may review and/or copy the study records. Source documents supplied to the CEC or Core Laboratory will have confidential subject identifiers redacted. All data used in the analysis and reporting of this study will not include subject names or other identifiable references.

8 Protocol Compliance

The investigator is required to conduct this study in accordance with the signed Investigator Agreement and clinical protocol. The investigator shall notify BIOTRONIK and the reviewing IRB in writing no later than 5 working days after any significant deviation from the clinical protocol 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 clinical protocol.

The site is responsible for reporting noncompliance via Protocol Noncompliance eCRFs. BIOTRONIK categorizes protocol noncompliance instances as either violations or deviations. Both protocol violations and deviations will be reported in the interim and final clinical progress reports to FDA.

BIOTRONIK will evaluate the noncompliance and issue corrective actions, as necessary, which may include but are not limited to, re-training, discontinuing enrollment at the study site, or closing the study site.

8.1 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 than deviations. Protocol violations are considered to potentially affect the subject's rights, safety, or well-being, and/or the scientific soundness/data reliability, accuracy, or completeness of the primary study endpoint data.

Protocol violations include, but are not limited to:

- Failure to obtain consent or other instances in which the subject did not provide consent.
- Subject inclusion/exclusion violations.
- Protocol requirement violations that affect the primary endpoint of the study design.

8.2 Protocol Deviations

Protocol deviations are defined as instances where protocol requirements or regulatory guidelines were not followed but are generally less serious in nature than violations. Protocol deviations generally do not affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study primary endpoint data. Instances of noncompliance should be considered a deviation if it does not meet the criteria for being considered a violation.

Protocol deviations include, but are not limited to:

- Informed Consent documentation issues such as incomplete ICF, missing dates for signature(s), missing initials or illegible information, subject signature date completed by someone other than subject, utilization of an outdated or non-IRB approved ICF, incomplete associated forms required at time of consent, etc. This is not an exclusive list.

- Procedure not performed within the allowed timeframe.
- Required data not obtained.

8.3 IRB Reporting of Noncompliance

The investigator must notify the reviewing IRB of all noncompliance issues per the IRB and protocol reporting requirements. At a minimum, all violations and noncompliance issues related to informed consent and informed consent documentation should be reported to the IRB.

In some instances, such as failure to obtain consent, the investigator should also seek guidance from the IRB to ensure the subject received appropriate information to consider their participation in the study.

The site should provide a copy of the IRB protocol noncompliance notification (as applicable) to BIOTRONIK.

8.4 Follow-up Compliance

Sites are expected to ensure follow-up visit compliance over the duration of the study.

Although the study sample size has been calculated with a 10% subject attrition rate over the first year, subject retention in a 5 year study may pose additional, unforeseen challenges. The EDC system includes an overview of each subject's follow-up schedule, including the windows for each follow-up. BIOTRONIK will provide additional tools to the sites in an effort to minimize the number of subjects that are lost to follow-up.

In addition, BIOTRONIK monitors will review subjects, including those that may be lost to follow-up, to ensure protocol and study visit compliance.

8.5 Audits/Inspections

Study centers may be audited during the course of and after completion of the clinical study by BIOTRONIK or BIOTRONIK designees, the FDA, IRB, or other applicable regulatory authorities.

The investigator must provide the auditor with all clinical study documents including the medical records for all enrolled subjects.

9 Risk Analysis

This is a post-approval study conducted using legally marketed devices implanted according to their approved labeling. BIOTRONIK foresees no additional risks associated with this study beyond those stated in the IFU for the Orsiro stent. The only research related risk is the potential loss of confidentiality that is minimized by PHI redaction in the study.

10 Study Organization

10.1 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. The sponsor, and/or other designees will ensure adherence to the sponsor general duties, selection of investigators, monitoring, supplemental applications, maintaining records and submitting reports.

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

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 deviations from the protocol, as appropriate.

BIOTRONIK or its designee will prepare written reports and a final report as directed.

10.2 Clinical Events Committee

A Clinical Events Committee (CEC) will be established consisting of independent physicians familiar with the treatment of coronary artery disease who are not participants in the study. The CEC will review and adjudicate all potential endpoint events reported by study sites. Source documents supplied to the CEC will have confidential subject identifiers and site identifiers redacted. To minimize bias, members will not participate as investigators.

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. The CEC will 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.

10.3 Angiographic Core Laboratory

An Angiographic Core Laboratory (Core Lab) will independently assess repeat and/or unscheduled angiograms submitted by clinical sites for a suspected restenosis of a target vessel during the study follow-up period. The Core Lab will provide independent review of angiographic follow-up of the treated target lesion, quantitative target lesion characteristics, and quantitative study stent results, to support the evaluation by the CEC.

Sites should obtain angiographic images in accordance with standard of hospital practice but should make efforts to ensure the final stent location is documented at the initial index procedure and that any re-evaluation includes the study stent.

Initial index procedure, staged procedure (if applicable), and repeat procedure angiograms for all subjects will be kept on file at the study sites. If coronary angiograms are performed during the trial follow-up period due to suspicion of restenosis of the target vessel, a revascularization of the target vessel, stent thrombosis or in follow-up to a myocardial infarction, sites should submit both the index procedure and follow-up angiography to the Core Lab for analysis.

The Core Lab will provide sites with a written procedural manual describing the procedures for submitting angiograms. Submission documentation of images to the Core Lab (i.e. Core Lab submission worksheet), as well as, a copy of the images submitted (via CD/DVD), should also be kept on file at the site.

10.4 Role of BIOTRONIK Personnel

BIOTRONIK Clinical Studies personnel will:

- Provide information, assistance, and training needed to conduct the study.
- Ensure proper monitoring throughout the study.
- Maintain proper records during and after the study.
- Compile and submit reports in accordance with regulations and requirements.

Please contact BIOTRONIK Clinical Studies personnel with any study related questions or concerns.

BIOTRONIK field personnel (including sales representatives and field clinical specialists) are allowed to:

- Review collected data for completeness and accuracy.
- Discuss general study progress with investigators and RCs.
- Answer technical questions on BIOTRONIK devices.

BIOTRONIK Personnel are NOT allowed to:

- Recruit subjects to participate in the study.
- Participate in the informed consent process with subjects or sign the subject informed consent forms as a witness.
- Assist with translation for non-English speaking subjects.
- Sign study worksheets on behalf of the site
- Perform data entry into the study Electronic Data Capture (EDC) systems.
- Request or retrieve subject medical records.
- Perform responsibilities of site study personnel such as completing or submitting IRB or other regulatory paperwork.
- Serve as a communication liaison between the site and IRB or FDA.
- Participate in any IRB or FDA inspections on behalf of the site.

11 Monitoring

11.1 Summary

The responsibility of BIOTRONIK as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the clinical study at sites. BIOTRONIK utilizes a risk-based monitoring strategy consistent with FDA's Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013. Risk-based monitoring starts with performing a study risk assessment of the identified critical data and processes. The resulting monitoring plan focuses on targeted source data verification and trend analyses to improve oversight and data quality, while integrating predefined triggers for monitoring visits. The detailed study risk-based monitoring plan developed by BIOTRONIK focuses on a combination of monitoring visits and centralized monitoring.

Monitors may periodically conduct on-site or remote monitoring visits during the clinical study in accordance with the monitoring plan. Sites are required to support monitoring visits and the study monitoring effort, including either direct monitor or site-assisted access to the applicable medical record systems. The principal investigator (PI) is encouraged to be available during monitoring visits. Monitoring visits will also provide an assessment of the continued acceptability of the facilities to continue participation in the study.

Centralized monitoring may be conducted throughout the course of the study in accordance with the monitoring plan. Centralized monitoring is conducted via investigator locked eCRFs through the source data verification of source documents uploaded to the eCRF. Some examples of data that may be monitored remotely include: informed consent forms, enrollment, eligibility, implant, study termination, and adverse events reported in the EDC system. Sites are required to support centralized monitoring by providing signed, dated, final source documents to BIOTRONIK in order to source data verify data reported in the EDC system and resolving queries in a timely manner.

The E6(R2) Good Clinical Practice: Integrated Addendum to International Council for Harmonisation (ICH) E6 (R1) Guidance for Industry dated March 2018 outlines the ALCOA-C guidelines for source documentation. All source documentation and study records should meet these ALCOA-C guidelines of attributable, legible, contemporaneous, original, accurate and complete. This guidance ensures the confidentiality, credibility, accuracy and validation of research records. All pages of source documents should be labelled with the subject ID. It is critical that the fully executed and unredacted informed consent form and all necessary source documentation are uploaded to the EDC in a timely manner.

Through centralized monitoring or monitoring visits, BIOTRONIK will assess the site's performance in the following areas:

- Verification that informed consent was obtained and documented properly
- Adherence to protocol eligibility criteria and requirements
- Conduct and documentation of procedures and assessments related to:

- Study objectives
- Protocol required data collection and procedures
- Evaluating, documenting, and reporting adverse events, and withdrawals, especially when a withdrawal may be related to an adverse event

- Investigator oversight and delegation of authority to site personnel
- Verification of study-specific required documentation
- Conduct and documentation of procedures essential to trial integrity
- Adherence to applicable requirements regarding the obligations of the investigator and maintenance of records.

Entries in eCRFs will be reviewed and source data verified by monitors (authorized BIOTRONIK personnel, or by authorized BIOTRONIK designees) to ensure that the investigator and the study team conducts the study in accordance with the protocol and applicable FDA and local laws and regulations to ensure adequate protection of the rights, safety and well-being of subjects and the quality and integrity of the resulting data.

If a monitor becomes aware that an investigator is not complying with the signed Investigator Agreement, the study protocol, applicable laws, and FDA and/or local regulations and any conditions of approval imposed by the reviewing IRB, the monitor is obliged to notify BIOTRONIK study management. BIOTRONIK will evaluate the noncompliance and issue corrective actions, as necessary, which may include but are not limited to, re-training, discontinuing enrollment at the study site, or closing the study site.

11.2 Monitors

Monitors are trained, qualified, and designated by BIOTRONIK management to oversee the progress of an investigation at the clinical site. Additional monitors may be appointed as necessary.

12 Study Completion or Early Termination

BIOTRONIK will notify the study site upon completion or termination of the clinical study or of the investigator's participation. At BIOTRONIK's request, an investigator will return any pertinent materials in their possession. Whenever possible, BIOTRONIK will provide a final report and a copy of the site's eCRFs to each study site as required by FDA regulations. BIOTRONIK will determine which sites will have an on-site close out visit and provide details on closure activities to all investigators to ensure the investigator understands any applicable regulatory requirements, including those related to record retention. All participating investigators are required to promptly notify BIOTRONIK if their financial disclosure information has any relevant changes during the course of the study or for 1 year following completion of the study, in accordance with 21CFR54.4.

13 Records and Reports

13.1 Investigator Records

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

- All correspondence relating to the study with another investigator, an IRB, BIOTRONIK, a monitor, or any other regulatory agency (e.g., a letter sent from the investigator to the IRB).
- A copy of the clinical study protocol.
- Signed investigator or research agreement.
- Signed Financial Disclosure Form.
- A copy of the IRB approval for the research study.
- A copy of the IRB approved subject Informed Consent Form.
- All documentation, including:
  - A copy of all signed Informed Consent Forms.
  - All supporting documentation for data entered into the EDC system.
  - Records of any adverse events, including supporting documentation.
  - Records pertaining to subject deaths during the study.
  - Documentation and rationale for any deviations from the clinical protocol.
  - Documentation of training.
  - Any other records required by BIOTRONIK.

The investigator must retain records related to the study for a minimum period of 2 years after the investigation is completed consistent with FDA regulations, IRB requirements, and institutional policies. Please ensure that BIOTRONIK is notified of any transfer of records, including changes to your site's address or Principal Investigator status during the required 2-year period.

13.2 Investigator Reporting Responsibilities

Investigators are required to prepare and submit to BIOTRONIK the following complete, accurate, and timely reports on this investigation as identified in the table below which outlines the responsibilities, including time constraints, for submitting required reports. Additionally, investigators are required to provide any other information upon the request of an IRB, regulatory authority, or BIOTRONIK.

Table 8: Investigator Reporting Responsibilities

Type of Report	Prepared by Investigator for:	Time Constraints of Notification
Subject death during investigation	BIOTRONIK, IRB	BIOTRONIK as soon as possible and as required by reviewing IRB
Withdrawal of IRB approval	BIOTRONIK	Within 5 working days of receipt of notice of withdrawal of approval
Progress Report(s)	BIOTRONIK, the monitor, IRB	Submitted no less than yearly
Significant deviations from study plan	BIOTRONIK, IRB	Within 5 working days after emergency to protect life or physical well-being of subject, otherwise prior approval by BIOTRONIK is required
Final report	BIOTRONIK, IRB	Within 3 months after termination or completion of the study or investigator's part of the study

13.3 Sponsor Records

BIOTRONIK will maintain the following records:

- All correspondence with the investigator(s), IRB, and FDA that pertains to the study
- Investigator agreements, financial disclosures, and curriculum vitae
- Name and address of each investigator and each IRB that is involved with the investigation
- Adverse events
- Adverse device effects
- Complaints
- Electronic Case Report Form data
- Confirmation of completed subject informed consent forms
- Clinical study protocol Screening visit reports
- Monitoring visit reports
- Clinical progress reports

13.4 Sponsor Reporting Responsibilities

BIOTRONIK is responsible for preparing the following reports, when necessary:

Table 9: Sponsor Reporting Requirements

Type of Report	Prepared by BIOTRONIK for	Time Constraints of Notification
Withdrawal of IRB approval	FDA, all reviewing IRBs and participating investigators	Within 5 working days after receipt of notice of withdrawal of approval
Withdrawal of FDA approval	Reviewing IRBs and participating investigators	Within 5 working days after receipt of notice of withdrawal of approval
Progress report	FDA, all reviewing IRBs	Submitted every 6 months during the first 2 years of the study and annually thereafter
Final report	FDA, all reviewing IRBs and participating investigators	A final report will be submitted within 6 months after completion or termination of the study.
Study closure	FDA, all reviewing IRBs, and participating investigators	Within 30 working days of completion or decision to terminate the study.

14 Publication Policy

BIOTRONIK intends to publish the results of this clinical study. BIOTRONIK reserves the right to include the report of this clinical study 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 study Principal Investigator reserve the right for the first publication of the clinical study 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.

The institution and the investigator have the right to publish the results of data obtained solely at their investigational site for the study. Before publishing, however, the institution and 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. BIOTRONIK 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, BIOTRONIK may extend such review period to file patent applications or take other steps to protect its intellectual property interests or to remove from the paper or presentation any language that may impact BIOTRONIK's intellectual property interests.

15 Prior Orsiro Clinical Trials

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[11] 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. The purpose of this trial was to compare the Orsiro sirolimus-eluting stent with the Xience Prime everolimus-eluting stent 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. 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. 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).[12]

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).[12]

Long-term 5 year clinical event rates were low and showed no significant differences between the two arms. The TLF rate was 10.4% in the Orsiro group compared to 12.7% in the Xience Prime group at 60 months (p=0.4728). No definite or probable stent thrombosis occurred in the Orsiro arm through 5 years.[13]

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.[14] The purpose of the registry was to evaluate safety and performance of the Orsiro sirolimus-eluting stent 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 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%.

BIOFLOW-III did not include mandatory angiographic follow-up and the rate of 12-month TLR was 3.0%. 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.

At 5 years, the TLF rate was 9.3% overall with definite or probably stent thrombosis rate of 0.7%. Among subgroups, the TLF rate for diabetic subjects was 13.0% and for subjects that had presented with acute MI was 10.6%.[15]

BIOFLOW-IV

BIOFLOW-IV is a prospective, international, multicenter, randomized controlled trial designed to assess the safety and effectiveness of the Orsiro stent in the treatment of subjects with up to two de novo coronary artery lesions. A total of 579 subjects were enrolled at 46 sites in Japan and Europe. 138 subjects were enrolled in Japan and 441 subjects were enrolled at sites in Europe. The BIOFLOW-IV clinical trial consists of a randomized control trial and a pharmacokinetic sub-trial. The BIOFLOW-IV randomized controlled trial (RCT) enrolled 579 subjects with up to two *de novo* lesions ≤ 26 mm in length in native coronary arteries 2.5–3.75 mm in diameter. Subjects were randomized in a 2:1 fashion to receive the Orsiro stent or the Xience Prime/Xpedition stent. The concurrent, non-randomized pharmacokinetic (PK) sub-trial at sites in Japan, enrolled 21 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 was 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 from September 2013 to January 25, 2015. The primary endpoint results of TVF at 12 months were 5.1% (19/374) for Orsiro and 6.6% (12/183) for Xience. The noninferiority hypothesis was confirmed with p=0.0003 in

the ITT population (absolute difference -1.48%, 95% CI of -5.70 to 2.74). There were no significant differences in the TVF sub-components of clinically- driven TVR, TV-MI, or cardiac death. The BIOFLOW-IV study supported the safety and efficacy of the Orsiro drug eluting stent as noninferior to the Xience drug eluting stent in treatment of subjects with coronary artery disease.

Clinical event rates at 3 years showed no significant differences between the two arms. The TVF rate was 10.4% in the Orsiro group compared to 9.7% in the Xience group at 36 months (p=0.8382). Definite or probable stent thrombosis rates were 0.8% in the Orsiro group compared to 0% in the Xience group at 36 months (p=0.5544). There were no late stent thrombosis events in either group.[16]

BIOFLOW-V

BIOTRONIK completed the BIOFLOW-V study as the pivotal US IDE trial for the Orsiro stent system.

BIOFLOW-V is a prospective, multicenter, randomized, controlled trial designed to assess the safety and efficacy of the Orsiro Sirolimus Eluting Coronary Stent System compared with the Xience Everolimus Eluting Coronary Stent System in subjects with up to three native de novo or restenotic (after standard PTCA only) coronary artery lesions.[2] A total of 1,334 subjects were) randomized at 90 clinical sites in 13 countries in North America, Europe, Israel and the Asia-Pacific regions between May 8, 2015 and March 31, 2016.

The primary endpoint was TLF at 1 year, defined as the composite of cardiac death, target vessel MI or clinically-driven TLR. For the analysis of the primary endpoint, the trial combined data on the randomized subjects with data from two prior studies (BIOFLOW-II and BIOFLOW-IV) by employing a Bayesian approach.

The 1-year TLF rate in the BIOFLOW-V study[3] was 6.2% for Orsiro and 9.6% for Xience utilizing the protocol-definition for peri-procedural MI and 2.6% for Orsiro and 4.5% for Xience utilizing the Society for Cardiovascular Angiography and Interventions (SCAI) definition[4] for peri-procedural MI.

In analyses of additional clinical endpoints, including MI, target vessel MI and the composite of cardiac-death or MI, significantly lower rates in the Orsiro group compared to the Xience group were observed (p=0.0129 for MI at 12 months, p=0.0155 for target-vessel MI at 12 months and p=0.0072 for cardiac death or MI at 12 months). The rates of death, cardiac death. clinically-driven TLR and stent thrombosis were comparable in the Orsiro and Xience groups.

The trial demonstrated the non-inferiority of Orsiro versus Xience with regards to 1-year TLF. These results support the safety and efficacy of the Orsiro stent compared to the Xience stent in a complex subject population undergoing percutaneous coronary intervention.

At 2 years, the significant differences observed at 1 year favoring Orsiro regarding composite endpoints of TLF, TVF, and MACE were maintained. The TLF rate was 7.5% in the Orsiro group compared to 11.9% in the Xience group at 24 months (p=0.015). The difference in TLF was driven principally by a significant difference in target vessel- MI (5.3% Orsiro vs. 9.5% Xience, p=0.01) in addition to significantly

lower clinically-driven TLR (2.6% Orsiro vs. 4.9% Xience, p=0.04). In a landmark analysis between 1 and 2 years, a significant difference in clinically-driven TLR emerged (0.7% Orsiro vs. 2.6% Xience, p=0.01). Definite and definite/probable stent thrombosis were numerically, but not statistically, lower with Orsiro (0.5% Orsiro vs. 1.2% Xience, p=0.17). However, combined late and very late rates of both definite and definite/probable stent thrombosis were significantly lower in the Orsiro cohort (0.1% Orsiro vs. 1.0% Xience, p=0.045 for both comparisons).[17]

BIOSCIENCE

The BIOSCIENCE study is a prospective, multicenter, randomized controlled trial that enrolled 2,119 subjects at 13 clinical sites in Switzerland. 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.[18]

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.

At 2 years the TLF rate for the Orsiro stent was 10.5% vs. 10.4% for the Xience stent (risk ratio [RR] 1.00, 95% CI 0.77–1.31, P=0.979). There was no significant difference in rates of cardiac death, target-vessel MI, TLR, and definite stent thrombosis. In the pre-specified subgroup of patients with ST-segment elevation myocardial infarction, Orsiro was associated with a lower risk of target-lesion failure compared with Xience (RR 0.48, 95% CI 0.23–0.99, P=0.043, $P_{interaction}$=0.026).[19]

At 5 years the TLF rate was not significantly different between the groups (20.2% Orsiro vs. 18.8% Xience; risk ratio [RR] 1.07, 95% CI 0.88–1.31, p=0.487). All-cause mortality was significantly higher in patients treated with Orsiro than in those treated with Xience (14.1% vs. 10.3%; RR 1.36, 95% CI 1.06-1.75; p=0.017), driven by a difference in non-cardiovascular deaths. There was no difference in cumulative incidence of definite stent thrombosis at 5 years (1.6% in both groups).[20]

BIO-RESORT

The BIO-RESORT study is a large-scale, investigator-initiated, multicenter, assessor and patient blinded, three-arm, randomized, non-inferiority trial conducted at four clinical sites in the Netherlands. The purpose of the study was to examine three drug eluting stents, each with a different drug coating (everolimus, sirolimus, and zotarolimus), with interest in performance of the stents and potential differences in

biodegradable vs durable polymers. The primary endpoint (TVF) was a composite of safety (cardiac death or target vessel-related MI) and efficacy (TVR) at 12 months of follow up, with analysis by intention to treat (non-inferiority margin 3.5%). Enrollment began on 21 December 2012, concluded on 24 August 2015, with results reported by von Birgelen et al. in The Lancet in October, 2016.[21]

The all-comers trial enrolled 3514 patients, of which 2449 (70%) had acute coronary syndrome, including 1073 (31%) presenting with ST-elevated myocardial infarction. Subjects were randomized with 1172 receiving everolimus-eluting stents, 1169 receiving sirolimus-eluting stents, and 1173 receiving zotarolimus-eluting stents. A total of 3490 patients (99%) completed 12-month follow-up. The primary endpoint of TVF was met by 55 (5%) of patients with everolimus-eluting stents, 55 (5%) of the 1169 patients with sirolimus-eluting stents, and 63 (5%) of the 1173 patients with zotarolimus-eluting stents. There were no significant differences in any outcome measures, including stent thrombosis, among the treatment arms.

At 2 years, the TVF rate for Orsiro was 6.6% vs. 6.8% for Synergy and 8.3% for Resolute Integrity. There were no statistical differences in the components of TVF.[22] At 3 years, the TVF rate for Orsiro was 8.5% vs. 8.8% for Synergy and 10.0% for Resolute Integrity. There were no statistical differences in the components of TVF.[23]

16 Abbreviations and Acronyms

Abbreviation / Acronym	Complete Term
ADE	adverse device effect
AE	adverse event
AMI	acute myocardial infarction
ARC	Academic Research Consortium
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCSC	Canadian Cardiovascular Society Classification
CEC	clinical events committee
CK	creatine kinase
CKMB	creatine kinase myoglobin band
cm	centimeter
Co-Cr	cobalt-chromium
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
dl	deciliter
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
ICF	Informed Consent Form
IDE	investigational device exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	intent-to-treat
IVUS	intravascular ultrasound

Abbreviation / Acronym	Complete Term
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
OCT	optical coherence tomography
PCI	percutaneous coronary 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
SES	sirolimus-eluting stent
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

Abbreviation / Acronym	Complete Term
TVR	target vessel revascularization
ULN	upper limit of normal
URL	upper range limit

17 Glossary

ANTICOAGULATION THERAPY

Anticoagulation therapy is the use of agents which thin the blood by binding or reducing production of clotting factors, or antithrombin III, i.e. warfarin, heparin, heparin derivatives, dabigatran, rivaroxaban, apixaban, and edoxaban.

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA[24]

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 precipitated 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[25,26]

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.

CARDIAC DEATH

See Deaths

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 quantitative coronary angiography (QCA), or revascularization of a target lesion with diameter stenosis ≥70% by QCA without either angina or a positive functional study.

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.

CORONARY ARTERY

Coronary artery includes entire territory of left anterior descending artery, left circumflex artery or right coronary artery and any major side branch of the specific artery; the ramus artery will be considered a branch of the left circumflex artery.

DAPT

Dual antiplatelet therapy (DAPT) refers to treatment of patients being treated with two types of antiplatelet medications to prevent clotting. These medications include aspirin plus a P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor, or ticlopidine).

***DE NOVO* LESION**

A native coronary artery lesion not previously treated.

DEATHS

All deaths reported during study will be 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.

ENROLLED SUBJECT

Subject who meets all clinical and angiographic eligibility criteria and has provided informed consent by properly signing an informed consent form.

Enrolled subjects will be followed in accordance with the protocol requirements.

EVALUABLE SUBJECT

Enrolled subject who meets all inclusion/exclusion criteria. Subject is part of the Intent-to-Treat analysis population.

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.

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.

MYOCARDIAL INFARCTION – PROTOCOL DEFINITION

Different criteria for spontaneous and peri-procedural MI will be utilized for the primary adjudication for endpoints for MI.

Peri-procedural < 48 hours post PCI
Society for Cardiovascular Angiography and Interventions (SCAI) definition[4]

1. In patients with normal baseline CKMB

- The peak CKMB measured within 48 hours of the procedure rises to ≥10 x the local laboratory ULN, or to ≥5 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB,
- OR in the absence of CKMB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70 x the local laboratory ULN, or ≥35 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.

2. In patients with elevated baseline CKMB (or cTn) in whom the biomarker levels are stable or falling

- The CKMB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3. In patients with elevated CKMB (or cTn) in whom the biomarker levels have not been shown to be stable or falling

- The CKMB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

Spontaneous MI > 48 hours(PCI)
Vranckx P et al[5]

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.

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 or visual estimate. (RVD: reference vessel diameter; MLD: minimal lumen diameter.)

PERCUTANEOUS CORONARY INTERVENTION (PCI)

All interventional cardiology methods for treatment of coronary artery disease.

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.

STENT THROMBOSIS – ACADEMIC RESEARCH CONSORTIUM-2 (ARC-2) DEFINITION[1]

Classification	Criteria
Definite stent thrombosis	Angiographic confirmation of stent thrombosis*
	The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent or in a side branch originating from the stented segment and the presence of at least 1 of the following criteria:
	Acute onset of ischemic symptoms at rest
	New electrocardiographic changes suggestive of acute ischemia
	Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)
	Or
	Pathological confirmation of stent thrombosis
	Evidence of recent thrombus within the stent determined at autopsy
	Examination of tissue retrieved following thrombectomy (visual/histology)
Probable stent thrombosis	Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/ scaffold thrombosis and in the absence of any other obvious cause.‡
Silent stent occlusion	The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.
Timing of ST (duration after stent implantation)	
Acute	0§–24 h
Subacute	>24 h–30 d
Late	>30 d–1 y
Very Late	>1 y

Early stent thrombosis is 0 to 30 days (acute plus subacute stent thrombosis).

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

†Occlusive thrombus: Thrombolysis in Myocardial Infarction grade 0 or 1 flow within or proximal to a stent/scaffold segment. Nonocclusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.

‡When the stented segment is in the left circumflex coronary artery or in the presence of preexisting electrocardiographic abnormalities (e.g., left bundle branch block, paced rhythms), definitive evidence of localization may be absent and Clinical Events Committee adjudication is based on review of all available evidence).

§Defined as the moment the patient is undraped and taken off the catheterization table.

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)

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

The target lesion is defined as the treated segment including the 5 mm margin proximal and 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)

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[27]

System developed during Thrombolysis in Myocardial Infarction (TIMI) trials for grading severity of stenosis and extent of blood flow through coronary arteries.

TIMI 0: No perfusion.

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

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).

18 Study Milestones / Timeline

The timeline of the BIOFLOW-VII study is dependent on the date of FDA approval of the study protocol, the ability to recruit a sufficient number of interested sites, and the ability to enroll subjects.

Progress reports will be submitted every 6 months during the first 2 years of the study and annually thereafter, unless otherwise specified by FDA.

Milestone	Window	Estimated Date
FDA Approval of Orsiro (P170030)	---	February 22, 2019
FDA approval of PAS protocol	Approval	November 2019
First IRB approval and first site opened to enrollment	Approval + 3 months	February 2020
First subject enrolled	Approval + 3 months	February 2020
Enrollment of 10 subjects	Approval + 5 months	April 2020
Enrollment of 100 subjects	Approval + 9 months	August 2020
All sites opened	Approval + 18 months	May 2021
Enrollment completion	Approval + 18 months	May 2021
Final 12-month follow-up visit (Primary Endpoint)	Enrollment Completion + 12 months + Visit Window (Approval + 31 months)	June 2022
Final 5-year follow-up visit (Study Completion)	Enrollment Completion + 60 months + Visit Window (Approval + 81 months)	July 2026
Final report submitted to FDA	Study Completion + 6 months (Approval + 87 months)	January 2027

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