BIOFLOW-VI

BIOTRONIK-Safety and Clinical Per**F**ormance of the Drug E**L**uting **O**rsiro Stent in the Treatment of Subjects **W**ith de novo Coronary Artery Lesions – **VI**

BIOTRONIK Orsiro Pre-Marketing Registration

CLINICAL INVESTIGATION PLAN

Version: V3.0

Product Name: Sirolimus Eluting Coronary Artery Stent System

Clinical Investigation Type: Medical Device Clinical Verification

Implementer: BIOTRONIK (Beijing) Medical Device Limited

Leading Organization Undertaking the Clinical Investigation: National Center For Cardiovascular Disease of Fuwai Hospital, CAMS & PUMC

Principal of the Clinical Investigation: Yang Yuejin

Unit of Statistic Analysis: Biostatistics Department of Cardiovascular Disease Prevention and Control Research Center, Ministry of Health

Statistician: Li Wei

Coronary Arteriography Core Lab: Medstar Research Health Angiographic Core Laboratory

Date: Dec 15, 2015

National Clinical Study Manager

Jing Wang

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Date Signature

Biotronik (Beijing) Medical Device Limited
1122 Interchina Commercial Building,
33 DengShiKou Street, Dongcheng District
100006 Bejing
P.R. China

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1 SYNOPSIS

Study Title	BIOTRONIK Orsiro Pre-Marketing Registration Clinical Investigation
Study Objective	To evaluate the effectiveness and safety of the BIOTRONIK Orsiro Sirolimus Eluting Stent (SES) with respect to in-stent Late Lumen Loss (LLL) in a non-inferiority study on de novo coronary lesions at 9 months.
Study Design	The clinical investigation is a non-inferiority, multicenter, blinding evaluation, randomized, parallel controlled clinical study enrolling up to 440 subjects. All subjects will be randomized 1:1 to receive the BIOTRONIK Orsiro SES or the Abbott Xience Prime™ EES, in order to evaluate the efficacy and safety of the SES drug eluting stent in the treatment of coronary artery disease. Clinical follow up visits will take place at 1, 6, 12, 24, 36, 48 and 60 months post procedure. At 9 months (+ 30 days) all subjects will undergo a standard quantitative coronary angiography (QCA) follow up to assess the in-stent LLL as the main efficacious evaluation. Use the major adverse cardiac event (all-cause death, Q-wave, non-Q wave MI and clinically driven TLR) within one year post procedure as the main safety indicator to evaluate the investigational product's safety. The clinical and angiographic data sorting, calculation and statistical analysis will be conducted by an independent data management center and angiographic core laboratory.
Study Sites Up to 15 sites	Less than 15 sites
Study Population	Subjects with coronary artery disease due to de novo stenotic lesions in native coronary arteries, with a reference vessel diameter $\geqslant$ 2.25 mm and $\leqslant$ 4.0 mm and a lesion lengths $\leqslant$ 36 mm.
Study Device	Investigational devices: BIOTRONIK Orsiro SES Control devices: Abbott Xience Prime™ EES

Inclusion Criteria -Clinical	1. Subject who can understand the investigation's goal has provided written informed consent, and is willing to comply with the study's follow-up requirements. 2. Subject is ⩾ 18 years and ⩽ 75 years old, male or female without pregnant. 3. Subject is an acceptable candidate for PCI. 4. Subject has clinical evidence of asymptomatic ischemia, stable or unstable angina pectoris or old myocardial infarction. 5. Subject has no contraindication for dual anti-platelet therapy treatment.
Inclusion Criteria -Angiographic	1. Target lesion must be in the major coronary artery or a branch (target vessel). 2. Target lesion must have angiographic evidence of ⩾ 70% and < 100% stenosis (by operator's visual estimate). 3. Subject has up to two target lesions (two target lesions in one target vessel, or for each target vessel, it has one target lesion). 4. Target lesion is suitable for drug-eluting stent PCI treatment. 5. Target lesion must be ⩽ 36 mm in length by operator's visual estimate, and can be completely covered by one stent. 6. Target vessel must have a reference vessel diameter of 2.25–4.0 mm by operator's visual estimate. 7. Target vessel must have a Thrombolysis In Myocardial Infarction (TIMI) flow ⩾ 2.
Exclusion Criteria -Clinical	*1.* Subject is pregnant and/or breastfeeding or intends to become pregnant during the duration of the study. *2.* Subject has clinical symptoms and/or ECG changes consistent with acute ST elevation MI (STEMI) within 7 days prior to the index procedure, including hemodynamically unstable non-STEMI (NSTEMI) subjects. 3. Subject is hemodynamically unstable. 4. Subject is an unacceptable candidate for CABG.

5. Subject has a known allergy to contrast medium that cannot be adequately pre-medicated, or any known allergy to thienopyridine, aspirin, both heparin and bivalirudin, L-605 cobalt-chromium (Co-Cr) alloy or one of its major elements (cobalt, chromium, tungsten and nickel), acrylic, fluoropolymers, silicon carbide, PLLA, sirolimus or everolimus.
6. Previous revascularization of any target or non-target vessel 9 months prior to the index procedure.
7. Planned surgery within 6 months of the index procedure.
8. Planned staged treatment during the index procedure or within 30 days after the index procedure.
9. History of a stroke or transient ischemic attack (TIA) within 12 months prior to the index procedure.
10. Subjects with active bleeding disorders, active coagulopathy, or any other reason, who are ineligible for DAPT.
11. Subject will refuse blood transfusions.
12. Subject has documented severe cardiac failure (over III level of NYHA) or left ventricular ejection fraction (LVEF) $\leqslant$ 40% as evaluated by echocardiogram, left ventricular angiography, radionuclide ventriculography or any non-invasive imaging method within 90 days prior to the index procedure.
13. Subject is dialysis-dependent.
14. Subject has impaired renal function (i.e., creatinine > 2.0 mg/dL or 175 μmol/L determined) within 7 days prior to the index procedure.
15. Subject has leukopenia (i.e. WBC < $3.5*10^{*9}$/L), thrombocytopenia (plt<$100*10^{*9}$/L) or thrombocytosis (PLT>$350*10^{*9}$/L).
16. Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent).
17. Subject is receiving oral or intravenous immunosuppressive therapy (inhaled steroids are excluded), or has known life-limiting immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematosus; diabetes mellitus is excluded).

	18. Subject has a life expectancy of < 3 years. 19. In the investigator's opinion, subject will not be able to comply with the follow-up requirements. 20. Subject is participating in another (medical device or drug) clinical study. Subjects may be concurrently enrolled in a post-market study, as long as the post-market study device, drug or protocol does not interfere with the investigational treatment or protocol of this study.
Exclusion Criteria -Angiographic	1. Target lesion is located within a saphenous vein graft or arterial graft. 2. Target lesion has any of the following characteristics: a) Lesion location is within the left main coronary artery, or within 3 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX). b) Involves a side branch of > 2.5 mm in diameter. *Note: Lesions within 3 mm of the origin of the right coronary artery may be treated.* 3. Target lesion is totally occluded (100% stenosis). 4. Target vessel has angiographic evidence of thrombus. 5. Target vessel/lesion is excessively tortuous/angulated or is severely calcified, preventing complete inflation of an angioplasty balloon. 6. Target vessel was treated with brachytherapy at any time prior to the index procedure.
Primary Endpoint	In-stent LLL at 9 months post procedure by core laboratory QCA analysis
Secondary Endpoints Treatment Success Indicators	1. Device success, defined as attainment of ⩽ 30% residual stenosis, TIMI=3, of the target lesion using the assigned study stent only. Note: Post-dilatation is allowed to achieve device success. 2. Lesion success, defined as attainment of ⩽ 30% residual stenosis, TIMI=3, of the target lesion using any percutaneous method. 3. Procedure success, defined as attainment of ⩽ 30% residual stenosis, TIMI=3, of the target lesion using the assigned study stent only, without occurrence of in-hospital major adverse cardiac events (MACE; composite of all-cause death, Q-wave or non–Q-wave MI, and any clinically-driven TLR).

Secondary Endpoints -Clinical	The following endpoints were followed up at 1, 6, and 12 months post-procedure, and once annually for up to 5 years. 1. All-cause death 2. Cardiac death 3. Myocardial infarction 4. MI of the target vessel 5. Stent thrombosis 6. All serious adverse device effects (SADEs) 7. Target Lesion Revascularization, TLR 8. Target Vessel Revascularization, TVR 9. Target Lesion Failure (TLF), composite of cardiac death, target vessel Q-wave or non-Q wave Myocardial Infarction (MI), Coronary Artery Bypass Grafting (CABG), clinically driven TLR 10. Target vessel failure (TVF), composite of cardiac death, target vessel Q-wave or non-Q wave Myocardial Infarction (MI) and clinically driven TVR 11. Major adverse cardiac event (all-cause death, Q-wave, non-Q wave MI and clinically driven TLR)
Secondary Endpoints-Angiographic	In-stent and in-segment binary restenosis rate angiographically assessed (⩾ 50% diameter stenosis) at 9 months post procedure, in-segment Late Lumen Loss (LLL) at 9 months post-procedure, in-stent and in-segment percent diameter stenosis and minimum lumen diameter (MLD) at 9 months post-procedure.

2 INTRODUCTION

Since the first Percutaneous Transluminal Coronary Angioplasty (PTCA) being successfully applied into human beings in 1977, this procedure has become a widely accepted treatment modality

for Coronary Artery Disease (CAD). However, all percutaneous techniques, regardless of the mode of intervention, have rather high rates of repeat interventions at the long-term follow up, representing a limitation of the strategy. This limitation is attributable to the process of restenosis or angiographic re-narrowing of the vessel's lumen following successful PTCA[1]. Being quite distinct from atherosclerotic lesions, restenosis following conventional angioplasty results from elastic recoil, vessel contraction, thrombus formation, smooth muscle cell proliferation and excessive production of extra cellular matrix. Depending on the subject population and angiographic diagnostic criteria, the reported incidence of restenosis after PTCA ranges from 30%-50%[2]. Such rates of recurrence have serious economic consequences.

The first type of stent used in Percutaneous Coronary Intervention (PCI), were Bare Metal Stents (BMS), designed to address the limitations of PTCA[1, 3, 4]. BMS reduced the angiographic and clinical restenosis rates in de novo lesions compared to PTCA on its own and decreased the need for CABG. BMS substantially reduced the incidence of abrupt artery closure, but restenosis still occurred in about 20%-40% of cases[5, 6], necessitating repeat procedures. The invention of Drug Eluting Stents (DES) significantly improved on the principle of BMS by adding an antiproliferative drug, which is either directly immobilized on the stent surface or released from a polymer matrix to inhibit neointimal hyperplasia. This allows for controlled release of the drug at the site of injury. The polymer drug carriers currently used on DES are either biodegradable or non-biodegradable.

The introduction of DES greatly reduced the incidence of restenosis and resulted in a better safety profile as compared to BMS with systemic drug administration. These advantages, as well as a lower cost compared to surgical interventions, have made DES an attractive option for the treatment of coronary artery disease[7].

2.1 Sirolimus and DES

Sirolimus is a natural macrocyclic lactone, first isolated from Streptomyces Hygroscopicus in the mid-1970s. It was approved by the FDA for the prophylaxis of renal transplant rejection in 1999. Thus, sirolimus has potent antiproliferative, anti-inflammatory and immunosuppressive effects. It acts by inhibiting the activation of mammalian target or (mTOR), ultimately causing the arrest of the cell cycle (progression from phase G1 to S). Thus sirolimus prevents cell proliferation that also includes T-cells and the proliferation and migration of smooth muscle cells, thereby, inhibiting the restenosis process[8]

Reduction of neointimal hyperplasia with sirolimus DES compared with BMS have been shown in porcine models[9]. Re-endothelialization occurred at a similar degree in both DES and BMS groups. This has also been confirmed in human coronary arteries[10, 11]. Sirolimus DES have been shown to reduce neointimal thickening when compared to both bare metal and polymer coated stents in various animal models and clinical studies[12-16].

The very first DES to be approved for the market was the Cypher® SES. It received the CE mark in 2002 and FDA approval in 2003 and has since then been extensively studied in a number of clinical investigations. The efficacy of the Cypher® and the improved Cypher Select+® SES has been proven in populations ranging from highly selected subjects with single de novo lesions to unselected all-comers[7,14,16-23]. The Cypher® stent has shown significant improvements in angiographic outcomes, with reduced rates of restenosis and less need for revascularization compared to BMS [7, 23].

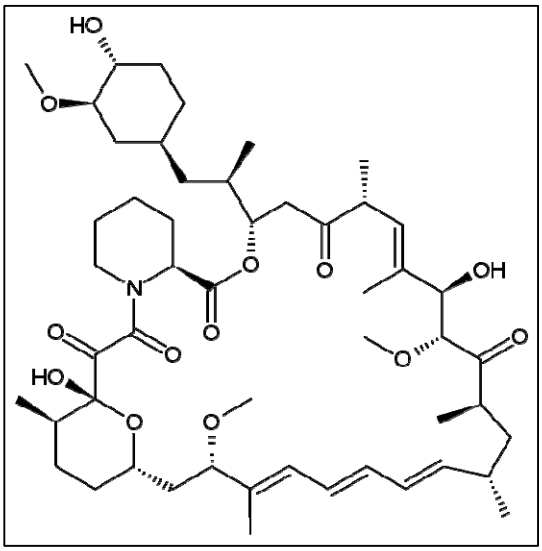

Figure 1: Structural formula of Sirolimus

Since the preliminary results from the first-in-man feasibility clinical investigation were presented, the Cypher® SES has now become available in more than 80 countries (Europe, Japan and US included) and has been used to treat +3 million subjects with CAD[24]. The Cypher® SES is one of the most studied DES today with a large body of clinical evidence demonstrating long-term safety and efficacy.

For the indications that will be treated in the clinical investigation, single de novo coronary artery lesions, safety and efficacy have been demonstrated in the Cypher® First in Man feasibility clinical investigation[16] and four randomized controlled studies with the Cypher® stent, RAVEL[20], SIRIUS[14], E-SIRIUS[25] and C-SIRIUS[21]. Clinical data for up to 5 years after stent implantation are available for these studies[11, 13, 26, 27].

2.2 Investigational Device

2.2.1 Platform and Delivery System

The Orsiro Sirolimus DES, which received the CE mark in Feb 2011, is based off the design of the approved and successfully marketed PRO-Kinetic ENERGY™ stent system. The predecessor product, PRO-Kinetic™, has proven to be both safe and effective in the treatment of coronary lesions.

The PRO-Kinetic ENERGY™ stent received the CFDA approval in Feb 2010. Its skeleton structure is made of a cobalt chromium alloy (Cobalt-Chromium L605), which is completely covered by a thin layer of amorphous silicon carbide (PROBIO®). This material has semiconducting properties that efficiently prevent the electron transfer from the fibrinogen to the metal surface in vitro. Thereby the conversion from fibrinogen to fibrin and it's deposition at the stent surface is reduced[28]. Additionally, the aSiC:H-coated stent exhibits a lower adhesion and activation of blood platelets and leucocytes[29]. Finally, the release of potentially allergenic ions from a silicon carbide coated stent is substantially reduced in comparison to an uncoated metal stent. The PROBIO® coating is used on all BIOTRONIK coronary stents and has undergone extensive clinical testing[30-34].

The PTCA delivery system of Orsiro Sirolimus and PRO-Kinetic ENERGY are nearly identical, based on a fast-exchanging PTCA catheter. The stent is securely crimped on a Nylon balloon situated at the distal tip of the catheter between two radiopaque markers made of a Platinum-Iridium alloy. The proximal shaft of the delivery system is a hypotube made of polyamide-covered 304 or 304L stainless steel. It has a single luer port for connecting an inflation/deflation device to inflate/deflate the balloon. The distal section of the catheter comprises of the inflation/deflation (balloon) lumen and guide wire lumen which starts at the catheter tip and ends at the guide wire exit port. It accepts guide wires of 0.014" diameter. The stent delivery system is compatible with guiding catheters with a minimal inner diameter of ≥ 0.056" (1.42 mm). Shaft exit markers are located on the hypotube 92 cm (brachial technique) and 102 cm (femoral technique) from the distal end of the catheter to indicate when the delivery system tip exits from the guiding catheter.

2.2.2 Carrier and Coating

The polymer compound used as a carrier material for the supply and release of Sirolimus is a high molecular Poly-L-Lactidic Acid (PLLA). The stent body surface is completely coated by a matrix consisting of the carrier PLLA and the Sirolimus. The maximal thickness of the surface is 25 µm. The largest stent design has a maximal coating mass of 42.3 µg per millimeter of stent length. PLLA is a highly biocompatible material. There is existing published experience with PLLA as a stent and stent coating material in humans[32-34].

2.3 Control Device

The Xience Prime™ Everolimus Eluting Stent (EES) is manufactured and marketed by Abbott Laboratories. Abbott received the CFDA approval and launched the Xience Prime™ EES in China in 2014. The Xience Prime™ and Xience V™ adopt the same drug and coating technology. Xience V™ uses BMS MULTI-LINK®, while Xience Prime™ adopts the BMS MULTI-LINK 8®, an updated version of the Xience V™ MULTI-LINK® Vision platform. Like Pro-Kinetic ENERGY™ the MULTI-LINK® family is made of a cobalt chromium alloy. Due to the technical similarity to Xience V™, the Xience Prime™ is expected to have a similar efficacy and safety profile. Thus, data known from the Xience V™ clinical program have been used for reference in the design of the current BIOFLOW-VI study.
The SPIRIT FIRST study (N=60) was a multi-center, single blinded First In Man (FIM) study with the Xience V™ EES, conducted to assess the feasibility and efficacy in the treatment of subjects with de novo native coronary artery lesions, compared to the BMS MULTI-LINK VISION RX Coronary Stent System. This feasibility trial showed clinical safety and the angiographic in-stent LLL observed was 0.10±0.21 mm, a reduction of 88% relative to the bare metal stent at six months[35], and a LLL of 0.24±0.27 mm at 12 months[36], which was a reduction of 71%.

The SPIRIT II, III, trials were a continuation of the assessment of the safety and performance of the Xience V™ EES. The in-stent LLL in the SPIRIT II and SPIRIT III clinical investigations were 0.11±0.27 mm[37] and 0.16±0.4 1 mm[38] respectively. Similar results were also shown in the Medtronic sponsored RESOLUTE III clinical investigation. The in stent late lumen loss in the Xience V™ group was 0.19±0.4 0 (N=182)[39].

2.4 Previous Evidence of the Investigational DES

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

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

BIOFLOW-I was a 30-subject feasibility study conducted at two sites in Romania. The purpose of the trial was to evaluate the safety and efficacy of the Orsiro stent in the 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 primary endpoint of in-stent late lumen loss at 9 months was 0.05 ±0.22 mm , the safety indicator included composite of cardiac death, target vessel MI and clinically-driven TLR was 6.7% (2/30)[40] at 1 year and 13.7% (4/30) at 2 years, and a composite rate of all-cause deaths, any MI and any revascularization of 16.7% (5/30) at 2 years.

BIOFLOW-II was a prospective, multicenter, randomized (2:1）, controlled, non-inferiority trial that enrolled 458 patients. The purpose of this trial was to compare the efficacy and safety of Orsiro SES with the Xience Prime™ Everolimus Eluting Stent (EES) in subjects with single de novo coronary artery lesions in up to two coronary arteries. Follow-up angiography 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. At 12 months, there were no significant differences between the two arms in MACE.

The BIOFLOW-III study was a prospective trial that enrolled a total of 1,356 subjects at 43 centers in 14 countries. 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 primary endpoint is TLF rate at 12 months. The result was similar to BIOFLOW I and BIOFLOW II, with the rate of TLF at 5.1% at 12 months.

The BIOSCIENCE study was 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. At 12 months, the TLF rate for the Orsiro stent (6.5%) was non-inferior to the Xience stent (6.6%).

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

3 INVESTIGATIONAL DEVICE DESCRIPTION

Investigational devices: BIOTRONIK Orsiro SES

Control devices: Abbott Xience Prime™ EES

The BIOTRONIK Orsiro SES is composed of four main components:

- PRO-Kinetic ENERGY BMS platform
- PLLA Biodegradable Polymer
- Sirolimus Drug Substance
- Stent Delivery System

Both devices have received the CE mark.

4 INVESTIGATIONAL PLAN

4.1 Study Objectives and Methods

In the present clinical investigation, the purpose is to evaluate the effectiveness and safety of the Orsiro SES in a prospective, multi-center, blinding evaluation, randomized, controlled setting, in subjects with de novo coronary artery lesions in one or a maximum of two coronary arteries.

Angiography will be performed to assess the different procedural steps, the immediate post-procedural success and the primary endpoint in-stent LLL at 9 months post procedure. All angiograms will be analyzed by an independent core laboratory, Medstar Research Health Angiographic Core Laboratory.

The clinical investigation will commence approximately in QII 2015 and recruitment is expected to be

complete by 2016.

4.2 Study Design

This is a prospective, multicenter, blinding evaluation, non-inferiority, randomized controlled clinical investigation. A population of up to 440 eligible subjects with single de novo coronary lesions up to 36 mm in length, in vessels with ≥2.25 and ≤4.0 mm reference diameter stenosis will be randomized, 1:1, to receive either the BIOTRONIK Orsiro SES or the Abbott Xience Prime™ EES. Planned follow-up investigations include clinical evaluation at 1, 6, 12, 24, 36, 48 and 60 months post procedure. At the 9 months follow up visit all subjects will undergo angiographic evaluation.

4.3 Endpoints

4.3.1 Primary Endpoint

The primary endpoint is the in-stent late lumen loss at 9 months, as assessed by the core laboratory QCA analysis.

4.3.2 Secondary Endpoints

4.3.2.1 Treatment Success Indicator

1) Device success, defined as attainment of ⩽ 30% residual stenosis, TIMI=3, of the target lesion using the assigned study stent only.
   Note: Post-dilatation is allowed to achieve device success.
2) Lesion success, defined as attainment of ≤ 30% residual stenosis, TIMI=3, of the target lesion using any percutaneous method.
3) Procedure success, defined as attainment of ≤ 30% residual stenosis, TIMI=3, of the target lesion using the assigned study stent only without occurrence of in-hospital major adverse cardiac events (MACE; composite of all-cause death, Q-wave or non–Q-wave MI, and any clinically-driven TLR).

4.3.2.2 Clinical Endpoints

The following endpoints were followed up at 1, 6, and 12 months post-procedure, and once annually for up to 5 years.

1) All-cause death
2) Cardiac death
3) Myocardial infarction
4) MI of the target vessel
5) Stent thrombosis
6) All serious adverse device effects (SADEs)
7) Target Lesion Revascularization，TLR
8) Target Vessel Revascularization，TVR
9) Target Lesion Failure (TLF), composite of cardiac death, target vessel Q-wave or non-Q wave Myocardial Infarction (MI), Coronary Artery Bypass Grafting (CABG), clinically driven TLR
10) Target vessel failure (TVF), composite of cardiac death, target vessel Q-wave or non-Q wave Myocardial Infarction (MI) and clinically driven TVR
11) Major adverse cardiac event (all-cause death, Q-wave, non-Q wave MI and clinically driven TLR)

4.3.2.3 Angiographic Endpoints

1) In-segment late lumen loss (LLL) at 9 months post-procedure
2) In-stent and in-segment (proximal and distal) minimum lumen diameter (MLD) at 9 months post-procedure
3) In-stent and in-segment binary restenosis rate angiographically assessed (⩾ 50% diameter

stenosis) at 9 months post procedure
4) In-stent and in-segment percent diameter stenosis (% DS) 9 months after procedure.

4.4 Inclusion Criteria

4.4.1 Clinical Inclusion Criteria

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

1) Subject who can understand the investigation's goal has provided written informed consent, and is willing to comply with the study's follow-up requirements.
2) Subject is ⩾ 18 years and ⩽ 75 years old, male or female without pregnant.
3) Subject is an acceptable candidate for PCI.
4) Subject has clinical evidence of ischemic heart disease, stable or unstable angina pectoris or documented silent ischemia.
5) Subject is eligible for dual anti-platelet therapy treatment with aspirin, plus either, clopidogrel, prasugrel, ticagrelor or ticlopidine.

4.4.2 Angiographic Inclusion Criteria

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

1) Target lesion must be in major coronary artery or branch (target vessel).
2) Target lesion must have angiographic evidence of ⩾ 70% and < 100% stenosis (by operator visual estimate).
3) Subject has up to two target lesions (two target lesions in one target vessel, or, for each target vessel, it has one target lesion).
4) Target lesion is suitable for drug-eluting stent PCI treatment.
5) Target lesion must be ⩽ 36 mm in length by operator's visual estimate, and can be completely covered by one stent.
6) Target vessel must have a reference vessel diameter of 2.25–4.0 mm by operator's visual estimate.
7) Target vessel must have a Thrombolysis In Myocardial Infarction (TIMI) flow ⩾2.

4.5 Exclusion Criteria

4.5.1 Clinical Exclusion Criteria

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

1) Subject is pregnant and/or breastfeeding or intends to become pregnant during the duration of the study.
2) Subject has clinical symptoms and/or ECG changes consistent with acute ST elevation MI (STEMI) within 7 days prior to the index procedure, hemodynamically unstable non-STEMI (NSTEMI) subjects included.
3) Subject is hemodynamically unstable.
4) Subject is an unacceptable candidate for CABG.
5) Subject has a known allergy to contrast medium that cannot be adequately premedicated, or any known allergy to thienopyridine, aspirin, both heparin and bivalirudin, L-605 cobalt-chromium (Co-Cr) alloy or one of its major elements(cobalt, chromium, tungsten and nickel), acrylic, fluoropolymers, silicon carbide, PLLA, sirolimus or everolimus.

6) Previous PCI of any target or non-target vessel 9 months prior to the index procedure.
7) Planned surgery within 6 months of the index procedure.
8) Planned staged treatment during the index procedure or within 30 days after the index procedure.
9) History of a stroke or transient ischemic attack (TIA) within 12 months prior to the index procedure.
10) Subjects with active bleeding disorders, active coagulopathy, or any other reason, who are ineligible for DAPT.
11) Subject will refuse blood transfusions.
12) Subject has documented left ventricular ejection fraction (LVEF) ≤ 40% as evaluated by angiography, echocardiogram, radionuclide ventriculography or any non-invasive imaging method within 90 days prior to the index procedure.
13) Subject is dialysis-dependent.
14) Subject has impaired renal function (i.e., creatinine > 2.0 mg/dL or 175 µmol/L determined within 7 days prior to the index procedure).
15) Subject has leukopenia (i.e. WBC < $3.5*10^{*9}$/L), thrombocytopenia (plt<$100*10^{*9}$/L) or thrombocytosis (PLT>$350*10^{*9}$/L).
16) Subject is receiving chronic anticoagulation (e.g. coumadin, dabigatran, apixaban, rivaroxaban or any other agent).
17) Subject is receiving oral or intravenous immunosuppressive therapy (inhaled steroids are permitted), or has known life-limiting immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematosus; diabetes mellitus is permitted).
18) Subject has life expectancy of < 3 years.
19) In the investigator's opinion, subject will not be able to comply with the follow-up requirements.
20) Subject is participating in another (medical device or drug) clinical study. Subjects may be concurrently enrolled in a post-market study, as long as the post-market study device, drug or protocol does not interfere with the investigational treatment or protocol of this study.

4.5.2 Angiographic Exclusion Criteria

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

1) Target lesion is located within a saphenous vein graft or arterial graft.
2) Target lesion has any of the following characteristics:
   a) Lesion location is within the left main coronary artery, or within 3 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX).
   b) Involves a side branch of > 2.5 mm in diameter.

   Note: Lesions within 3 mm of the origin of the right coronary artery may be treated.
3) Target lesion is totally occluded (100% stenosis).
4) Target vessel has angiographic evidence of thrombus.
5) Target vessel/lesion is excessively tortuous/ angulated or is severely calcified, preventing complete inflation of an angioplasty balloon.
6) Target vessel was treated with brachytherapy any time prior to the index procedure.

5 ENROLMENT AND PROCEDURES

The enrolment, randomization and follow up process are outlined in Figure 2.

Figure 2 Clinical investigation flowchart

5.1 Informed Consent

If the basic screening of a subject's medical record meets the inclusion and no exclusion criteria, the subject should be given the clinical investigation informed consent information form and informed consent signature form (abbreviated as informed consent form). The informed consent form includes but is not limited to the following:

- Explanation of the clinical investigation
- Duration
- Expected benefits, risks or inconveniences
- Explanation of alternatives
- Medical record access and subject confidentiality
- Whether the data will be used for publications or submission for reimbursement support.

No clinical investigation specific examination may be performed before the subject has signed the informed consent signature form. Informed consent should be singed in accordance with the applicable regulations, the Declaration of Helsinki, Good Clinical Practice and ISO 14155:2011(E).

The person signing the informed consent shall:

- Avoid undue influence on subject's willingness to participate
- The subject's legal rights should be protected
- Make the subject understand the trial and provide ample time for the subject to consider his/her participation.
- Assure that the informed consent form is fully completed i.e. Including dated signatures of the subject or the subject's legal representative as well as the person obtaining the informed consent.

The signed informed consent form will be retained by the investigator and made available (for review only) to the clinical investigation monitors, auditors and inspectors on request. A copy of the signed and dated informed consent form must be provided to the subject.

5.2 Enrolment

Subjects are considered enrolled once they signed the informed consent signature form. However, the subjects are eligible for the clinical investigation only after fulfilling the in- and exclusion criteria The Intention to Treat (ITT) and the CIP population will only be based on eligible subjects.

All target lesions must be treated in one procedure. Planned staged procedures are not allowed. Only Orsiro SES or Xience Prime™ EES may be implanted during the index procedure. There is no restriction in the enrolment of eligible subjects per site.

5.3 Baseline Examinations

Subject clinical investigation eligibility must be confirmed prior to the intervention, through the following tests and examinations:

- Demographics
- For premenopausal women, a pregnancy test must be performed within 72 hours prior to angiography
- Review of in- and exclusion criteria
- Physical examination and relevant medical history including anginal status or myocardial ischemia
- A 12-lead electrocardiogram within 72 hours of the intervention
- Laboratory examination with 7 days of the intervention, including:
  - Infectious diseases screening (hepatitis B surface antigen, hepatitis C antibody, syphilis

antibody (TPPA), and HIV antibody)
- ➢ Blood routine (total WBC count, platelet count, hemoglobin, hematocrit, and RBC count)
- ➢ Liver function test (ALT、AST)
- ➢ Serum creatinine
- ➢ Serum glucose
- ➢ Serum lipid (triglyceride, cholesterol, high density lipoprotein, low density lipoprotein)
- ➢ Cardiac biomarkers CK (optional), CK-MB and Troponin I and/or T

5.4 Medication

Unless clinically contraindicated, all subjects should receive the medication regimen listed below (take each hospital and surgeon's general use into consideration). The use of GPIIb/IIIa inhibitors is allowed but not mandatory.

The generic name of all medications administered must be recorded in the subject's medical record.

Table 1 Medication List

Timing	Medication	Procedure
Prior to Procedure	Heparin	Left to the discretion of the interventionist
	Aspirin	100 mg for 3 days prior to procedure or a 300mg prior to procedure.
	Clopidogrel	Loading dose < 6 hours prior or during the procedure of 300- 600 mg Subjects on Clopidogrel therapy (at least 6 days): no loading dose required
	Ticagrelor[2]	180mg prior to procedure.
During Procedure	Heparin(IV or LMWH)	Per routine hospital practice, it is recommended to maintain an ACT > 250 seconds.

During Procedure	GPIIb/IIIa Inhibitor	Left to the discretion of the interventionist
	Intracoronary Nitroglycerin	100-200 µg post angiography, prior to stent implantation, and post intervention angiograms
Post-Procedure	GPIIb/IIIa Inhibitor	Per routine hospital practice
	Aspirin	100 mg per day
	Clopidogrel[1]	75 to 150 mg per day Left to the discretion of the interventionist
	Ticagrelor[2]	90 mg twice per day
Discharge	Aspirin	100 mg per day
	Clopidogrel[1]	75 to 150 mg per day for a minimum of 12 months. Dosage left to the discretion of the interventionist
	Ticagrelor[2]	90 mg twice per day for, a minimum of 12 months.
[1]Interventionist may substitute to Prasugrel, Ticlopidine or Ticagrelor for subjects who are allergic to Clopidogrel. Subjects on Ticlopidine must have CBC(s) performed per instructions for use. [2] Interventionist may choose to use Aspirin together according to the haemorrhage risk other than Clopidogrel.		

5.5 Interventional Procedure

All implanting interventionists must sign the clinical investigation site signature log and provide a signed and dated CV. All implanting interventionists must also receive adequate CIP training prior to clinical investigation procedure.

Preparation and percutaneous access should be performed according to the standard hospital practice. Both femoral and radial accesses are accepted. The procedure begins once percutaneous access has been made.

5.5.1 Baseline Angiography

Following intracoronary injection of nitroglycerin or isosorbide dinitrate, a baseline angiography of the target vessel must be performed according to the QCA corelab guidelines in at least 2 orthogonal views, presenting the target lesion free of foreshortening or vessel overlap.

5.5.2 Randomization

After in- and exclusion criteria have been checked and written informed consent has been obtained prior to PCI, subjects will be randomized with the eCRF.

- 1/2 Treatment with Orsiro SES
- 1/2 Treatment with Xience Prime™ EES

A randomization may only be done once. If by mistake a subject is randomized twice or more, the first assigned treatment arm will be used.

5.5.3 Puncture and Predilatation

The target lesion should be crossed with a 0.014" guide wire. If predilatation is necessary it is recommended to choose following pre-dilation balloons.

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

Furthermore, the selected pre-dilatation balloon must be a minimum of two millimeters shorter than the nominal length of the Orsiro stent that is planned to be implanted.

5.5.4 Stent Implantation

Please note that a stent package may not be opened prior to randomization.

The investigator is free to assess the artery diameter and the lesion length either visually or by online QCA during the procedure, always considering the instructions for use. The stent length should cover the target lesion from normal reference vessel proximal to normal reference vessel distal to assure full coverage of the lesion.

Only one clinical investigation stent should be used per lesion. Overlapping is only allowed if the primary stent failed to completely cover the target lesion. In such case the second stent must be the same stent the subject was randomized to, unless clinically contraindicated. Please refer to the IFU of each stent for details of overlapping procedures.

If the stents overlap, the overlapped part must at least be 2mm.

After stent implantation, an angiography must be performed. Following intracoronary injection of nitroglycerin or isosorbide dinitrate, angiograms should be made in the exact same 2 orthogonal views as pre-stenting according to the core lab instructions.

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5.6 Process before Discharge

Between the end of the procedure and hospital discharge, the following data has to be collected:

- Cardiac biomarkers CK (optional), CK-MB and Troponin I and/or T must be taken within 6-24 hours after procedure.
- Liver function tes (ALT、AST) within 24 hours post-procedure
- Serum creatinine within 24 hours post-procedure
- After the index procedure a 12-lead ECG must be completed within 6-24 hours or at discharge (whichever comes first).

A physical examination will be conducted to verify the anginal status according to CCS or Braunwald classification just prior to discharge. Adverse events and effects, concomitant medications, and any interventional treatment that occurred since the procedure must be recorded before discharge.

Note: Every effort must be made to obtain myocardial enzymology values within the specified time ranges. Results of all enzyme target, even measurements performed outside the time range must be documented on the CRFs.
If CK, CKMB and/or Troponin I and/or T elevation is abnormal post-procedure, CK and Troponin measurements should be performed every 8 hours and documented in the eCRF until values have returned to normal.

5.6.1 Antiplatelet / Anticoagulation Regimen

Forl medication please refer to Table 1 under section 5.4

5.7 Follow Up Visits

All subjects will be followed through to hospital discharge and will undergo follow-up evaluations at following time points:

5.7.1 One Month Clinical Follow Up

All subjects will be contacted for clinical evaluation at 30 days post-procedure (± 7 days), including:

- Assessment of the anginal status (CCS or Braunwald),
- Any adverse, or serious adverse events
- Anti-platelet/anti-coagulant treatment plan

5.7.2 6 Months Clinical Follow Up

All subjects will be contacted for clinical evaluation at 180 days post-procedure (± 30 days), including:

- Assessment of the anginal status (CCS or Braunwald),
- Any adverse, or serious adverse events
- Anti-platelet/anti-coagulant treatment plan

5.7.3 9 Months Clinical Follow Up

All subjects will return to the clinic for an angiography at 270 days (+ 30 days) post- procedure including:

- Ischemic/anginal status (CCS or Braunwald),
- Any adverse, or serious adverse events/effects
- Anti-platelet/anti-coagulant treatment plan
- Blood routine (total WBC count, platelet count, hemoglobin, hematocrit, and RBC count)
- Liver function test (ALT、AST)
- Serum creatinine
- 12-Lead ECG
- Angiographic assessment of the target lesion

Catheter and imaging position applied by coronary angiogram should be with the same time of stent implanting.

5.7.4 12, 24, 36, 48, 60 Months Clinical Follow Up

All subjects will be contacted for clinical evaluation at 12, 24, 36, 48, 60 months post-procedure (±30 days), including:

- Assessment of the anginal status (CCS or Braunwald),
- Any adverse, or serious adverse events
- Anti-platelet/anti-coagulant treatment plan

Table 2: Schedule of treatments and assessments-baseline to 12-month follow up

	Baseline	Procedure	Discharge	30 days ± 7days	180 days ±30 days	270days +30 days	12, 24, 36, 48, 60 months ±30 days
Signed informed consent	X						
Inclusion/Exclusion Criteria	X	X					
Pregnancy Screening	X[1]						
Medical and Cardiac History	X						
Medication		X[2]	X[3]	X[3]	X[3]	X[3]	X[3]
Blood Routine	X[4]					X	
Infectious diseases screening	X[4]						
Serum Creatinine	X[4]		X[6]			X	
Liver function test	X[4]		X[7]			X	
Serum glucose	X[4]						
Serum lipid	X[4]						
CK / CK-MB	X[4]		X[8]				
Troponin I or T	X[4]		X[8]				
Physical examination and/or Ischemic status	X		X	X	X	X	X
Intervention		X					
Angiography		X[9]				X[10]	
12-lead ECG	X[5]		X[11]			X	

1. For premenopausal women, a pregnancy test must be performed within 72 hours prior to angiography
2. Procedure Medication
3. Anti-platelet/anti-coagulant medical therapy
4. Within 7 days prior to procedure
5. Within 72 hours prior to procedure
6. Serum Creatinine within 24 hours post-procedure
7. Liver function test(ALT、AST) within 24 hours post-procedure
8. CK & CK-MB & Troponin within 6-24 hours post-procedure
9. Angiography of all procedure steps and Pre- and Post- procedure in two orthogonal views
10. Angiography in the same two orthogonal views as at index procedure
11. ECG within 6- 24 hours or before discharge

5.8 Unscheduled Coronary Angiogram Follow Up

Any unplanned angiography and revascularization must be followed by a full clinical evaluation. The required data is to be entered into the eCRF. All films must be sent to the angiographic core laboratory for review.

- If the subject undergoes a clinically driven angiography within 6 months post procedure, having no re-intervention of the target lesion(s), the subject must return for the angiographic follow up visit, 9months post procedure.
- If the subject undergoes a clinically driven angiography between 6-9 months post procedure, this will be considered as the 9 months follow up angiography.
- If the subject has a re-intervention for in-stent restenosis at any time prior to the 9 months follow up the subject will not have an additional angiography at the 9 months follow up visit.
- However, if the subject has two treated target vessels with the study stent, whereof only one was re-intervened, the subject must return for the repeat angiography at the 9 months follow up visit. If one had revascularization and in-stent restenosis during 6-9 months, the 9 months follow up visit is not needed.

5.9 Treatment Failures

Failure to implant the study stent at the intended target lesion must be recorded on the Case Report Form as a treatment failure. If possible and feasible, another study stent will be chosen as first choice to treat this lesion.

5.10 Additional Stent Treatment

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

5.11 Bailout-Staged Procedure

Planned staged procedures are not allowed in this clinical investigation. If during the intervention it becomes clinically necessary to postpone the treatment, this is regarded as a staged procedure and must be documented in CRF.

6 CLINICAL INVESTIGANTION PLAN DEVIATIONS

A Clinical Investigational Plan (CIP) deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the clinical investigation.

All measures must be undertaken to avoid deviations from the CIP. Deviations from the CIP must

be documented in the Case Report Form. Original clinical information should be reserved to report the reasons of plan deviations.

Investigators must also adhere to procedures for reporting CIP deviations to their Ethic Committee (EC) in accordance with their specific EC reporting guidelines and procedures. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

7 Study Participation Status

7.1 Status Definitions

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

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

Enrolled- A provisionally enrolled subject who meets all clinical and angiographic eligibility criteria, and has been randomized. These subjects will be followed in accordance with the protocol requirements.

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

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

7.2 Subject Study Exit

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

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

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

In any of the situations noted above, data collected up to and including the exit of the subject will be used in data analysis. No data will be collected after the exit of the subject from the study. Study exits are expected and will be taken into consideration during data analysis as described. Additionally, subject attrition has been calculated into the study sample size. Therefore, all subjects exited from the study will be counted toward the randomization goal and will not be replaced. Investigators must document, in subject medical records, the reasons and circumstances for all subject exits.

In cases where further participation in the study poses potential risk to the subject, study exit should

be considered. In addition to subject safety, consideration should be given to the scientific validity of the primary endpoints when making decisions concerning subject exit. Study follow-up options and requirements for subjects exiting from the study should be determined and applied to all subjects exiting for similar reasons. Deviations in subject eligibility, as defined in the protocol, should be considered protocol violations and reported to the Institutional Review Board (IRB) or Ethics Committee (EC) immediately upon discovery, in accordance with local regulations.

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. Identification of vital status will be handled at the investigational site level. Subjects have the right to discontinue from the study at any time or be discontinued at the investigator's discretion.

7.2.1 Subject Lost to Follow-up

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

If the subject is able to be contacted, all efforts should be made to perform the required study visit and complete the relevant case report forms. However, if a subject is contacted and a study visit cannot be performed, the study site should complete the relevant case report forms with any relevant data obtained from the subject contact by phone. If a subject is unable to be contacted at any of the remaining study visits, either a missed visit will be entered for each visit or the subject may be exited as lost to follow-up, using the date of last actual contact as the study exit date.

Likewise, due to unforeseen circumstances, subjects may relocate during the course of the study and may no longer be able to return for study follow-up visits. Attempts to collect data from these subjects should be made by the investigator in collaboration with the subject's new provider. All data that is obtained may be utilized in data analysis, but it should be documented that it was collected by an unapproved investigator. If no data can be collected from the subjectas collected by an unapproved investigator. If or study follow-up visits. Attempts to collect data from these subjects should be made by the invest

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

8 DATA REPORTING AND STATISTICAL ANALYSIS

8.1 Determination of Sample Size

The calculation of the sample size is based on the primary endpoint only: In-stent late lumen (LLL). The trial is based on a non-inferiority hypothesis test, with 2 groups (Orsiro and Xience stents), with a sample allocation ratio 1:1

Since Late Lumen Loss is a quantitative variable and the sample size will be larger enough (at least 200 subjects per group) to invoke the Central Limit Theorem, a student's t-test for independent samples will be used. And since it is a non-inferiority hypothesis, only 1-tail will be tested.

In order to put forward a reasonable LLL hypothesis, data from three different studies is considered. The values are related to in-stent Late Lumen Loss and are displayed in the Table 3.

In-stent Late Lumen Loss (Table 3)							
Product	Study	N	Fup	mean	std. dev.	95% CI	%CV
Xience	Resolute Vs Xience	220	13 mths	0.19	0.40	[0.14,0.24]	211%
	Bioflow II	172	9 mths	0.11	0.29	[0.07,0.15]	264%
	Xience VS Paclitaxel	772	8 mths	0.14	0.41	[0.11,0.17]	293%
Orsiro	Bioflow II	332	9 mths	0.10	0.32	[0.07,0.13]	320%

According to the above data, we first calculate the weighted mean of the control group Xience:
Table 4

Product	n	Mean	N*Mean
Xience	220	0.19	41.80
	172	0.11	18.92
	772	0.14	108.08
Orsiro	332	0.10	33.20
Total	1496		202.00

$$\bar{x} = \frac{n_1\bar{x}_1 + n_2\bar{x}_2 + \cdots + n_k\bar{x}_k}{n_1 + n_2 + \cdots + n_k}.$$

The final weighted mean is 0.14 and assum that both Orsiro and Xience can achieve tha same LLL level.
About non-inferiority study: .

$$H_0: \mu_{Orsiro} - \mu_{Xience} > \Delta$$
$$H_A: \mu_{Orsiro} - \mu_{Xience} \leq \Delta$$

μ_{Orsiro} is the LLL level of Orsiro stent at 9 month, and μ_{Xience} is the LLL level of Xience stent at 9 month.

It was assumed $\mu_{orsiro} = \mu_{Xience} = 0.14$; standard deviation for the Late Lumen Loss mean at 9 months is equal for both stents; $\sigma_{Xience} = \sigma_{Paclitaxel} = 0.41$ (the max value for all tests in table 3); $\Delta = 0.41/3 = 0.137$; power of 85%; $\alpha = 0.025$; test: one-sided student's t-test for independent samples; 25% loss for follow-up. Each group of 162 subjects per group, needs to confirm the hypothesis, as well as 216 subjects per group considering a 25% loss for follow-up..

The calculation formula of sample size:

$$n_1 = n_2 = 2\left[\frac{(u_\alpha + u_\beta)}{\Delta/\delta}\right]^2 + \frac{1}{4}u_\alpha^2$$

8.2 Statistical Analysis

8.2.1 The study population is divided into the following categories

- Full analysis set (FAS): The subjects set determined by the intention to treat (ITT) principle refers to the data set constituted by all the subjects participating randomly, using investigational devices and having a baseline curative effect evaluation.
- Per protocol analysis (PPS): Refer to the treatment subpopulation eliminating the serious violation

cases.
- Safety analysis set (SS): Refer to the subjects set receiving randomization and minimal one safety evaluation post baseline.

The curative effect evaluation is on the basis of FAS and PPS. All the baseline demographic statistical analysis is on the basis of FAS, and the safety evaluation is on the basis of SS.

8.2.2 The statistical analysis method

Descriptive analysis: Count data is described by proportion, meterage data is described by mean, standard deviation, maximum, minimum description, median, the 25th and 75th percentile.

Baseline demographic statistical analysis: Comparison between groups of count data adopts continuous correction of the $\chi 2$ test. When a cell theory frequency is exceeding 25% is less than 5, use the Fisher exact test. Comparison between groups of normal distribution meterage data adopts the group t-test (two groups) or variance analysis (multigroup). Comparison between groups adopts the Wilcoxon Rank Sum test.

Curative effect evaluation: After the test of homogeneity of variance in each center for the primary endpoint of in-stent LLL, comparison between groups uses covariance analysis of adjustment center and baseline effect, and provides the minimum mean square of dependent variable (LLL), minimum variance between groups and 95% confidence interval. For other curative effect indexes, group comparison of normal distribution meterage data adopts the paired t-test. Group comparison of abnormal distribution meterage data adopts the Wilcoxon Sign Rank test. The method of comparison between groups is the same as a baseline analysis.

Safety evaluation: According to the investigational and control group, describe the normal number and proportion pre-procedure, and the abnormal number and proportion post procedure respectively. Use the number and incidence of cases to describe the adverse event, and use the continuous correction of $\chi 2$ test or the Fisher exact test for this ratio. Meanwhile, describe in detail the relationship between the specific performance, extent of all the adverse events in each group and the stent implantation.

All the statistical analyses will be conducted at the bilateral, 0.05 significant level. Use SAS® 9.13 statistical software for statistical analysis, and EPIDATA 3.0 entry software for data management.

9 DATA COLLECTION, MONITORING, INSPECTIONS AND AUDITS

9.1 Data collection- eCRF

All required data for this clinical investigation will be collected on eCRF. All site staff must be trained on the correct completion of eCRF before they are given access for data entry.

Subjects will only be identified in eCRFs by a unique reference number, month and year of birth. eCRFs are confidential documents and will only be available to BIOTRONIK, the investigator, the clinical investigation statistician, and competent authority. Each site should keep all subjects' document for follow-up.

Appropriate internet access is required for data entry.
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9.2 Monitoring

Monitoring will be performed by BIOTRONIK or by BIOTRONIK designees, to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the CIP, Declaration of Helsinki, ISO 14155:2011(E) and GCP, to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

During monitoring visits, the clinical monitor will perform source data verification as defined in the monitoring plan. For this purpose, the investigator must permit access to medical/subject records (source data) throughout the clinical investigation. In the case of electronic medical/subject records, the Investigator has to ensure that the monitor receives appropriate access or that print outs of all clinical investigation or relevant source documents is given.

9.3 Audits

Study centers may be audited during and after the course of the clinical investigation by BIOTRONIK, ethic committees and other applicable regulatory authorities, and provide all subjects' medical data.

If an auditor becomes aware that investigation is not complying with the requirements mentioned above, the auditor is obliged to notify BIOTRONIK. BIOTRONIK will evaluate the non-compliance and issue corrective actions, discontinue enrolment or, as a last measure, close the clinical investigation site. In such a case, the investigator must return all unused devices to BIOTRONIK.

9.4 Source documentation

All clinical record must be recorded and maintained in the medical files and saved in each investigational center's National Drug Clinical Trial Institution. All the source data and CRF should be saved for ten years after the investigational product appears on the market. The clinical information must contain, but is not limited to, the following information:

- Date of informed consent
- Subject participation in the clinical investigation
- Demographics
- Date of the discharge
- Documentation of medical/surgical history and previous medication
- Vessel and lesion sizes and characteristics
- All angiographies, ECGs
- Cardiac ischemia/anginal status
- Description of interventional procedure (material used, drugs administered during the procedure, date, time, complications etc.)
- All adverse event(s): Diagnosis and symptom(s), onset and end date, severity, action taken, outcome
- Concomitant medication
- Date of clinical investigation completion or withdrawal

The following additional documents are considered as source

- Subject's contact information
- SAE reports

9.5 Data Management

The data manager is responsible for providing a clean data set at the end of the clinical investigation. Queries should be resolved by the investigator or a person designated by the investigator

in a timely manner. When all data is complete the database will be locked and the data analyzed.

9.6 Record Retention

All clinical investigation records and reports must remain on file at the clinical investigation centers by the national legislation. The investigator must contact BIOTRONIK before destruction of any records and reports related to the clinical investigation. BIOTRONIK must be informed if the investigator plans to leave the clinical investigation site. In such case the site must name a new contact person before the investigator parts from the clinical investigation site.
BIOTRONIK is responsible for retaining the Trial Master File (TMF) according to national legislation and BIOTRONIK Standard Operating Procedure (SOPs)..

10 APPROVALS of Investigation

10.1 Ethics Committee Approval

Prior to the clinical investigation, the investigator is responsible for submitting the clinical investigational plan, informed consent form and relative files to Medical Ethics Committee of the hospital. Approval from the EC must be acquired prior to initiating the clinical investigation. Any modification of the study plan must be approved by the EC before initiating. Any severe adverse event that happened during investigation must be reported to the EC in written form.

The investigator has the obligation to submit the applicable document for ethical approval to the EC, and meanwhile, a copy of this document should be provided to BIOTRONIK. A copy of the EC opinion, approval and EC voting members list should also be provided to BIOTRONIK. If further information is needed by the EC, the investigator should submit these in time.

The investigator must report to the EC any new information that may affect the safety of the subjects or the conduct of the clinical investigation.

Upon completion of the clinical investigation, the investigator shall provide the EC with a brief report on the outcome of the clinical investigation as required by the local EC.

10.2 Competent Authority Approval

BIOTRONIK is responsible for obtaining approval from the Competent Authority (CA), if applicable, prior to any site initiation. BIOTRONIK must report to the CA any new information that may affect the safety of the subjects or the conduct of the clinical investigation.

10.3 Investigator Responsibilities

Prior to shipment of the first clinical investigation device and first implantation, the investigator must read and sign this CIP as well as the Investigator's Agreement prior to enrolling any subjects national and local regulatory requirements must be fulfilled.

Each clinical investigation site must have, but is not limited to, the following documents:

- Competent authority approval (GCP Certification)
- Ethics committee approval
- Signed investigator's agreement
- Signed and dated CVs for all investigators participating in the clinical investigation.
- Laboratory Accreditation and the normal ranges

10.4 Investigational Device Accountability

10.4.1 Traceability Records

A device accountability system will be maintained during the clinical investigation at each site; documenting device use at the site. Date of use, size, reference and lot numbers of the BIOTRONIK Orsiro will be documented in the eCRF system.

10.4.2 Change of Device

All device failures and malfunctions should be reported in the e-CRF and the stent should be returned to BIOTRONIK.

10.5 Non-CIP Research

BIOTRONIK has a legal responsibility to the regulatory authorities to fully report all the results of sponsored clinical studies. No investigative procedures other than those stated in this CIP shall be undertaken on the enrolled clinical investigation subjects without the agreement of the EC and BIOTRONIK

10.6 Amendments to the CIP

Amendments to the CIP should be confirmed by BIOTRONIK. All changes must be documented in a signed CIP amendment. All amendments must be submitted to the EC for approval prior to implementation.

10.7 Subject Insurance

Subjects who participate in this study will be insured against study related injury. BIOTRONIK has issued clinical trial liability insurance with appropriate coverage for the continuation of the entire study.

11 SAFETY

During the course of this clinical investigation, adverse events may occur. Adverse event information will be collected throughout the clinical investigation in the eCRF by the investigator or by the investigator delegated person. Any adverse event should be followed until it is resolved or resolved with sequelae. Based on the nature and/or the severity of the event it is categorized as either:

- Adverse Event
- Serious Adverse Event
- Adverse Device Effect
- Serious Adverse Device Effect
- Unanticipated Serious Adverse Device Effect

11.1 Reporting to Sponsor (BIOTRONIK)

Adverse events classified to be 'serious' will be reported to BIOTRONIK within 24 hours after awareness by the investigator. Reporting should be done using the 'Adverse Event Form' in the EDC, email or

the fax number indicated in the investigator file. According to the Clinical Event Committee (CEC)'s requirment, the investigator is obliged to provide all kinds of source data about the serious adverse event, and then scan and upload these to the EDC system . If additional information or documentation is needed the clinical project manager or a designee will contact the investigator to retrieve the necessary information.

Primary Contact for Serious Adverse Events Reporting at BIOTRONIK is:

Jing Wang
National Clinical Study Manager
Phone: 021-65223851-852
Fax: 021-65223852

11.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence (including abnormal laboratory findings) in subjects, whether or not related to the investigational medical device

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

Relation to the clinical investigation device and procedure will be assessed

11.2.1 List of Anticipated Adverse Events

The anticipated adverse events are those related to regular percutaneous interventions, including drug and polymer.

The following adverse events may be associated with the use of coronary stenting devices, PTCA:

- Cardiac events: including MI (determine whether or not it is related to PCI's acute MI, the troponin should > 5 times of the normal upper limit) or unstable angina, coronary artery occlusion, coronary artery rupture, coronary artery spasm, restenosis of the treated coronary artery (restenosis >= 50%), cardiogenic shock, cardiac tamponade, puncture or tear of coronary artery or aorta, cardiac perforation, emergency surgery (peripheral vessel or CABG), pericarditis, pericardial effusion.
- Arrhythmia events: VT, VF, atrial fibrillation, atrio ventricular block.
- Stent system events: no stent delivered to the target lesion, dislocation from the delivery system, stent dislocation, stent deformation, thrombosis in stent, thrombogenesis in stent, stent fracture, stent migration, stent compression, balloon filling shortage, balloon rupture, catheter withdrawal difficulties.
- Disease of the respiratory system: acute pulmonary edema, respiratory failure
- Vessel events: pain in the pucture position, bleeding or hematoma, high/low blood pressure, aneurysm, pseudoaneurysm, arteriovenous fistula, retroperitoneal hematoma, acute vascular occlusion, vascular tear or perforation, vascular stenosis, thrombosis or occlusion, vasospasm, peripheral ischemia, distal embolization (air, fat).
- Nervous system: stroke or TIA, periphery or femoral nerve injury.
- Bleeding events: bleeding or hematoma at the position of puncture, bleeding events which need a blood transfusion or other treatment.

- Allergic reaction to contrast agent, antiplatelet medicine, stent coating, anticoagulant drug, cobalt-chromium alloy, sirolimus and everolimus.
- Death

The occurrence of the above listed adverse events may lead to repeat revascularization, MI, emergency bypass surgery, or death.

The side effects/adverse events of the PLLA polymer are no different than those of other stent coatings and may include but are not limited to the following:

- Allergic reaction
- Focal inflammation at the site of stent implantation
- Restenosis of the stented artery

Potential adverse events related to sirolimus drugs (following oral administration) include but are not limited to:

- Abnormal liver function test
- Anemia
- Asthralgias
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including anaphylactic/anaphylactic type reactions
- Hypertriglyceridemia
- Hypokalemia
- Infections
- Interstitial lung disease
- Lymphoma and other malignancies
- Thrombocytopenia

11.3 Serious Adverse Events

In case any of the following criteria is applicable to the Adverse Event it classifies as Serious Adverse Event.

- Led to in-patient or prolonged hospitalization
- Led to injury
- Led to operational capability affected
- Led to serious deterioration in the health of the subject
- Led to permanent impairment of a body structure or a body function
- Led to the injury need intervention treatment
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

11.4 Adverse Device Effects (ADE) & Serious Adverse Device Effects (SADE)

An adverse device effect is an adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from misuse and the adverse events because of the device itself.

If an ADE or SADE has occurred, any retrievable part of the Orsiro Stent System should be returned to BIOTRONIK AG or audit company for analysis.

11.5 Unanticipated Serious Adverse Device Effects (USADEs)

USADE is any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

11.5.1 CEC

The CEC is composed of three independent physicians with excellent experience in the targeted indication. The CEC will adjudicate all reportable SAEs, ADEs, SADEs, and UADEs in the clinical investigation.

BIOTRONIK will supervise and ensure that the centers provide source documents for the CEC to analysis. Final adjudication of the event will be done by the CEC. The adjudication by the CEC will overrule the one of the investigator, should the investigator and CEC disagree.

12 RISK ANALYSIS

12.1 Risks

For more detailed information on the risks of implantation of both stents, including a complete list of warning, precautions and potential adverse events, please refer to the Instructions for Use of both devices, which are provided with the products.

Anticipated adverse events for the BIOTRONIK Orsiro SES, including events related to regular PCI, as well as risks related to angiography are listed in section 11.3

This study will collect data prospectively on subjects that are randomly assigned to be implanted with either the Orsiro SES or the Xience Prime™ EES. Both investigation devices have received the CE mark. Implantation of the devices will therefore not bring additional risk to the subjects.

However, the study will put some additional risk to the subjects compared to routine procedures:

- All subjects will undergo repeat angiography at 9 months.
- ECG's will be required at screening and prior to discharge. Clopidogrel will be administered for a minimum of 12 months in all subjects unless medically contraindicated.

12.2 Benefits

In this clinical investigation all subjects will have a more intense medical follow ups then in standard practice, which can be beneficial to the long term clinical outcome for the individual.

In addition, two CE marked drug eluting stents will be used which are developed with the latest technology of medicine coating.

General benefits include that data will be used to retrieve more information on the safety and efficacy of the Orsiro SES or the Xience Prime™ EES.

13 STUDY TERMINATION

BIOTRONIK will monitor the progression of the clinical investigation. The clinical investigation

may be suspended or discontinued early if there is an observation of serious adverse event.

BIOTRONIK may terminate investigator and site participation in the clinical investigation if there is evidence of failure to maintain adequate clinical standards, failure to comply with the CIP, fraud or any other form of misconduct. In the event of clinical investigation termination or suspension, BIOTRONIK will send a report outlining the circumstances to the EC, CA if applicable, and all investigators. A suspended or terminated clinical investigation may not be re-initiated without approval of the reviewing EC and CA.

14 FEASIBILITY ANALYSIS

14.1 Feasibility analysis of success

The Orsiro Sirolimus Eluting Stent (SES) is based on the design of PRO-Kinetic ENERGY™ stent system. The predecessor product, PRO-Kinetic™, has been proven to be both safe and effective in the treatment of coronary lesions. The PTCA delivery system of Orsiro and PRO-Kinetic ENERGY are nearly identical, based on a fast-exchange PTCA catheter. This product is supposed to be safe and efficacious.

14.2 Feasibility analysis of failure

The main reasons leading to procedure failure or adverse effects may be related to the following factors: 1) procedure proficiency; 2) post-procedure nursing level; 3) uncertainty of the pre-procedure disease progression of the patient.

15 FINAL REPORT

The clinical trial report should be consistent with the study protocol, which shall be signed and dated by the investigators, then be audited, sealed and dated by the clinical trial institution of medical device. The final report shall ensure the authenticity and confidentiality of the clinical data.

16 PRINCIPLE OF CONFIDENTIALITY

All the ancillary data of this agreement and clinical study are confidential and belong to the sponsor. Investigators should take the duty of confidentiality, including patent applications, manufacturing process and the unpublished data which the sponsor has provided to the researchers, and shall not disclose to any third party unless they get the sponsor's agreement. The obligation of confidentiality is still effective after the termination or closure of the study.

17 PUBLICATION POLICY

The investigator has the right to write a thesis and report about this investigation. However, the investigator should notice the sponsor in writing before publishing and should not violate the agreed duty of confidentiality.

18 COMPLIANCE STATMENT

The execution of clinical investigation shall comply with the applicable human clinical trials and regulations, especially the followings:

- Declaration of Helsinki (Fortaleza 2013 version)

- ISO 14155 (2011 version)
- ICH/GCP (2002 version)
- Related requirements applicable to the country and local

The clinical investigation shall only be implemented when approved by the Ethics Committee and relative monitoring organizations. Meanwhile, the investigation must meet any related requirements from the EC and monitoring organizations.

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Declaration of investigator:
I agree that:
1. Implement the clinical investigation strictly according to the Declaration of Helsinki, Chinese existing laws and regulations, and the investigation plan.
2. Record all the needed data correctly in the CRF, and finish the clinical investigation final report on time.
3. Only use the investigational product in the clinical investigation. During the process, record and save the received and useful information of the investigational product completely and correctly.
4. Allow the auditor and supervision department authorized or delegated by the sponsor to audit and inspect the clinical investigation.
5. Strictly comply to the clinical investigation contract and terms of relative agreement signed by both parties.

I have read all contents of the clinical investigation plan and the above declaration. I agree with all the requirements listed above.

Clinical Investigator	Department	Duty	Title
Illegible	Cardiology (5)	Chief Physician	Chief Physician
Wang Lin	Cardiology (5)	Illegible	Associate Chief Physician

Opinion from the EC:

(seal: illegible)
Sep 14, 2015

Opinion from the medical institution undertaking the clinical investigation:

(seal: illegible)
Sep 24, 2015

Opinion from the implementer:

(seal: illegible)
July 3, 2015

Appendix – Enterprise Qualification Files