Orsiro®

Sirolimus Eluting Coronary Stent System

English

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

STERILE EO

BIOTRONIK
excellence for life

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1 Description

The Orsiro® Sirolimus Eluting Coronary Stent System (hereinafter Orsiro) is a drug- eluting balloon-expandable stent that is pre-mounted on a fast-exchange PTCA catheter delivery system with a working length of 140 cm. There are two stent configurations - small and medium. Their respective diameters and lengths are shown in Table 2.

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 nominal strut thicknesses are 60 µm for the small stent diameters and 80 µm for the medium stent diameters.

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 a 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.

The proximal shaft of the delivery system is a hypotube and has a single luer port for connecting an inflation/deflation device to inflate/deflate the balloon. The catheter has a hydrophobic coating on the outer surface of the proximal shaft and a hydrophilic coating on the outer surface of the distal shaft. The guide wire lumen starts at the delivery system tip and ends at the guide wire exit point 29cm from the distal end.

Orsiro is compatible with guide wires with a diameter of 0.014" (0.36 mm) and guiding catheters with an inner diameter of ≥ 0.056" (1.42 mm).

To indicate when the delivery system tip exits from the guiding catheter, shaft exit markers are located on the hypotube 92 cm (brachial technique) and 102 cm (femoral technique) from the distal end of the delivery system.

The click-in hypotube fastener on the hub is designed to facilitate the handling of the stent system when it is stored on the preparation table.

Table 1: Product Description

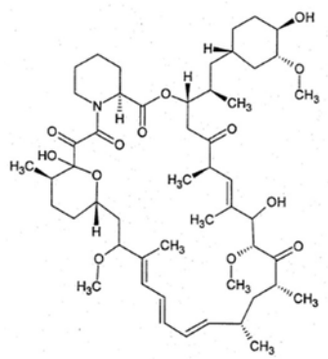
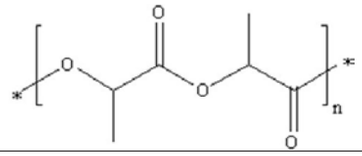
Stent Material		Cobalt chromium alloy (L-605)
Stent Geometry		Circular end segments, a transition zone and repeating helical segments which are connected by three interconnecting longitudinal struts
Drug Component	Drug Substance	SIROLIMUS 23,27-Epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine (-)-Rapamycin 
	Polymer Carrier	PLLA Poly(L-lactide) 
Nominal Drug Content		1.4 µg of sirolimus per mm²
Guiding Catheter Compatibility		Inner diameter of ≥ 0.056" (1.42 mm)
Guide Wire Compatibility		Diameter of 0.014" (0.36 mm)

Table 2: Nominal Product Specifications

Stent Design			SMALL				MEDIUM	
Strut Thickness			60 µm*				80 µm	
% Stent Free Area			70%	73%	75%	77%	80%	82%
Sizes	Stent Inner Diameter (mm)		2.25	2.50	2.75	3.0	3.5	4.0
	Stent Length (mm)	9	X	X	X	X	X**	X
		13	X	X	X	X	X	X
		15	X	X	X	X	X	X
		18	X	X	X	X	X	X
		22	X	X	X	X	X	X
		26	X	X	X	X	X	X
		30	X	X	X	X	X	X
		35	-	X	X	X	X	X
		40	-	X	X	X	X	X

* mean value 62 µm
** % stent free area is 79% for size 3.5/9

Table 3: Total Drug Load

Stent Design		SMALL				MEDIUM	
Stent Inner Diameter (mm)		2.25	2.50	2.75	3.0	3.5	4.0
Stent Length (mm)	9	55 µg				70 µg	
	13	80 µg				95 µg	
	15	93 µg				113 µg	
	18	109 µg				131 µg	
	22	134 µg				162 µg	
	26	159 µg				193 µg	
	30	184 µg				224 µg	
	35	213 µg				261 µg	
	40	247 µg				298 µg	

2 How Supplied

Sterile. Non-pyrogenic. Device is sterilized with ethylene oxide.

3 Contents

- One (1) Stent System and one (1) Compliance Chart in a sealed peel-open pouch.
- One (1) Patient Implant Card.

4 Storage

Store in a dark, dry location at max. 25°C / 77°F.

5 Indications for Use

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

6 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.

7 Warnings

- This device is designed and intended for single use only. Do not re-sterilize and/or re-use. Re-use of single-use devices creates a potential risk of patient or user infections. Contamination of the device may lead to injury, illness or death of the patient. Cleaning, disinfection and sterilization may compromise essential material and design characteristics leading to device failure
- Do not use the stent system if the outer package and/or inner package are/is damaged or opened, or if any information provided is obscured or damaged.
- Do not use device after the 'use by date' indicated on the label.
- Do not attempt to remove or readjust the stent on the delivery system as it may damage the stent, polymer system and/or lead to stent embolization. The stent must not be removed from its dedicated delivery system and placed on another balloon catheter.
- Do not expose and/or suspend the stent within any liquid solution on the sterile field prior to the preparation and the insertion as the drug carrier coating may be susceptible to damage or premature drug elution.
- Administration of appropriate anticoagulant, antiplatelet and vasodilation therapy is critical to successful stent implantation (refer to the "Patient Selection/ Individualization of Treatment" and "Pre- and Post-procedure Antiplatelet Therapy" sections).
- Manipulate the stent system under angiographic guidance when it is in the body.
- Use stents with a similar composition when multiple stents are required to treat the lesion as the risk of corrosion increases when stents of dissimilar metals contact one another.
- Do not exceed the original diameter of the vessel proximal and distal to the lesion when inflating the balloon to reduce the potential for vessel damage.
- Balloon pressure should not exceed the Rated Burst Pressure (RBP). Use of a pressure-monitoring device is mandatory to prevent over-pressurization.
- Use only an appropriate balloon inflation medium (e.g. 50:50 mixture by volume of contrast medium and saline). Never use air or any gaseous medium to inflate the balloon.
- Subsequent restenosis may require repeat dilation of the arterial segment containing the stent. The long-term outcomes following repeat dilation of endothelialized stents are unknown.
- Use outside of the specified indications is prohibited. The use of DES in patients and lesions outside the labeled indications may have an increased risk of adverse events, including stent thrombosis, stent embolization, myocardial infarction (MI) or death.

8 Precautions

8.1 General Precautions

- This device should only be used at medical facilities by physicians who are adequately trained and experienced in performing vascular interventions (including cases of life-threatening complications).
- If the stent system was removed prior to expansion, Do not re-insert as the stent and/or the delivery system may have been damaged during the initial attempt to cross the lesion or during withdrawal (refer to the "Special Retrieval Techniques" section for instructions).
- This device carries an associated risk of thrombosis, vascular complications and/or bleeding events. Therefore, careful selection of patients is critical (see "Patient Selection/Individualization of Treatment" section). The long-term effects of DES and the risks associated with these implants are unknown. The limited availability of long- term clinical data should be considered before making a risk/benefit assessment for the patient prior to implantation.
- Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death. Data from the BIOFLOW clinical trials have been prospectively evaluated and adjudicated using the definition developed by the Academic Research Consortium (ARC) (see "Clinical Studies" section for more information). The rate of stent thrombosis for Orsiro was low in the BIOFLOW clinical trials and did not differ significantly from expectations for a current generation DES.
- The patient's exposure to the drug and polymer system is directly related to the number of stents and the stent length implanted.
- Potential interactions of Orsiro with other DES have not been evaluated and should be avoided whenever possible.

8.2 Pre- and Post-Procedure Antiplatelet Therapy Recommendations

Antiplatelet/anticoagulation medication should be used in combination with Orsiro.

Physicians should consider the information from the current drug-eluting stent literature and the current ACC/AHA guideline recommendations on PCI concerning the selection, dosage, duration and combination of different antithrombotic drugs. Specific needs and the risk profile of individual patients may influence the antiplatelet/anticoagulation regime to be used.

In the BIOTRONIK BIOFLOW-V Clinical Trial, dual antiplatelet therapy (DAPT) with aspirin and a p2Y12 inhibitor was administration prior to the index procedure and then continued for a minimum of 6 months. The protocol highly recommended continuing DAPT for 12 months in subjects who were not at a high risk of bleeding. Aspirin was recommended to be continued indefinitely to reduce the risk of thrombosis. In the BIOTRONIK BIOFLOW-V Clinical Trial, 96.2% and 91.8% of the subjects remained on dual antiplatelet therapy at 6 months and 12 months, respectively.

The optimal duration of antiplatelet therapy, specifically P2Y12 inhibitor therapy, is unknown and DES thrombosis may still occur despite continued therapy. Provided herein are recent recommendations for post-procedural antiplatelet therapy from the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease; see the "Oral Antiplatelet Therapy" section below. Also refer to the "Warnings" and "Clinical Studies" sections for more information on DAPT usage.

8.3 Oral Antiplatelet Therapy

Dual antiplatelet therapy (DAPT) using a combination treatment of aspirin with a P2Y12 platelet inhibitor after percutaneous coronary intervention (PCI) reduces the risk of stent thrombosis and ischemic cardiac events but increases the risk of bleeding complications. The optimal duration of DAPT (specifically, a P2Y12 platelet inhibitor in addition to aspirin) following DES implantation is unknown, and DES thrombosis may still occur despite continued therapy. It is very important that the patient is compliant with the post-procedural antiplatelet recommendations.

Per 2016 ACC/AHA guidelines[1], a daily aspirin dose of 81 mg is recommended indefinitely after PCI. A P2Y12 platelet inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS).

Consistent with the DAPT Study[2] and the 2016 ACC/AHA guidelines, longer duration of DAPT may be considered in patients at higher ischemic risk with lower bleeding risk.

In patients at higher risk of bleeding, DAPT discontinuation may be reasonable after 3 months in stable patients or 6 months in ACS patients.

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and patient preference.

Premature discontinuation or interruption of prescribed antiplatelet medication could result in a higher risk of stent thrombosis, MI or death.

Prior to PCI, if premature discontinuation of antiplatelet therapy is anticipated, physicians should carefully evaluate with the patient whether a DES and its associated recommended DAPT regimen is the appropriate PCI choice.

Following PCI, if elective non-cardiac surgery requiring suspension of antiplatelet therapy is considered, the risks and benefits of the procedure should be weighed against the possible risk associated with interruption of antiplatelet therapy.

Patients who require premature DAPT discontinuation should be carefully monitored for cardiac events. At the discretion of the patient's treating physician(s), the antiplatelet therapy should be restarted as soon as possible.

1 Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016; doi:10.1016/j.jacc.2016.03.513. For full text, please refer to the following website: http://content.onlinejacc.org/article.aspx?doi=10.1016/j.jacc.2016.03.513

2 Mauri L, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents. N Engl J Med. 2014;371:2155–66.

8.4 Handling Precautions

- Prior to procedure, the stent system should be visually examined to ensure that the stent is centered between the two radiopaque markers on the balloon and that its size is suitable for the specific procedure for which it is to be used.
- Exercise care during device handling to reduce the possibility of disrupting the delicate placement of the stent on the balloon and accidental breakage, bending, kinking of the stent system shaft. Special care must be taken not to handle or in any way disrupt the drug coating of the stent. This is important during catheter removal from the packaging, placement over the guide wire and advancement through the rotating hemostatic valve adapter and the guiding catheter hub.
- The click-in hypotube fastener is intended to hold only the hypotube section of the delivery system; the distal shaft should not be held by the click-in fastener.
- Take care when removing the stent system from the spiral packaging as forceful movements may dislocate the protector and the stent.
- When removing the stent protector, always pull at the very distal end of the protector to avoid dislocation of the stent. DO NOT touch the part of the protector over the stent.
- Avoid excessive manipulation of the stent during flushing of the guide wire lumen. Special care must be taken not to handle or in any way disrupt the stent coating a n d the stent itself on the balloon. Manipulation e.g. rolling the mounted stent with your fingers may loosen the stent from the delivery system balloon and cause dislodgement. Should there be movement of or damage to the stent, DO NOT use.

information.

8.5 Stent Placement Precautions

If the stent system is unable to reach/cross the lesion easily, stop the procedure and follow the instructions listed under “Removal of an Unexpanded Stent” subsection. In order to avoid causing damage to the stent/coating and/or premature dislodgement of the stent from the balloon or its centered positioning on the balloon:

- Do not apply negative pressure to the stent system at any time prior to the placement of the stent across the target lesion.
- Do not apply excessive force while attempting to cross the lesion.
- Do not force the passage if any resistance is felt at any time during lesion access. Determine the cause of resistance before proceeding.
- Do not attempt to move an unexpanded stent in and out through the distal end of the guiding catheter.
- Ensure that the rotating hemostatic valve of the guiding catheter is fully open when inserting and positioning the stent system.

For correct stent placement:

- Do not torque the catheter more than one (1) full turn.
- Ensure that the guide wire exit port, 29 cm from the distal tip of the delivery system, remains in the guiding catheter during the procedure.
- Do not inflate the balloon if vacuum cannot be held, as this indicates a leak in the delivery system. If a vacuum cannot be held, follow the instructions listed under the “Removal of an Unexpanded Stent" subsection.
- Placement of a stent has the potential to compromise side branch patency.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion and could cause an acute closure of the vessel and require additional intervention (e.g. coronary artery bypass grafting, further dilation or placement of additional stents).
- Do not post-dilate the stent to more than the maximum expandable diameter.
- Avoid barotrauma outside the stent margins during post-dilation.
- Additional expansion of a deployed stent may cause a flow limiting dissection. This may be treated by implanting another stent. When multiple stents are implanted, the ends should overlap slightly.
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent in placement of the distal stent and reduces the risks for dislodging the proximal stent.
- The use of brachytherapy treatment, mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters to treat in-stent restenosis is not recommended.

8.6 Stent/Delivery System Removal Precautions

- If an unusual resistance is felt at any time during the procedure or when removing the stent/delivery system, refer to the "Special Retrieval Techniques" section for correct removal steps. Failure to follow these instructions may potentially result in loss or damage to the stent and/or delivery system components.
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications can include bleeding, hematoma or pseudoaneurysm.

8.7 Post-implant Precautions

- Exercise care when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter or any other device to avoid disrupting the stent placement, apposition, coating or stent geometry.
- Refer to the “MRI Safety Information” section for the stent’s MRI compatibility

8.8 Use in Special Populations

8.8.1 Pregnancy

Pregnancy Category C. There are no well-controlled studies in pregnant women or men intending to father children. The Orsiro stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus. Effective contraception should be initiated before implanting an Orsiro stent and for 1 year after implantation.

8.8.2 Lactation

A decision should be made whether to discontinue nursing prior to stent implantation, taking into account the importance of the stent to the mother.

8.8.3 Gender

The BIOFLOW-V randomized controlled clinical study was not powered to study the safety or effectiveness of the Orsiro stent in sex-specific subgroups, however exploratory analyses were performed. Refer to the "Clinical Studies" section for more information on the gender analysis.

8.8.4 Ethnicity

Clinical trials did not include sufficient patient numbers within ethnicity groups to permit ethnicity-related analysis of the safety and effectiveness of the Orsiro stent. Refer to the "Clinical Studies" section for more information on the demographics of patients included in the clinical trials.

8.8.5 Pediatric Use

The safety and effectiveness of the Orsiro stent in pediatric patients have not been established.

8.8.6 Geriatric Use

The BIOFLOW-V clinical trial did not have an upper age limit for patient inclusion. Among the 1334 BIOFLOW-V patients included in the study, 211 were older than 75 years of age and 1123 were aged 75 or younger at the time of the index procedure. A pre- specified sub-group analysis demonstrated that patients > 75 years old had a TLF rate at 12 months similar to those ≤ 75 years old and there was no evidence ($p = 0.178$) of an interaction between the primary endpoint and age groups observed.

8.9 Lesion / Vessel Characteristics

The safety and effectiveness of Orsiro has not yet been established in patients with the following:

- In-stent restenosis.
- 3 vessel coronary disease.
- An unresolved thrombus at the lesion site.
- Coronary artery reference vessel diameters < 2.25 mm or > 4.0 mm.
- Lesion length > 36 mm.
- Chronic total occlusion (CTO).
- Lesions located in a saphenous vein graft, in the left main coronary artery, ostial lesions, or bifurcation lesions.
- Target vessel/lesion is excessively tortuous / angulated or is severely calcified that would prevent complete inflation of an angioplasty balloon.
- Recent acute MI where there is evidence of thrombus or poor flow.
- Brachytherapy treatment of the target lesion.

9 Drug Information

9.1 Mechanism of Action

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

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

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

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

9.2 Pharmacokinetics

A human PK sub-study of the BIOFLOW-IV clinical trial was conducted with a total of 21 Japanese patients implanted with an Orsiro stent. Table 4 summarizes the whole blood sirolimus PK parameters in these patients following implantation of the Orsiro stent.

Table 4: Pharmacokinetic Parameters of Sirolimus in Whole Blood Following Treatment with Orsiro1

Parameter	Mean	Standard Deviation	CV (%)	Range(Min, Max)
C_{max} (ng/mL)	0.5337	0.2443	45.76	(0.2690, 1.368)
T_{max} (hour)	0.98	0.40	41.22	(0.50, 2.00)
$AUC_{0\text{-}24h}$ (ng*hours/mL)	7.28	2.77	38.06	(3.89, 16.10)
$AUC_{0\text{-}\infty}$ (ng*hours/mL)	27.11	10.44	38.50	(10.13, 51.63)
$t_{1/2}$ (hours)	57.29	27.74	48.43	(27.69, 140.77)
CL (L/h)	5.06	1.71	33.77	(2.12, 9.18)

[1] Mean (range) total sirolimus load124 mcg (93 – 193 mcg); 16 males and 5 females 68.5 (48 – 80) years old
Cmax (maximum whole blood sirolimus concentration); Tmax (time to Cmax); $AUC_{0\text{-}24}$ (Area under the whole blood sirolimus concentration-time curve from time 0 to 24 hours after stent implantation); $AUC_{0\text{-}\infty}$ (AUC from time 0 to infinity after stent implantation); $t_{1/2}$ (elimination half-life); CL (clearance)

Following implantation of Orsiro containing a mean sirolimus load of 124 µg, maximum whole blood sirolimus concentrations averaging 0.5337 ng/mL were observed at 1-hour post-implantation. At 24 hours post-implantation, the whole blood sirolimus concentrations were measurable in all 21 patients with a mean value of 0.21 ng/mL. At 72 hours post-implantation, the whole blood sirolimus concentrations were below the limit of quantification (0.080 ng/mL) in 3 of 21 patients with a mean value of 0.13 ng/mL. A linear trend was observed between the sirolimus dosage and the total sirolimus exposures.

9.3 Drug Interactions

Drug interaction studies have not been performed. Sirolimus is metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g. ketoconazole) may cause increased sirolimus exposure to levels associated with systemic effects, especially if multiple stents are deployed. Systemic exposure of sirolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

While no specific data are available, drugs like tacrolimus, which act through the same binding protein (FKBP) may interfere with the efficacy of sirolimus.

9.4 Metagenesis

Sirolimus was not mutagenic in the in vitro bacterial reverse mutation assay with or without metabolic activation up to 5000 µg/plate, the Chinese hamster ovary cell chromosomal aberration assay with and without metabolic activation, the mouse lymphoma cell forward mutation assay with and without metabolic activation, or the in vivo mouse micronucleus assay.

9.5 Carcinogenicity

Carcinogenicity studies were conducted in animals. In an 86-week female mouse study at sirolimus doses 30 to 120 times higher than the 2 mg daily clinical dose (adjusted for body surface area), there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical dose (adjusted for body surface area), hepatocellular adenoma and carcinoma in males were considered sirolimus-related. In a 104-week study in rats with 0, 0.05, 0.1, and 0.2 mg/kg/day dosages, there was an increased incidence of testicular interstitial cell adenoma in the 0.1 and 0.2 mg/kg/day groups. There were no significant findings for animals treated with equal or lower doses than the clinical dose of 2 mg/day (adjusted for body surface area). Although not directly measured in the study, it is conceivable that this increase may be related to altered luteinizing hormone levels secondary to decreased serum testosterone levels.

As luteinizing hormone receptors are different in humans and rats and the age of onset of the tumors is also different, the increased incidence in rats may therefore be considered not predictive for humans.

Carcinogenicity studies with sirolimus indicate that the intrinsic potential for carcinogenicity was secondary to that induced by the pharmacological action. The mechanism is non-genotoxic and it was stated that the involved receptor is different in human and animals. Moreover, the doses where the effects were detected were higher than the clinical human doses which are currently used.

Reproductive Toxicity

The study of the effects of sirolimus on the different stages of the reproductive process were conducted in rats. Male rats showed decreased fertility and testicular atrophy (giant cells and hypospermia in the testes and epididymides). The fertility of female rats was not affected, but a reduced size of ovaries and uteri were observed. Sirolimus was associated with embryo and fetal toxicity in rats, but no teratogenic effects were observed.

Pregnancy and Lactation

Sirolimus belongs to the FDA Pregnancy Category C. There are no adequate and well- controlled studies available for use in pregnant or lactating women. During pregnancy, the stent should be considered only if the potential benefit outweighs the potential risk to the embryo/fetus. Effective contraception must be initiated before stent implantation and for 12 months after the procedure.

It is not known whether sirolimus is excreted into breast milk. A decision to discontinue breastfeeding during the mother's exposure to sirolimus may be needed.

10 Overview of Clinical Studies

The principal safety and effectiveness for Orsiro derives from the BIOFLOW Clinical Program of global trials that were performed for regulatory approval. An overview of the BIOFLOW-II, BIOFLOW-IV and BIOFLOW-V trial designs are presented in Table54.

10.1 BIOFLOW-II Clinical Trial

BIOFLOW-II is a prospective, multi-center, randomized, controlled, non-inferiority trial that randomized 458 patients at 24 clinical centers in 8 European countries.[A] There were 452 randomized intent-to-treat (ITT) patients and 6 patients that were considered non-ITT (4 due to no study device implantation attempt and 2 with withdrawn consent prior to implantation). The purpose of this trial was to compare the Orsiro (sirolimus- eluting) DES and Xience Prime[1] (everolimus-eluting) DES in patients with single de novo coronary artery lesions in up to two coronary arteries with diameters of 2.25–4.0 mm. Patients were randomized (2:1) to receive the Orsiro stent or the Xience Prime stent. All patients underwent repeat angiography at 9 months post–index procedure. One subset of approximately 66 pre-specified patients underwent an IVUS examination at both baseline and 9 months. An additional subset of approximately 65 pre-specified patients underwent optical coherence tomography (OCT) examination at both baseline and 9 months. The primary efficacy endpoint was late lumen loss at 9 months post–index procedure. Patient follow-up will continue for five years.

10.2 BIOFLOW-IV Clinical Trial

BIOFLOW-IV is a prospective, international, multi-center, randomized controlled trial (RCT) designed to assess the safety and effectiveness of Orsiro in the treatment of patients with up to two de novo coronary artery lesions. A total of 579 patients were enrolled at 46 sites in Japan (138 patients) and Europe (441 patients). The BIOFLOW-IV RCT enrolled 579 patients with up to two de novo lesions ≤ 26 mm in length in the native coronary arteries with 2.5–3.75 mm diameters and were randomized (2:1) to receive the Orsiro stent or the Xience Prime/Xpedition[2] stent.

The primary endpoint 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. Patient follow-up will continue for five years.

As stated in the "Pharmacokinetics" subsection, the BIOFLOW-IV study included a human PK sub-study as a part of regulatory requirement for the Japanese regulatory agency. A total of 21 Japanese patients with up to two de novo lesions ≤ 26 mm in length in the native coronary arteries with 2.5–3.75 mm diameters were included in the concurrent, non-randomized PK sub-trial enrollment at sites in Japan. All 21 patients in the PK sub-study were successfully implanted with an Orsiro stent. No patient experienced an adverse device effect during the PK phase of the study.

10.3 BIOFLOW-V Clinical Trial

BIOFLOW-V is a prospective, international, multi-center, RCT designed to evaluate the safety and effectiveness of Orsiro (sirolimus-eluting) DES compared to the Xience (everolimus-eluting) DES for the treatment of atherosclerotic lesions ≤ 36 mm in length in the native coronary arteries with 2.25-4.00 mm diameters (by visual estimate).[B] The BIOFLOW-V study was designed to test the hypothesis that the rate of 12-month TLF in patients treated with an Orsiro stent was non-inferior to the rate of 12-month TLF in patients treated with a Xience stent. The analysis of the primary endpoint of 12-month TLF was a non-inferiority analysis combining data from BIOFLOW-V patients with data from prior BIOFLOW-II and BIOFLOW-IV patients employing a Bayesian approach.

A total of 1334 patients (884 Orsiro and 450 Xience) were randomized at 90 clinical sites in 13 countries in North America, Europe, Israel and the Asia-Pacific regions. Of the 1334 patients included in the ITT analysis set, a total of 1260 patients (833 Orsiro and 427 Xience) were evaluable for the 12-month primary endpoint.[C] The follow-up schedule includes clinical assessments at 30 days, 6 and 12 months and 2, 3, 4 and 5 years post- index procedure.

1 Xience Prime is a registered trademark of Abbott Cardiovascular Systems Inc.
2 Xience Xpedition is a registered trademark of Abbott Cardiovascular Systems Inc.

Table 5: Comparison of BIOFLOW Clinical Studies

Study name	BIOFLOW-II RCT	BIOFLOW-IV		BIOFLOW-V RCT
		RCT	PK	
Purpose	Evaluation of safety and effectiveness in native de novo coronary lesions	Evaluation of safety and effectiveness in native de novo coronary lesions	Evaluation of sirolimus blood levels	Evaluation of safety and effectiveness in native de novo and PTCA only restenoticcoronary lesions
Study design	Prospective, randomized, controlled, multi-center non- inferiority to Xience Regulatory trial	Prospective, randomized, controlled, multi-center non- inferiority to Xience Regulatory trial	Prospective, multi-center, observational study	Prospective, randomized, controlled, multi-center non- inferiority to Xience IDE Trial
Devices	2:1 Orsiro vs. Xience	2:1 Orsiro vs. Xience	Orsiro	2:1 Orsiro vs. Xience
Primary endpoint	9-month late lumen loss	12-month TVF	N/A (observational)	12-month TLF
Secondary/Long-term endpoints	TLF: cardiac death, target vessel Q-wave or non-Q wave MI, emergent CABG, clinically-driven TLR; ST	TLF: cardiac death, target vessel Q-wave or non-Q wave MI, emergent CABG, clinically-driven TLR; ST	N/A	TLF: cardiac death, target vessel Q-wave or non-Q wave MI, clinically-driven TLR (including CABG); ST
Number of patients (ITT)	452 Orsiro: 298 Xience: 154	575 Orsiro: 385 Xience: 190	21 Orsiro	1334 Orsiro: 884 Xience: 450
Target lesion criteria	1-2 de novo lesions Native arteries 50 to <100% stenosis	≤ 2 de novo lesions Native arteries 50 to <100% stenosis		≤ 3 de novo/ PTCA restenotic lesions/ 2 target vessels Native arteries 50 to <100% stenosis
Lesion criteria: Reference Vessel Diameter (RVD) (by visual estimate)	2.25 - 4.0 mm	2. 5 – 3.75 mm		2.25 - 4.0 mm
Lesion criteria: Lesion Length (LL) (by visual estimate)	≤ 26 mm	≤ 26 mm		≤ 36 mm
Follow-up	1, 6, 9 and 12 months, annually 2-5 years	1, 6 and 12 months, annually 2-5 years		1, 6 and 12 months, annually 2-5 years

References

[A] Windecker S, Haude M, Neumann FJ, et al. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW-II trial. Circ Cardiovasc Interv. 2015 Feb;8(2):e001441.

[B] Doros G, Massaro JM, Kandzari DE et al. Rationale of a novel study design for the BIOFLOW V study, a prospective, randomized multi-center study to assess the safety and efficacy of the Orsiro sirolimus-eluting coronary stent system using a Bayesian approach. Am Heart J. 2017 Nov. 193: 35-45.

[C] Kandzari DE, Mauri L, Koolen JJ et al. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet. 2017 Aug 26.

11 Adverse Events

11.1 Observed Adverse Events

The observed major clinical events from post-procedure to 12 months for the BIOFLOW-V study are reported in Table 6.

11.2 Potential Adverse Events/Complications

Potential adverse events associated with percutaneous coronary intervention with Orsiro stent placement include, but are not limited to:

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

Furthermore, all procedure-related adverse events as described in the national and international guidelines of the respective medical associations apply.

Potential adverse events related to oral administration of sirolimus include, but are not limited to, abnormal liver function tests, anemia, arthralgia, diarrhea, hypercholesterolemia, hypersensitivity (including anaphylactic/anaphylactoid type reactions), hypertriglyceridemia, hypokalemia, infections, interstitial lung disease, thrombocytopenia, leukopenia, lymphoma and other malignancies.

Table 6: BIOFLOW-V Major Clinical Events from Post-Procedure to 12 Months

Category	BIOFLOW-V RCT	
	Orsiro (n=884)	Xience (n=450)
In-hospital all death, MI, TVR	4.0% (35/883)	6.9% (31/449)
All death	0.1% (1/883)	0.2% (1/449)
Cardiac death	0.1% (1/883)	0.1% (1/449)
Non-cardiac death	0.0% (0/883)	0.0% (0/449)
MI*	3.9% (34/882)	6.7% (30/449)
Cardiac death or MI	4.0% (35/883)	6.7% (30/449)
TVR	0.2% (2/882)	0.5% (2/449)
TLR	0.2% (2/882)	0.5% (2/449)
30-day all death, MI, CD TLR (MACE)	4.4% (39/879)	7.1% (32/448)
30-day TLF	4.2% (37/879)	7.1% (32/448)
30-day TVF	4.3% (38/879)	7.1% (32/448)
12-month TLR	2.0% (17/832)	2.4% (10/422)
12-month all-cause death, MI, TLR (MACE)	7.0% (59/839)	10.3% (44/429)
All cause death	0.8% (7/837)	1.4% (6/428)
Cardiac death	0.1% (1/831)	0.7% (3/425)
Non-cardiac death	0.7% (6/836)	0.7% (3/425)
Any MI	4.9% (41/832)	8.7% (37/425)
Q-wave MI	0.1% (1/831)	1.0% (4/422)
Non-Q-wave MI	4.8% (40/831)	8.0% (34/425)
Cardiac death or MI	5.0% (42/833)	9.1% (39/427)
12-month TVR	3.2% (27/833)	3.6% (15/422)
Acute (≤24 hours) ARC stent thrombosis	0.1% (1/884)	0.0% (0/450)
Definite or probable	0.1% (1/884)	0.0% (0/450)
Definite	0.1% (1/884)	0.0% (0/450)
Probable	0.0% (0/884)	0.0% (0/450)
Subacute (>24 hours, ≤30 days) ARC stent thrombosis	0.2% (2/878)	0.2% (1/448)
Definite or probable	0.2% (2/878)	0.2% (1/448)
Definite	0.2% (2/878)	0.2% (1/448)
Probable	0.0% (0/878)	0.0% (0/448)
Late (> 30 days, ≤ 1 year) ARC stent thrombosis	0.1% (1/830)	0.9% (4/424)
Definite or probable	0.1% (1/830)	0.5% (2/422)
Definite	0·1% (1/830)	0.5% (2/422)
Probable	0.0% (0/830)	0.0% (0/422)
12-month ARC stent thrombosis	0.5% (4/831)	1.2% (5/424)
Definite or probable	0.5% (4/831)	0.7% (3/422)
Definite	0.5% (4/831)	0.7% (3/422)
Probable	0.0% (0/830)	0.0% (0/422)
Possible	0.0% (0/830)	0.5% (2/424)

Numbers are % (count/sample size).

Abbreviations: MI=myocardial infarction; TVR=target vessel revascularization; TLR=target lesion revascularization; ARC=Academic Research Consortium, CD=clinically-driven.

* The MI definitions for BIOFLOW-V:

- Peri-procedural MI:
  - Baseline CKMB and troponin < 1xURL: enzyme confirmed by CKMB > 3xURL (in the absence of CKMB, troponin > 3xURL was used).
  - Baseline CKMB or troponin > 1xURL: enzyme confirmed by a rise in CKMB ≥ 50% above the previous level and > 3xURL or, in the absence of CKMB, a rise in troponin above the previous level and > 3xURL. Also needed evidence that cardiac biomarkers values were decreasing prior to the suspected MI.
  - New pathologic Q-waves in 2 contiguous ECG leads.
- Spontaneous MI:
  - Recurrent chest pain or ischemic equivalent and new pathologic Q-waves in 2 contiguous ECG leads and any CKMB >1xURL (in the absence of CKMB, troponin > 1xURL. In the absence of CKMB and troponin CK > 1xURL may be used).
  - Confirmed cardiac enzyme data CK ≥ 2xURL confirmed by CKMB > 1xURL or in the absence of CKMB, troponin > 1xURL. In the absence of CK, CKMB > 3xURL. In the absence of CK and CKMB, troponin > 3xURL.

12 Patient Counseling Information

In addition to counseling the patient about the procedure, stent and applicable post- procedural information (e.g. risks/benefits, follow-up visits, medication and healthy lifestyle changes), advise the patient to:

- Always carry the Patient Implant Card.
- Read the Patient Information Guide available online (manuals.biotronik.com).
- Register the stent and the conditions under which it can be scanned safely with the MedicAlert Foundation (www.medicalert.org) or equivalent organization.

13 Directions for Use

13.1 Patient Preparation and Stent System Selection

1. Prepare the patient and vascular access site for a PCI procedure according to the institution's standard clinical practice. Prepare the lesion site according to standard practice.
2. Predilation of the lesion is mandatory and performed using a recommended balloon diameter 0.5 mm smaller than the reference vessel diameter and balloon length equal to or shorter than the target lesion length. Select the stent inner diameter according to the reference vessel diameter of the target lesion. Stent length must be equal or longer than the lesion length.
3. Refer to the product label for further information on the stent crossing profile dimensions.

13.2 Stent System Preparation

4. Check and ensure that the outer packaging is not damaged or opened prior to use. Open the outer packaging and remove the sterile pouch.
5. Inspect the pouch and ensure that there is no damage to the sterile barrier before proceeding. Open the pouch.
6. Exercise care when pulling out the stent system from the protection ring and place it onto a sterile field.
7. Pull at the distal end of the protector and carefully remove the balloon/stent protector.
8. Visually check the stent crimping for uniformity, no protruding struts and centering on the balloon. Verify that the stent is positioned between the proximal and distal balloon markers. DO NOT use if any defects are noted.

13.3 Flushing of the Guide Wire Lumen

9. Connect a syringe containing heparinized normal saline to an appropriately-sized flushing needle. Carefully apply the needle to the distal tip of the delivery system and flush the guide wire lumen until fluid exits the guide wire port.
10. Remove the syringe and the flushing needle.
11. Leave the prepared stent system at ambient pressure.

13.4 Insertion and Stent Positioning

12. Attach a rotating hemostatic valve to the luer port of the guiding catheter positioned within the vasculature.
13. Position the guide wire under fluoroscopy in accordance with techniques.
14. Back-load the distal tip of the delivery system onto the proximal portion of the guide wire while maintaining the guide wire position across the target lesion.
15. Open the rotating hemostatic valve completely to allow for easy passage of the stent.
16. Carefully insert the stent system through the rotating hemostatic valve.
17. Advance the stent system through the guiding catheter using fluoroscopic guidance to determine when the delivery system tip approaches the distal tip of the guiding catheter. The shaft exit markers on the hypotube may be used to approximate when the stent system has reached the distal end of the guiding catheter.
18. Carefully advance the stent system into the coronary artery over the guide wire while maintaining a stable guiding catheter seating and a stable guide wire placement across the target lesion.
19. Position the stent within the lesion using the balloon radiopaque markers as reference points. If any resistance is felt or the lesion cannot be reached or crossed, do not apply force, stop the procedure and refer to the steps listed under "Removal of an Unexpanded Stent" subsection.
20. Verify the stent position using angiographic guidance to assure an adequate coverage of the lesion including the proximal and distal margins. If the position of the stent is not optimal, it should be carefully repositioned or removed (refer to the "Removal of an Unexpanded Stent" subsection). Expansion of the stent should not be undertaken if the stent is not properly positioned within the target lesion segment of thevessel.
21. Tighten the rotating hemostatic valve.

13.5 Remove Air from the Delivery System

22. Connect a three-way stopcock to the luer port of the catheter.
23. Prepare and remove air from a 20 ml capacity inflation/deflation device according to the manufacturer's recommendations and instructions.
24. Attach the inflation/deflation device containing 3 ml of balloon inflation medium to the stopcock.
25. Open the stopcock so that an open fluid path between the catheter and the inflation/ deflation device is established.
26. Pull the plunger of the inflation/deflation device and aspirate air from the catheter for at least 30 seconds. Release the plunger to neutral for contrast refill.
27. Close the stopcock so that the fluid path to the catheter is closed and evacuate all air from the inflation/deflation device through the stopcock.
28. Repeat steps 25-27 if necessary to ensure that the air contained in the stent system is removed to prevent uneven stent expansion. Release the inflation/deflation barrel to normal pressure.
29. Open the fluid path of the stopcock and avoid allowing air back into the system. Set the system on neutral aside for use.

13.6 Stent Deployment

30. Prior to stent expansion, reconfirm the correct position of the stent relative to the target lesion. Under angiographic guidance, verify that the stent has not been damaged or shifted during positioning and control the following stent expansion with consideration of vessel morphology. Inflate the dilatation balloon carefully and gradually expand the stent to the calculated diameter in accordance with the Compliance Chart. Hold that pressure for 15-30 seconds.

Note: Diameter values listed on the Compliance Chart were assessed in non-clinical testing with no lesion-resistance during inflation. Clinical conditions may differ.

31. Use multiple fluoroscopy views to ensure that the stent has been completely expanded.
32. If necessary, the delivery system balloon may be dilated once more or further dilated in order to achieve complete apposition of the stent to the artery wall.
33. If the stent is still not completely apposed to the vessel wall, the stent can be re- crossed and further expanded with a larger balloon. Deployed stents should not be left under-dilated. Stent wall apposition should be verified through routine angiography or IVUS.

13.7 Balloon Deflation and Delivery System Removal

34. Deflate the balloon in accordance with standard PCI procedures. Apply negative pressure to the balloon for at least 35 seconds. Deflation of the balloon should be confirmed by absence of contrast within the balloon.
35. Open the rotating hemostatic valve to allow removal of the delivery system.
36. Maintain the position of the guiding catheter and guide wire to prevent them from being drawn into the vessel. Whilst under fluoroscopic control and maintaining the negative pressure, carefully pull the completely deflated delivery system out of the target vessel and into the guiding catheter. If resistance is felt, remove the delivery system and the guiding catheter as a single unit. If the deflated balloon cannot be easily withdrawn from the wall-apposed stent, slightly advance and retract the delivery system carefully. If resistance is still felt, repeat the operation until it is possible to gently pull the balloon out of the stent.
37. After removal of the delivery system, tighten the rotating hemostatic valve.
38. Inspect the device immediately upon removal from the patient for any signs of breakage or fragmentation.
39. Observation of the patient and angiographic evaluation should be performed periodically in the 15 minutes after the stent implantation.
40. After use, dispose the product and packaging in accordance with hospital, administrative and/or local government policy.

14 Special Retrieval Techniques

14.1 Removal of an Unexpanded Stent

1. If removal of the stent system is required prior to deployment, ensure that the guiding catheter is coaxially positioned relative to the delivery system and avoid any acute angle between the floppy part of the delivery system and the guiding catheter.
2. Slowly pull back the stent system into the guiding catheter. The entry of the stent into the guiding catheter must be performed slowly under fluoroscopic control to avoid dislodgement of the stent from its position on the delivery system balloon.

Caution: If resistance is felt when pulling the stent system into the guiding catheter, remove the stent system and the guiding catheter as a single unit (proceed as directed).

3. The lesion must be pre-dilated again or otherwise prepared before a second attempt at stenting is undertaken using a new stent system.

14.2 Removal of the Delivery System/Stent System and the Guiding Catheter as a Single Unit

1. DO NOT retract the stent system/delivery system into the guiding catheter. Maintain guide wire placement across the lesion and carefully pull-back the stent system/ delivery system. Position the proximal balloon marker just distal to the tip of the guiding catheter. Advance the guide wire into the artery as distally as safely possible.
2. Advance the guide wire into the artery as distally and safely as possible. Remove the guiding catheter and the delivery system as a single unit.
3. Tighten the rotating hemostatic valve to secure the stent system/delivery system to the guiding catheter.
4. Remove the guiding catheter and the stent system/delivery system as a single unit.

15 MRI Safety Information

Non-clinical tests demonstrated that the Orsiro stent is MR conditional. Patients with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 T and 3.0 T.
- Maximum spatial field gradient of 3000 gauss/cm (30 T/m).
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (normal operating mode).

Under the scan conditions defined above, the Orsiro stent is expected to produce a maximum temperature rise of less than 5.7 °C after 15 minutes of continuous scanning.

In non-clinical tests, the image artifact caused by the device extended approximately 7 mm from the Orsiro stent when imaged with a gradient echo pulse sequence and a 3.0 T MR system. The artifact may obscure the device lumen.

Compliance Chart

Inflation Pressure			Stent Inner Diameter (mm)					
			SMALL				MEDIUM	
	atm	(kPa)	2.25	2.50	2.75	3.0	3.5	4.0
	6	(608)	2.20	2.44	2.67	2.90	3.45	3.89
NP	**7**	**(709)**	**2.26**	**2.52**	**2.75**	2.99	**3.54**	**4.00**
NP	**8**	**(811)**	2.31	2.59	2.82	**3.07**	3.62	4.10
	9	(912)	2.36	2.65	2.89	3.14	3.68	4.17
	10	(1013)	2.41	2.71	2.94	3.20	3.74	4.24
	11	(1115)	2.44	2.75	2.99	3.25	3.79	4.29
	12	(1216)	2.48	2.79	3.02	3.29	3.83	4.34
	13	(1317)	2.50	2.82	3.06	3.32	3.86	4.38
	14	(1419)	2.53	2.86	3.09	3.36	3.89	4.42
	15	(1520)	2.55	2.88	3.11	3.39	3.92	4.45
RBP	**16**	**(1621)**	**2.57**	**2.92**	**3.14**	**3.42**	**3.95**	4.48
NP	In vitro tests have shown that the balloons reached their nominal size at given nominal pressure.							
RBP	In vitro tests have shown that with 95% confidence, 99.9% of the balloons will not burst at or below the rated burst pressure. DO NOT exceed RBP.							

Maximum Diameter for Post-dilation

Stent Design	SMALL				MEDIUM	
Stent Inner Diameter (mm)	2.25	2.50	2.75	3.0	3.5	4.0
Maximum Diameter for Post-dilation	3.5 mm				4.5 mm	

Note: If post-dilation is required, DO NOT post-dilate more than the maximum expandable diameter.

16 Clinical Studies

16.1 BIOFLOW-II Clinical Trial

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

Design: Patients aged 18 years or older with stable or unstable angina pectoris, silent ischemia, or clinical evidence of MI undergoing planned stent implantation in a single de novo native coronary lesion were eligible for enrollment. Angiographic inclusion criteria included a reference vessel diameter between 2.25 and 4.0 mm with lesion length of ≤26 mm (by visual estimation). Principal angiographic exclusions included chronic total occlusions, bifurcations involving a side branch with a diameter of >2.0 mm, bypass graft stenoses and in-stent restenosis. Further exclusion criteria included thrombus in the target vessel, unprotected left main coronary artery disease (stenosis > 50%), evidence of MI within 72 hours prior to the index procedure, heavily calcified lesions, ostial target lesions within 5.0 mm of vessel origin, and target lesions in or supplied by an arterial or venous bypass graft were also excluded. The protocol recommended antiplatelet therapy for a minimum of 6 months unless contraindicated.

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

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

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

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

Results: The mean in-stent late lumen loss at 9 months was 0.10±0.32mm for Orsiro as compared to 0.11±0.29mm for the Xience Prime (Table 7). The non-inferiority hypothesis was confirmed with a P-value <0.0001. At 12 months, the TLF Kaplan Meier estimate was 6.5% (95% CI [4.2%, 10.0%]) in the Orsiro group compared to 8.0% (95% CI [4.6%, 13.7%]) in the Xience Prime group (Table 8).

Table 7: BIOFLOW-II Primary Endpoint, Late Lumen Loss - Angiographic Follow-up Results at 9 Months

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

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

Table 8: BIOFLOW-II, Kaplan-Meier Estimates of Endpoints at 12 Months, ITT Patients

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

Number of events (Kaplan–Meier–based incidence rates [%]) are reported. No CABG revascularization events were reported. Target lesion failure is the composite of cardiac death, target-vessel MI, CABG, or clinically-driven TLR. Target vessel failure is the composite of cardiac death, target-vessel MI, CABG, or clinically-driven TVR.

Abbreviations: CI, confidence interval; MI, myocardial infarction; TLR, target-lesion revascularization; TV, target vessel; TVR, target-vessel revascularization.

* Event rates for MI in the table are reported according to the Joint ESC/ACCF/AHA/ WHF Task Force universal definition of MI.

16.2 BIOFLOW-IV Clinical Trial

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

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

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

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

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

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

Results: The 12-month TVF rate in the ITT population, frequentist analysis based on the MI Universal Definition, was 5.1% in the Orsiro group compared to 6.6% in the Xience group, with a difference of -1.5% [95% CI: -5.7%, 2.7%] and the primary endpoint was met (p=0.0003, for non-inferiority). The Kaplan-Meier Estimates of Secondary Endpoints at 12 months are presented in Table 9.

Table 9: BIOFLOW-IV, Kaplan-Meier Estimates of Secondary Endpoints at 12 Months

Endpoints	Orsiro (n=385)	Xience (n=190)
TVF (MI Universal Definition)	5.5%	7.5%
TVF (MI Extended Historical Definition)	4.0%	4.9%
Clinically-driven (CD) TVR	3.7%	3.9%
TLF (MI Universal Definition)	4.2%	5.4%
TLF (MI Extended Historical Definition)	2.6%	2.8%
TLR (CD)	2.1%	1.8%
MI (Universal Definition)	3.7%	3.2%
MI (Extended Historical Definition)	1.8%	0.5%
Death (all-cause)	1.6%	2.9%
Death (Cardiac)	0.0%	0.5%
Death (Non-cardiac)	1.6%	2.4%
Stent thrombosis (Definite/ Probable)	0.8%	0.0%

Number of events (Kaplan–Meier–based incidence rates [%]) are reported.

16.3 BIOFLOW-V Clinical Trial

Primary Objective: The primary objective of the BIOFLOW-V trial was to evaluate the safety and effectiveness of the Orsiro compared to the Xience DES for the treatment of atherosclerotic lesions ≤ 36 mm in length (by visual estimate) in the native coronary arteries of 2.25 mm to 4.00 mm in diameter (by visual estimate).

Design: Eligible patients aged 18 years or older with ischemic heart disease undergoing planned stent implantation in de novo native coronary lesions were eligible for enrollment. Enrollment criteria permitted treatment of no more than three coronary artery lesions in a maximum of two native target vessels. Patients with non-ST elevation acute coronary syndromes (including non-ST elevation MI) without hemodynamic instability were eligible for enrollment. Angiographic inclusion criteria included a reference vessel diameter between 2.25 and 4.0 mm with lesion length of ≤ 36 mm (by visual estimation). Principal angiographic exclusions included chronic total occlusions, bifurcations involving a side branch with diameter > 2.0 mm, bypass graft stenoses and in-stent restenosis. Calcified lesions requiring atherectomy were permitted following instances of inadequate angioplasty balloon pre-dilation. Patients with recent (<72 hours) ST-segment elevation MI, left ventricular ejection fraction <30%, active stent thrombosis, creatinine clearance <30 mL/min, any prior PCI within 30 months or within 9 months involving the target vessel and those unlikely to adhere to DAPT were also excluded. The protocol recommended antiplatelet therapy for a minimum of 6 months and highly recommended for 12 months for patients who were not at a high risk of bleeding.

The BIOFLOW-V study was designed to test the hypothesis that the rate of 12-month TLF in patients treated with the Orsiro stent was non-inferior to the rate of 12-month TLF in patients treated with the Xience control. The analysis of the primary endpoint of 12-month TLF was a non-inferiority analysis combining data from BIOFLOW-V patients with data from prior BIOFLOW-II and BIOFLOW-IV patients employing a Bayesian approach.

A total of 1334 patients (884 Orsiro and 450 Xience) were randomized and enrolled at 90 clinical sites in North America, Europe, Israel and the Asia-Pacific region. Of the 1334 patients included in the intent-to-treat analysis set, a total of 1260 patients (833 Orsiro and 427 Xience) were evaluable for the 12-month primary endpoint. Follow-up included clinical assessments at 30 days, 6, 12 months and 2, 3, 4 and 5 years post-index procedure.

Demographics: Patients were well-matched for baseline demographics. The average patient age was 64.5±10.3 and 64.6±10.7 in the Orsiro and Xience groups, respectively. Approximately 74.7% of patients in the Orsiro group and 72.9% of patients in the Xience group were male, and 34.0% of patients in the Orsiro group and 37.0% in the Xience group had diabetes. More than half of the patients presented with acute coronary syndrome and more than a quarter presented with elevated cardiac enzymes within 24 hours of the index procedure.

Baseline lesion characteristics: Mean reference vessel diameter (RVD) was 2.59±0.54mm and 2.60±0.58mm for the Orsiro and Xience, respectively. Average lesion length was 13.3±7.6mm and 13.2±7.7mm for the Orsiro and Xience groups, respectively. The percentage of lesions treated that were type B2/C was 72.6% and 75.9% for Orsiro and Xience respectively.

Results (Frequentist Analysis): The principal safety and effectiveness outcomes are presented in Table 10. The analyses are based on the ITT population. A frequentist analysis for the primary endpoint for the BIOFLOW-V population was performed for 12-month TLF rate and its components. The primary endpoint rate of 12-month TLF was significantly lower in the Orsiro group compared to the Xience group: 6.2% compared to 9.6% (P=0.040), primarily driven by a significantly lower rate of target vessel MI: 4.7% compared to 8.3% (P=0.016).

Table 10: BIOFLOW-V Principal Safety and Effectiveness Outcomes at 12 months, ITT.

Category	Orsiro (n=884)	Xience (n=450)
Target-lesion failure	6.2% (52/833)	9.6% (41/427)
Cardiac death	0.1% (1/831)	0.7% (3/425)
Target-vessel myocardial infarction	4.7% (39/831)	8.3% (35/424)
Clinically-driven target-lesion revascularization	2.0% (17/832)	2.4% (10/422)
Death from any cause	0.8% (7/837)	1.4% (6/428)
Any myocardial infarction	4.9% (41/832)	8.7% (37/425)
Q-wave	0.1% (1/831)	1.0% (4/422)
Non-Q-wave	4.8% (40/831)	8.0% (34/425)
Cardiac death or any myocardial infarction	5.0% (42/833)	9.1% (39/427)
Major adverse cardiac events	7.0% (59/839)	10.3% (44/429)
Target-vessel failure	7.2% (60/834)	10.5% (45/427)
Cardiac Death	0.1% (1/831)	0.7% (3/425)
Target-vessel myocardial infarction	4.7% (39/831)	8.3% (35/424)
Clinically-driven target-vessel revascularization	3.2% (27/833)	3.6% (15/422)
ARC Stent Thrombosis	0.5% (4/831)	1.2% (5/424)
Definite/Probable	0.5% (4/831)	0.7% (3/422)
Definite	0.5% (4/831)	0.7% (3/422)
Probable	0.0% (0/830)	0.0% (0/422)

Results (Bayesian Analysis): In the pooled primary endpoint analysis that included patient level outcomes from the BIOFLOW-II and BIOFLOW-IV trials, the Bayesian posterior probability that Orsiro was non-inferior to Xience was 100.0% with a Bayesian estimate TLF rate difference -2.6% (95% Credible Interval, -5.5% to 0.1%) (Table 11).

Table 11: BIOFLOW-V Primary Endpoint Results, Bayesian Analysis -Pooled Data from BIOFLOW-V, BIOFLOW-IV and BIOFLOW-II, ITT

Bayesian Analysis	Orsiro (n=1466)	Xience (n=742)	Rate Difference	Posterior Probability
				Non-inferiority*
Target-lesion failure at 12 months, Posterior Mean (estimate of SD), % 95% Credible Interval (Lower, Upper)	6.3 ± 0.8 (5.0, 8.0)	8.9 ± 1.2 (6.7, 11.4)	-2.6 ± 1.4 (-5.5, 0.1)	100.0%
* Non-inferiority Margin = 3.85%				

Table 12: BIOFLOW-V TLF at 12 Months, Primary Endpoint Results by Gender, ITT

TLF at 12 Months	Orsiro (n=884)	Xience (n=450)	Difference [95% Credible Interval]
Male	6.2% (39/628)	8.9% (28/312)	-2.8% [-6.6%, 0.8%]
Female	6.3% (13/205)	11.3% (13/115)	-5.0% [-12.0%, 1.4%]
The trial was not powered to assess the TLF difference by gender. Numbers are % (count/sample size).			

16.4 BIOFLOW-V Diabetes Subgroup Analysis (Post hoc)

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

A frequentist analysis of the diabetic subgroup was performed on 12-month TLF and its components using only BIOFLOW-V data. Among BIOFLOW-V ITT diabetic subjects, the 12-month TLF rate was 6.43% in the Orsiro group compared to 9.80% in the Xience group (difference of -3.38% [95% confidence interval (CI): -9.57% to 1.77%]; P=0.255 for superiority). A lower rate of target vessel MI was observed in the Orsiro group but was not statistically significant: 4.30% compared to 7.95% (difference of -3.65% [95% CI: -9.37% to 0.89%]; P=0.127).

17 Patient Selection/Individualization of Treatment

Judicious selection of patients according to the intended use is necessary since the use of this device carries the associated risks of complications listed in the "Adverse Events" section. The risks and benefit should be considered for each patient before using Orsiro. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy (see "Pre- and Post-procedure Antiplatelet Therapy Recommendations" section). Special consideration should be given to those patients with recently active gastritis or peptic ulcer disease and patients with high risk of bleeding in which anticoagulation therapy would be contraindicated.

It is very important that the patient is compliant with the post-procedure antiplatelet recommendation. Premature discontinuation of prescribed antiplatelet medication can result in a higher risk of thrombosis, MI or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether the DES and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended, the risk and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant bleeding should be monitored carefully for cardiac events, and once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

Patient co-morbidities that may increase the risk of poor results or emergency referral for bypass surgery (i.e. renal failure and severe obesity) should be reviewed. A review of the vessel location, reference vessel size, lesion length, qualitative target lesion characteristics and the amount of myocardium in jeopardy from acute or subacute thrombosis must also be considered.

Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3 mm, intra-procedural thrombus and dissection following stent implantation. In patients who have undergone coronary stenting, the persistence of thrombus or dissection should be considered a marker for subsequent thrombotic occlusion. Following PCI, the patients should be monitored very carefully during the first month after stent implantation.

18 Warranty/Liability

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